Original Article

A prospective randomised controlled trial of concurrent chemoradiation versus concurrent chemoradiation along with gefitinib in locally advanced squamous cell carcinoma of head and neck

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ABSTRACT

Background: The primary aim of the study was to find out whether addition of Gefitinib to standard cisplatin-based chemo-radiation can offer better treatment outcome at the cost of acceptable toxicities. **Materials and Methods:** Between January 2011 and June 2012, 64 patients were enrolled in the study following obtaining institutional ethical committee clearance and proper informed consent from the patients. Patients recruited were randomly allocated into a control arm (who received External Beam Radiotherapy with conventional 2 Gy/fraction, 5 days a week for 7 weeks up to total dose of 66 Gy along with concomitant injection cisplatin at the dose of 30 mg/m^2 of body surface area on every week during radiation) and study arm (who received radiotherapy with 2 Gy/fraction, 5 days a week for 7 weeks up to total dose of 66 Gy, along with concomitant injection cisplatin at the dose of 30 mg/m^2 of body surface area on every week during radiation, plus Tablet Gefitinib (250 mg/day orally) during the total duration of radiation treatment). However, only 61 patients (31 in the control arm and 30 in the study arm) were available for analysis. The two groups were comparable in terms of age distribution, sex distribution, performance status, stage, primary site and histological grade. **Results:** 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 + partial response) 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 ($P = 0.515$). Addition of Gefitinib to standard concurrent cisplatin-based chemoradiation was well-tolerated with no significant increase in acute skin or mucosal toxicity. There was no significant increase in late toxicities like subcutaneous tissue fibrosis and xerostomia in the study arm. The only acute toxicity that was significantly worse in the study arm was diarrhea. However, it could be managed easily with supportive measures and did not contribute to delay in completion of treatment. **Conclusion:** We can conclude 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. However, these encouraging results did not reach the level of statistical significance. Larger studies involving much greater number of patients across multiple institutions are required to validate those encouraging results and clearly define the role of addition of Gefitinib to current standard of care in locally advanced squamous cell carcinoma of head and neck.

Key words: Chemo-radiation, cisplatin, Gefitinib, squamous cell carcinoma of head and neck

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INTRODUCTION

World-wide, nearly 650,000 people develop head and neck cancer (HNC) each year and there are 350,000 deaths from this disease.[1,2] Around 60% of the patients present with loco-regionally advanced, but non-metastatic disease. The extensive use of tobacco products is one of the reasons behind the ever increasing number of HNC in the developing

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nations who can least afford to treat them. In India also cancers of oral cavity, tongue, pharynx and larynx contribute a major share. The age adjusted incidence for these sites in Indian male population range from 10.8 to 38.8/100,000 populations and 6.4-14.9 in 100,000 female populations.[3,4]

Treatment of locally advanced head neck squamous cell carcinoma (LAHNSCC) has been the subject of intensive investigations in last few decades. Radiotherapy alone was the standard treatment for advanced disease for long time. However, it was observed that radiotherapy alone resulted in local control of 50-70% and improvement in disease free survival (DFS) of 30-40%. Multiple trials established the superiority of concurrent chemo-radiotherapy for the locally advanced head neck carcinomas with improvement of survival. Cisplatin is the cornerstone of the cytotoxic drugs that have been tried along with radiation therapy (RT) to increase its efficacy and cisplatin-based concurrent chemo-radiation is the current standard of care for locally advanced squamous cell carcinoma of head and neck region.

The introduction of targeted agents against the epidermal growth factor receptor (EGFR) pathway has improved survival in LAHNSCC. A study done by Bonner *et al.*,[5] demonstrated in a phase III randomized trial that concomitant RT plus cetuximab, an EGFR-specific antibody, improved loco-regional control (LRC), DFS and overall survival (OS) in LAHNSCC patients.

Gefitinib works as a potent and specific EGFR tyrosine kinase inhibitor (EGFR-TKI) by competing with adenosine triphosphate for the binding site on the intracellular domain of the receptor and by noncompetitively inhibiting epidermal growth factor peptide ligand. Agents that target EGFR radiosensitize tumor cells by a variety of mechanisms, including reduction in the proportion of cells in the radioresistant S phase by inducing G_0/G_1 cell cycle arrest, inhibition of RT-induced damage repair, and induction of apoptosis.[5] Gefitinib has been shown to inhibit repair of Radiation-induced deoxyribonucleic acid (DNA) double-strand breaks. EGFR expression levels in HNC cell lines correlated with increased RT resistance[6] and Gefitinib enhanced radiosensitivity in HNC cells.

Gefitinib 250 mg or 500 mg/day along with concurrent chemoradiation with cisplatin (30 mg/m^2) weekly has been shown to be well-tolerated and also efficacious in terms of both local control and DFS in western population. A phase III Trial sponsored by the Eastern Co-operative Oncology Group and collaborated by National Cancer Institute, United States is currently going on to assess the benefit of addition of Gefitinib with docetaxel in metastatic squamous cell carcinoma of head and neck (SCCHN).

However, there is a paucity of studies, particularly in Indian population, regarding whether addition of Gefitinib along with standard cisplatin-based concurrent chemoradiation brings about any tangible improvement in local control and DFS rates, and it also needs to be assessed whether such an improvement comes at an acceptable expense of acute and late toxicities. With growing number of patients being diagnosed with squamous cell carcinoma of head and neck region, and most of them presenting in a locally advanced stage, such a study becomes almost essential.

MATERIALS AND METHODS

The entire study was conducted in the Department of Radiotherapy, Medical College Hospital, Kolkata between January 2011 and June 2012. It was a single-institutional prospective randomized controlled trial to study whether addition of Gefitinib to standard cisplatin-based chemo-radiation can offer better treatment outcome with acceptable toxicities. A total of 64 patients, belonging to age range 18-70 years and sufficing the following criteria were included in the study: Attending the radiotherapy out-patient department with histologically proven squamous cell carcinoma of oral cavity, oropharynx, hypopharynx, larynx (supraglottic) of locally advanced stage (AJCC stage groups III, IVA, IVB); Karnofsky performance status more than 60; normal hematological, renal and hepatic function. Patients with pregnancy and lactation, history of prior surgery, chemotherapy or radiotherapy, uncontrolled comorbid conditions and with evidence of distant metastasis were excluded from the study. Institutional ethical committee clearance was obtained and proper informed consent was taken from all the patients.

Patients recruited were randomly allocated into a control arm (who received External Beam Radiotherapy with conventional 2 Gy/fraction, 5 days a week for 7 weeks up to total dose of 66 Gy along with concomitant injection cisplatin at the dose of 30 mg/m^2 of body surface area on every week during radiation) and study arm (who received radiotherapy with 2 Gy/fraction, 5 days a week for 7 weeks up to total dose of 66 Gy, along with concomitant injection cisplatin at the dose of 30 mg/m^2 of body surface area on every week during radiation, plus tablet Gefitinib (250 mg/day orally) during the total duration of radiation treatment). Every other patient was recruited in the study arm. External beam radiotherapy was delivered using Telecobalt unit THERATRON 780C (Theratronics), Custom made immobilization devices for head and neck, computed tomography (CT)-Simulator (Brilliance CT 16-slice configuration, Philips Health Care) and ASHA treatment planning system.

Patients in both arms were followed-up weekly to assess acute toxicities. They were examined 1 month after the

completion of the treatment for assessing the response. Thereafter, they were evaluated every 2 months up to 1 year and every 3 months thereafter.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 20. For categorical variables, Chi-Square and Fisher Exact tests were used, whereas for continuous variables, the mean and standard deviation were compared using Independent samples *t*-test with 95% confidence interval. All tests were 2-tailed and $P < 0.05$ was taken as significant.

RESULTS

Totally 64 patients were studied and their characteristics are shown in Tables 1-4. Three patients were excluded from analysis, among them 1 patient of control died within the study period due to hemorrhagic stroke before completing the treatment ($n = 1$) and 1 patient of the study arm was lost to follow-up and 1 patient of study arm discontinued allotted treatment due to unknown reasons. So at the end of study, 61 patients were eligible for analysis with 30 patients in study arm and 31 patients in control. Baseline profiles of both groups were comparable in terms of age distribution, sex distribution, performance status, stage, primary site and histological grade.

Patients were evaluated 6 weeks following completion of treatment for response which was evaluated according to Response Evaluation Criteria in Solid Tumors criteria (version 1.1). In the control arm, 9 patients (29.03%) achieved complete response (CR) while 11 patients (36.67%) achieved CR in the study arm (Chi-square: 0.403, $P = 0.5255$, not significant). Hence, although more patients achieved CR in the study arm than the control arm [Figure 1], it did not reach the level of statistical significance, presumably due to small sample size as the study was a single-institutional one. In the control arm, 10 patients (32.26%) achieved partial response (PR) while 12 patients (40%) achieved PR. Hence, 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 in number of patients achieving overall response between the study arm and the control arm was not statistically significant (Chi-square: 1.681, $P = 0.1947$, not significant).

Number of patients having grade 2 or more acute skin toxicity was 14 (45.16%) in control arm while it was 19 (63.33%) in study arm ($P = 0.243$) [Figure 2]. Hence, it can be inferred that although incidence of grade 2 or more skin toxicity was more in study arm, it was not statistically significant. One patient in the study arm developed in-field rash during radiation but it was manageable and did not contribute to treatment delay. Number of patients having grade 2 or more acute mucositis was 20 (64.52%) in control arm while it was 21 (70%) in study arm ($P = 0.648$) [Figure 3]. So, it can be inferred that although incidence of grade 2 or more mucositis was marginally more in study arm, it was not statistically significant. Number of patients having grade 2 or more diarrhea was 2 (6.45%) in control arm while it was 10 (33.33%) in study arm ($P = 0.01$) [Figure 4]. Hence, it can be inferred that incidence of grade 2 or more diarrhea is more in study arm and it is statistically significant as well.

The common late toxicities met in the present study included subcutaneous tissue fibrosis and xerostomia (salivary gland toxicity). Number of patients having grade 2 or more subcutaneous tissue fibrosis was 12 (38.71%) in control arm while it was 10 (33.33%) in study arm ($P = 0.791$) [Figure 5]. So, it can be inferred that incidence of grade 2 or more subcutaneous tissue fibrosis was comparable in two arms. Number of patients having grade 2 or more xerostomia (salivary gland toxicity) was 13 (41.94%) in control arm while it was 11 (36.67%) in study arm ($P = 0.794$) [Figure 6]. So, it can be inferred that incidence

Table 1: Sex distribution of patients in control and study arms

Sex	Control arm (*n*=31) (%)	Study arm (*n*=30) (%)
Male	27 (87.1)	27 (90)
Female	4 (12.9)	3 (10)

P=0.7220 not significant

Table 2: Age distribution of the patients in the control and study arms

Age group	Control arm (*n*=31) (%)	Study arm (*n*=30) (%)
40-49 years	7 (22.58)	6 (20)
50-59 years	11 (35.48)	10 (33.33)
60-69 years	13 (41.94)	14 (46.67)

Table 3: Distribution of patients according to Karnofsky performance status in control arm and study arms

Karnofsky performance status	Control arm (*n*=31) (%)	Study arm (*n*=30) (%)
60	7 (22.58)	7 (23.33)
70	11 (35.48)	12 (40)
≥80	13 (41.94)	11 (36.67)

P=0.9076 not significant

Table 4: Distribution of patients according to primary site

Primary site	Oral cavity (%)	Oropharynx (%)	Hypopharynx (%)	Larynx (%)
Control arm (*n*=31)	2 (6.45)	9 (29.03)	8 (25.8)	12 (38.7)
Study arm (*n*=30)	3 (10)	7 (23.33)	6 (20)	14 (46.67)

P=0.9843 not significant

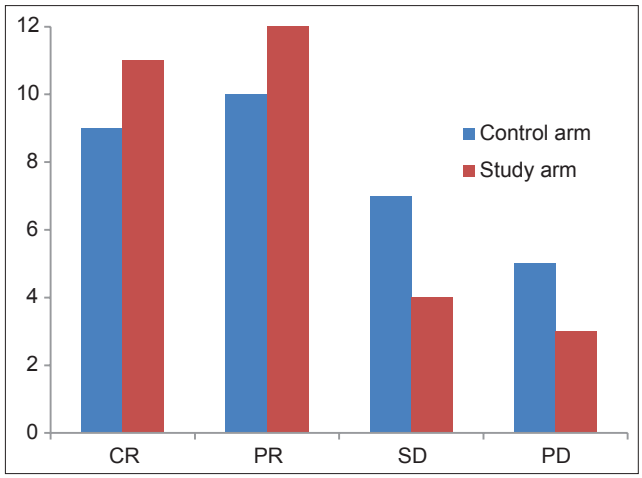

Figure 1: Bar chart showing the comparison of patient outcome in control arm and study arm

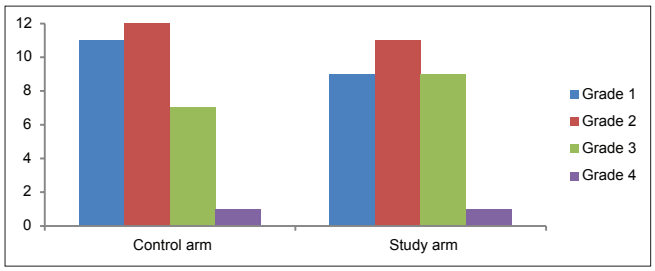

Figure 3: Bar chart showing comparison between distributions of grades of mucositis in two arms

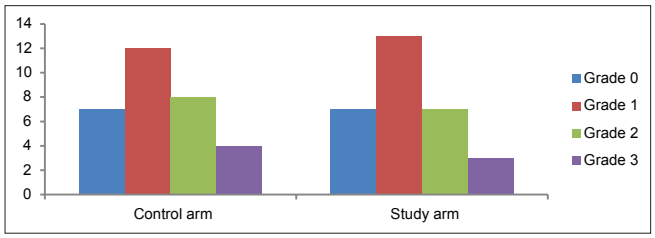

Figure 5: Bar chart showing comparison between distributions of grades of subcutaneous tissue fibrosis in two arms

of grade 2 or more xerostomia (salivary gland toxicity) was comparable in two arms.

Among 9 patients achieving CR in the control arm, 2 patients relapsed within a follow-up period of 12 months, respectively at 10 months and 11 months. Both recurrences were nodal recurrence and proven histopathologically. Among 11 patients achieving CR in the study arm, 1 patient relapsed locally at 11 months (within 1 year). So, at 1 year of follow-up, 7 patients of the control arm (22.58%) and 10 patients of study arm (33.33%) were disease free. As such, DFS rate at 1 year in the control arm was 22.58% and in study arm was 33.33% ($P = 0.515$, not significant).

Quality of life (QoL) in both arms was assessed using the EORTC QLQ-C30 (version 3.0) and the QLQ-H and N35

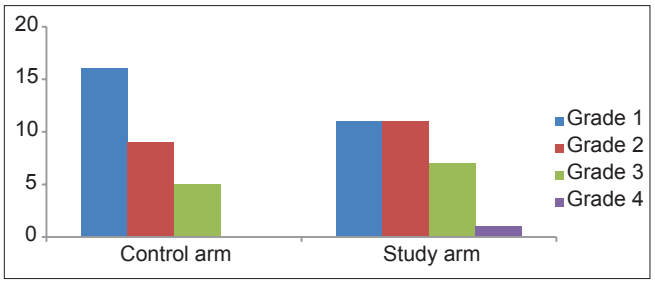

Figure 2: Bar chart showing comparison between distributions of grades of skin toxicity in two arms

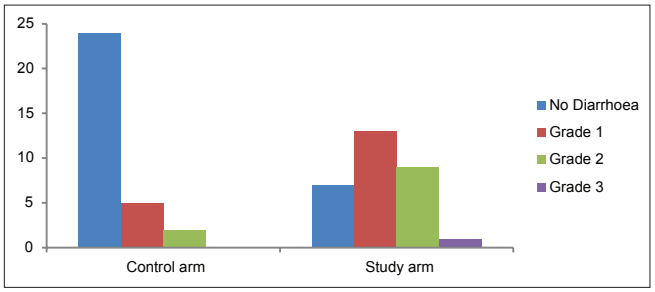

Figure 4: Bar chart showing comparison between distributions of grades of diarrhoea in two arms

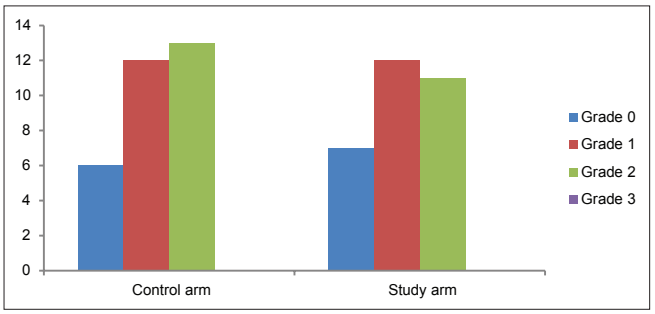

Figure 6: Bar chart showing comparison between distributions of grades of xerostomia (salivary gland toxicity) in two arms

instruments. Higher scores in functioning and global health status/QoL scales indicate a higher level of functioning and a better QoL, respectively, whereas higher scores in symptom scales represent a higher level of symptom. The score obtained are described in Table 5. QoL in this study was measured at the time of response evaluation.

DISCUSSION

SCCHN constitutes about 30-40% of all cancer in this country. Unfortunately, majority present with advanced stage or recurrence after initial definitive therapy. Before 1980, the initial treatment of patients with locally advanced stage III or IV (M0) was mainly surgery and/or RT. Radiotherapy alone was the "traditional" single treatment for patients with unresectable and/or inoperable locally advanced HNC. Historically, patients with unresectable head neck squamous cell carcinoma treated by RT alone have LRC rates between 50% and

Table 5: QOL in both arms was assessed using the EORTC QLQ-C30 (version 3.0) and the QLQ-H and N35 instruments

QOL scales	Study arm	Control arm
Functional scale scores		
Physical function PF2	89 (76-93)	78 (69-81)
Global health/QOL		
Symptom scale scores		
Pain PA	50 (45-55)	66 (60-70)
Fatigue FA	33 (28-38)	50 (45-55)
Nausea vomiting NV	83.3 (78-88)	83.3 (78-88)
Appetite loss AP	92.3 (89-98)	92.3 (89-98)
Symptom scale of HN35		
Pain HNPA	56.5 (45-60)	89.8 (81-96)
Swallowing HNSW	72 (66-80)	80.2 (75-90)
Speech HNSE	67.3 (60-70)	87 (80-95)
Dry mouth HNDR	42 (38-48)	65.2 (57-70)
Nutritional supplement HNNU	48 (41-51)	54 (49-61)
Weight loss HNWL	52 (45-58)	56 (50-62)

EORTC: European Organization for Research and Treatment of Cancer, QLQ: QOL core questionnaire, QOL: Quality of life

70%,[5] and 5-year survival rates of 10-20%. Advantages of concurrent chemoradiation over radiation alone in the therapy of advanced HNC have been found for both definitive and post-operative therapy, using cisplatin as the mainstay chemotherapy. The rationale was not only to increase the probability of LRC by amplifying the radiotherapy efficacy by using together two different tumoricidal agents but also to reduce the incidence of distant metastases that can account for up to 30% in some patients at high-risk (i.e. patients with large tumors, node involvement in the lower neck).

Many meta-analyses have been conducted to show whether chemo-radiotherapy association is better than radiotherapy alone as concerns LRC or survival.[7-9] Among these meta-analyses, the more important one is the French meta-analysis (MACH-NC), based on individual patient data, published by Pignon *et al*.,[10] in 2000 and updated in 2004; it showed that adding chemotherapy to radiotherapy in locally advanced disease: (1) OS is improved by 5% at 5 years with any chemotherapy association or timing of association, (2) OS is improved by 8% at 5 years if a concomitant association is employed; (3) neoadjuvant chemotherapy followed by radiotherapy alone is less effective than concomitant association; (4) a benefit is evident if cisplatin is used in the combined approach; (5) poly-chemotherapy does not appear to be better than mono-chemotherapy; (6) the benefit is less evident in patients over 70 years. In the updated French meta-analysis the OS gain was better for CT-altered fractionation RT (hazard ratio-[HR] =0.73) compared with CT-conventional fractionation RT (HR = 0.83), indicating that alteration of fractionation might boost the effect of chemo-radiotherapy.

One field which is contributing significantly in the development of new drugs is molecular biology. 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. Theoretically, these agents act on specific cellular pathways and receptor expressed on cancer cells. As such, they are indeed much less toxic than usual cytotoxic agents. HNC which is known to express EGFR also has been the focus for targeted therapy. Agents being tried include either monoclonal antibodies (Cetuximab) or TKI (Gefitinib or Erlotinib).

The role of EGFR inhibitors in first-line, combined modality therapy for patients with HNC remains undefined.[11] A study done by Bonner *et al*. demonstrated that concomitant RT plus Cetuximab improved LRC, DFS, and OS in LAHNC patients.[5] Interestingly, it has been suggested that this novel less toxic agent (Cetuximab) could be offered to patients unfit for chemotherapy or explored for ones with a low performance status. In last few years, a number in last few years, a number of studies have begun to shed light on factors that predict the probability of response to Gefitinib in patients with lung cancer. In particular, it appears that patients with mutations in exons 18-21 of the EGFR gene (corresponding to the ATP binding site) are more likely to respond to treatment. Recently, deletions in exon 19 have been reported in three of 41 Korean patients with squamous cell cancer of the head and neck. These discoveries have given renewed impetus to the prospect of using Gefitinib in patients with HNC.

A phase II study has evaluated oral Gefitinib as first-or second-line monotherapy in patients with recurrent or metastatic HNC resulting in disease control rate of 53%.[12,13] In another study, the disease control rate was 36%, the median TTP was 2.6 months (range: 0-9 months). The median survival was 4.3 months (range: 0-13 months). In an Indian study, Rao *et al*. have reported their experience with Gefitinib in the treatment of recurrent SCCHN. Authors have reported symptomatic improvement in about 63% of patients and radiological response (PR or disease stabilization) in 7 of 10 patients who were assessed.[15] Preclinical studies did strongly suggest the radio-sensitizing ability of EGFR antagonist. Anti-EGFR agents radio-sensitize tumor cells by a variety of mechanisms, including reduction in the proportion of cells in the radio-resistant S phase by inducing G0/G1 cell cycle arrest, inhibition of RT induced damage repair and induction of apoptosis. Gefitinib has been shown to inhibit repair of RT-induced DNA double-strand breaks.

In a phase I trial by Chen *et al*., one cohort received, Gefitinib concurrent with radiation and another one received Gefitinib in combination with chemoradiation for patients with locally advanced squamous cell HNC. They concluded that Gefitinib at daily dose of either 250 or 500 mg was

well-tolerated with concomitant boost RT or concurrent chemo-radiotherapy with weekly cisplatin arm. In this trial, the rate of grade 3-4 mucositis was 62.5%, which was consistent with that reported in larger altered fractionated RT trials (52-77%). Gefitinib-related acne-like skin rash occurred in 18 patients (78.3%).[16]

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. For this purpose, patients recruited were divided into a control arm (who received External Beam Radiotherapy with conventional 2 Gy/fraction, 5 days a week for 7 weeks upto total dose of 66 Gy along with concomitant injection cisplatin at the dose of 30 mg/m^2 of body surface area on every week during radiation) and study arm (who received radiotherapy with 2 Gy/fraction, 5 days a week for 7 weeks up to total dose of 66 Gy, along with concomitant injection cisplatin at the dose of 30 mg/m^2 of body surface area on every week during radiation, plus tablet Gefitinib [250 mg/day orally] during the total duration of radiation treatment). The two groups were comparable in terms of age distribution, sex distribution, performance status, stage, primary site and histological grade.

Overall response (CR + PR) was achieved in 61.29% patients in the control arm, which was comparable with other studies. The study arm, although a greater proportion of patients achieved overall response (76.67%), could not yield a statistically significant outcome in terms of the same parameter. Nearly 29.03% patients achieved CR in the control arm while 36.67% patients achieved CR in the study arm CR. 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.

However, toxicities in both the arms were comparable. Addition of Gefitinib to concurrent cisplatin based chemoradiation was found to be well-tolerated in our study, as no significant increase in skin or mucosal toxicity was noted. No significant increase in late toxicities was noted as well. An exception to these findings was diarrhea, which occurred significantly more in the Gefitinib containing arm. However, diarrhea could be adequately managed with supportive care and usually did not contribute to treatment delay. There was no grade 4 diarrhea and only a single case of grade 3 diarrhea in the study arm.

As the study was single institutional, the sample size was relatively small; prolonged follow-up and detailed survival analysis was beyond the scope of this study. However, 7 patients of the control arm (22.58%) and 10 patients of study arm (33.33%) were disease free at 1 year follow-up. So, DFS rate at 1 year was 22.58% for the control arm and 33.33% for the study arm. Again, we failed to demonstrate a statistical significance of better DFS rate at 1 year in the study arm. Small sample size was thought to be the reason.

As such, we can comment that addition of Gefitinib to standard cisplatin based chemoradiation is generally well-tolerated. Encouraging results were found in the present study in terms of CR, Overall Response and DFS rate at 1 year, but those findings could not be attributed statistical significance. The major limitations of this study included its small sample size and short follow-up period. It is known that most of the SCCHN over-express EGFR which adds to the rational of using Gefitinib in this disease. However, EGFR Expression study could not be done in all patients due to financial reasons as it involves considerable cost. So, a subgroup analysis with EGFR wild type, mutated or over-expression parameters was not possible. Larger multi-centric trials are needed to confirm and validate the encouraging results of our study before Gefitinib could be recommended in routine clinical practice along with concurrent cisplatin-based chemo-radiation which is the current standard of care in locally advanced SCCHN.

CONCLUSION

It can be stated that addition of Gefitinib to standard concurrent cisplatin based chemoradiation is well-tolerated. The current study found better overall response and DFS (at 1 year) with addition of Gefitinib to standard concurrent chemoradiation. Unfortunately, these encouraging results could not be validated statistically. Larger multi-centric studies recruiting greater number of patients are required to validate those encouraging results and clearly define the role of addition of Gefitinib to current standard of care in locally advanced SCCHN.

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