http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i8.67

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Research Paper

Radiotherapy plus EGFR inhibitor- Geftinib, a single Institutional Experience

Authors

Dr Aachum Kichu[1], Dr Madhumathi, DMRT, MDRT[2*]

[1]MD (Radiotheraphy) post graduate, Department of Radiotheraphy, Barnard Institute of Radiology and Oncology, Madras Medical College, Chennai - 600001

[2]Sr. Assistant Professor, Department of Radiotheraphy Barnard Institute of Radiology and Oncology, Madras Medical College, Chennai - 600001

*Corresponding Author

Dr Madhumathi, DMRT, MDRT

Abstract

Context: *Concurrent chemoradiotherapy in locally advanced squamous cell carcinoma of head and neck with Gefitinib and Cisplatin*

Aims: *The aim of this study was to evaluate the use of Gefitinib and weekly Cisplatin concurrently with conventional radiation in locally advanced squamous cell carcinoma of head and neck.*

Settings and Design: *Single arm prospective study with a Phase II design.30 patients presenting to the department of Radiotherapy with locally advanced head and neck squamous cell carcinoma fulfilling the inclusion criteria were recruited for the study.*

Methods and Material: *Single arm prospective study with a Phase II design.*

Statistical Analysis Used: *Observational analysis*

Results: *76.6% of patients had complete response and 23.4% had partial response to the treatment.*

Conclusions: *the problem of head and neck cancer continues to grow. More amount of patients are presenting with locally advanced cancers. The addition of Gefitinib to the standard concurrent chemoradiation protocol seems to be a good option showing a better response rates than the standard arm. The regimen is also well tolerated with no severe increase in the toxicity and patient compliance is good.*

Keywords: *Chemoradiotherapy, Geftinib, locally advanced squamous cell carcinoma of Head & Neck.*

Key Messages: *Addition of Geftinib to chemoradiation shows better response rate.*

Introduction

In India, cancer of the head and neck ranks amongst the second most common in males and the fourth most common in females. The incidences also varies according to the geographic location and the habits of the local people which expose them to the causative agents of cancer, mainly tobacco. The aim of this study was to evaluate the use of Gefitinib and weekly Cisplatin concurrently with conventional radiation in locally advanced squamous cell carcinoma of head and neck. To assess the acute toxicity of the treatment regimen. To assess the immediate locoregional response in patients with locally advanced head and neck cancer treated with concurrent chemoradiation using weekly cisplatin and Tablet Gefitinib.

Literature Review

The most commonly used method of delivering radiation is the conventional fractionation method

where 220 CG y is delivered five times per week used by Fletcher at all this best compromise between the tumor cell kill and normal tissues sparing following sufficient time for the recovery of normal cells from the effects of radiation.

The EORTC in their landmark trial 2279 compare conventional fractionation with hyperfractionated radiotherapy, one arm receiving the conventional fractionation of 70 Gy in 2 Gy perfection 5 fractions while the other arm received hyperfractionate RT of 80.5Gy delivered in 70 fraction 1.15 Gy perfection delivered as twice daily schedule in interval of 4 to 6 hours between the fractions . There was 219 percent significant increase in locoregional control and and non statistically significant improvement in the overall survival. The acute toxicity was enhanced in the hyperfractionated arm but the lead toxicity between the two arms was similar[(1)] Danish DAHANCA8 trial accelerated radiotherapy was compared with conventional radiotherapy . In this trial there was a 15% improvement in the locoregional control and as with the hyper fractionated radiotherapy trial there was an increase in the acute toxicity but late toxicity was similar.[(2)].

Till now the combination of chemotherapy with radiation has provided the best results in terms of tumour control and overall survival.

An important meta analysis MACH-NC trial which prove that concurrent use of chemotherapy along with radiation has best results. The initial publication of MACH- NC meta-analysis of chemotherapy in head and neck study analyse data from randomised control trials from 1965 to 1993 and published the findings. Date of about 10,000 patients from 63 trials were analysed. In the controller the overall survival was 32% in 5 years. Chemotherapy at anytime of treatment resulted in the absolute benefit of 4% which meant that it increase the 5 year survival from 32 % to 36%[(3)]

The greatest benefit with the use of chemotherapy concurrently is 8% improvement in the overall survival at the end of 5 years weekly cisplatin better tolerated may became the treatment of choice.

Weekly cisplatin trial

In a study by Akihiro Homo et al, where patients with locally advanced head and neck cancer where treated with conventional radiotherapy and weekly cisplatin of 40 m per metre square the overall survival rate and disease free survival 93.7 percent and 88% respectively. Toxicity we're well manageable.[(4)]

Indian study conducted at the Tata memorial Hospital where to 64 patient of locally advanced head and neck cancer where treated with conventional radiotherapy and weekly cisplatin dose of 30 milligram per metre square they concluded that weekly cisplatin has moderate efficacy with acceptable toxicity.[(5)]

In a study conducted at the University of Wisconsin train not at all patient with locally advanced head and neck cancer where is heated with a weekly cisplatin dose 30 mg per metre square along with conventionally fractionated radiotherapy of 73 delivered by imrtthe conclusion was that weekly cisplatin is well tolerated and is efficacious.[(6)]

Trials using Gefitinib

In a phase 1 trial conducted by mango Changhu Chen et al, Gefitinib with two doses of 250 mm and 500 milligram was combined weekly cisplatin of 30 milligram per metre square and radiotherapy with can commit and boost they concluded that the use of daily chapter name with concomitant boost radiotherapy or concurrent chemotherapy was well tolerated.[(7)]

Bella Pajares et Al perform the study where the compared conventional chemo radiation with cisplatin Vs radiotherapy with Geftinib in patients who were positive for HPV viral infection. They formed after a median follow-up of 35 months those who were p16 positive showed an improved outcome with radiotherapy and Gefitinibcompared with those treated with radiotherapy and cisplatin. They concluded that p16 positive tumors main benefit more from radiotherapy plus EGFR inhibitor the conventional chemoradiotherapy.[(8)]

Bhattacharya performed a prospective randomised controlled study in Indian patients where we compare chemoradiation using weekly cisplatin 40 milligram per metre square and conventional fractionated RT to a dose of 66Gy with or without addition of Geftinib. They concluded that addition of Geftinib2 standard concurrent cisplatin-based chemoradiation was well tolerated and had better overall response and DFS at 1 year with addition of Geftinibas compared to standard concurrent chemoradiation[9].

In another trial by charu Singh patients of locally advanced head and neck cancer were divided into two groups one group received concurrent chemoradiation which 70 Gy RT and weekly cisplatin 30 milligram per metre squareand yadav group received additional Gefitinib 250 milligram daily the overall response rates where 88% versus 79% in favour of Geftinib arm. 79% of patients achieved a complete response in the Gefitinib Om as compared to 62% into other arm.except for dermatitis there was no significant difference in the toxicity profile of the two arms.the author concluded the targeted therapy with destiny band chemoradiation is well tolerated with some enhanced but manageable toxicity and as shown to improve the local control[10].

Subjects and Methods

Study Design

Single arm prospective study with a Phase II design.

Study Duration: March, 2015– August, 2015

Study Centre

Department of Radiotherapy, Barnard Institute of Radiology & Oncology, Madras Medical college, Chennai.

Sample Size

30 patients presenting to the department of Radiotherapy with locally advanced head and neck squamous cell carcinoma

Ethical Committee Approval: Approval from the institute ethical committee was obtained on march2014.

Informed Patient Consent

All the patients recruited for the study were explained in detail about the study

Inclusion Criteria

- Biopsy proven newly diagnosed squamous cell carcinoma of the head and neck
- Primary tumor sites: oral cavity, oropharynx, hypopharynx, larynx
- Stage III or IVA disease without any evidence of distant metastases
- Age < 70 years
- ECOG performance Status ≤ 2
- No previous surgery or radiotherapy or chemotherapy
- Adequate bone marrow reserve and normal hepatic and renal functions
- No associated comorbidities
- Signed informed consent prior to initiation of protocol specific procedures

Exclusion Criteria

- Non squamous histology
- Tumours of the nasal cavity, paranasal sinuses, nasopharynx, salivary glands
- Previously received treatment for any other malignancy
- Inadequate hepatic and renal functions and bone marrow reserve
- Patients not consenting for chemotherapy at any point in the treatment

Pre Treatment Work Up

Thorough history and clinical examination

Upper aerodigestive tract evaluation by direct and indirect laryngoscopy, anterior and posterior rhinoscopy and endoscopy if indicated to know the extent of disease and rule out a second primary.

Biopsy from the primary tumor or fine needle aspiration cytology from the metastatic lymph node.

Blood grouping and typing.

Complete blood count, Renal function test, Liver function test.

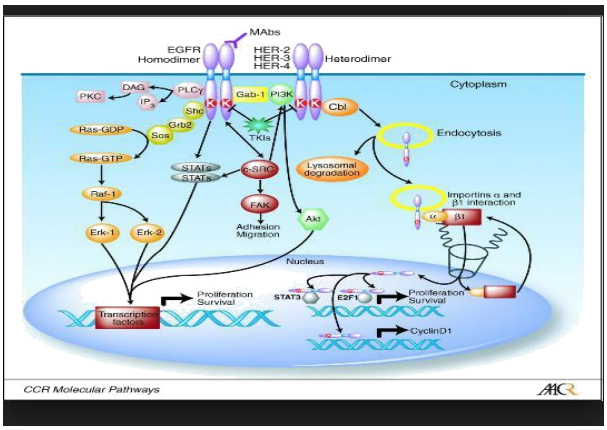
CT scan of the head and neck, plain and contrast, before initiating treatment and also after treatment for response assessment.
Chest X ray
Cardiac evaluation and fitness.
Naso-gastric tube insertion if indicated
Dental prophylaxis including scaling, dental filling and extraction if required.
Tumour stage, performance status and weight were recorded, and body surface area were recorded
Staging was done based on American Joint Committee staging manual 7th edition Weekly CBC, RFT, LFT before each cycle of chemotherapy.

General Preparation of the Patient

A large percentage of the patients present with dysphagia upfront. They were advised for nasogastric tube insertion. For those without dysphagia, they were counseled about the possibility of developing dysphagia themselves due to mucositis and the need of doing a nasogastric insertion at such times. They were also advised to take at least 1.5-2 litres of water per day in regular intervals.

Treatment Protocol

30 patients of locally advanced squamous cell carcinoma of the head and neck enrolled in the study underwent the full pre-treatment work up and preparation. They were then started on concurrent chemoradiation using weekly cisplatin and daily tablet Gefitinib.



EGFR Pathway

Radiation Therapy

Patients were treated using theratron phoenix telecobalt machine with conventional 2D planning using bilateral opposed fields which included the primary and the nodes. The patients were treated with conventional 2 Gy per fraction 5 fractions per week to a total dose of 66 Gy. At 40 Gy the posterior border was shifted anteriorly so as to avoid the spinal cord. The planned duration of the treatment was six and half weeks.

Chemotherapy

Patients were started on chemotherapy from day 1 of radiation. Injection Cisplatin 30mg/m^2 diluted in 500ml of Normal Saline was infused over 2 hours after premedications. Radiation was started within one hour of completion of chemotherapy. Patients received the subsequent cycles of chemotherapy at one week intervals. Patients also received tablet Gefitinib 250mg once daily before Radiation. Patients were advised to take the tablets about 4 hours before the start of RT. The peak plasma level of Gefitinib is reached by 3-7 hours of oral intake.

Premedication

Inj. Ondansetron 8 mg IV.
Inj. Dexamethasone 8mg IV.
Inj. Ranitidine 50 mg IV.
Inj. Chlorpheniramine 4mg IV.
Injection Cisplatin 40mg/m^2 mixed in 1 point of NS was infused over 2 hours.

Toxicity Assessment

The patients were examined everyday to see for any toxicities like mucositis, skin reactions, dysphagia, laryngitis, xerostomia. The findings were recorded and graded according to the RTOG acute toxicity criteria. Other effects of chemotherapy like nausea, vomiting, diarrhea, skin rash were also looked for and graded. Blood tests were done every week before the initiation of chemotherapy and then if there was any abnormality like anemia or leucopenia, they were corrected by blood transfusions and G-CSF injections. For any abnormalities in the renal and

liver functions, opinions from the specialist like nephrologist were obtained.

Response Evaluation

Clinical evaluation and imaging by using contrast enhanced CT were done at after 6 weeks of completion of Chemo RT for response assessment. Response to treatment was described based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1 version) Criteria.

Follow Up

- The patients were advised to come after 6 weeks for response assessment after the completion of chemoradiation or to review SOS if they developed any significant problems in between.
- After the initial response assessment patients were kept on monthly follow up as per our institution protocol.
- They were advised continued abstinence from the use of tobacco and alcohol, to keep good oral hygiene.

Statistical Analysis

All the results were compiled and analysed and expressed in terms of percentage. This is a single arm study with a sample size of 30

Results

Performance Status

Most of the patients had an ECOG performance status of 2 at the time of presentation.

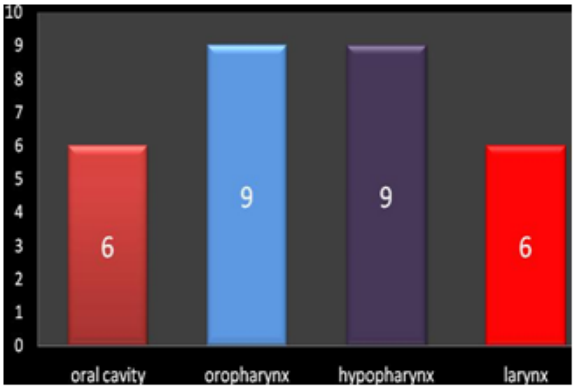


Fig 1 Primary Site

Primary Site

Oropharynx and hypopharynx were the most common sites for primary. Each making up 30% of the study population.

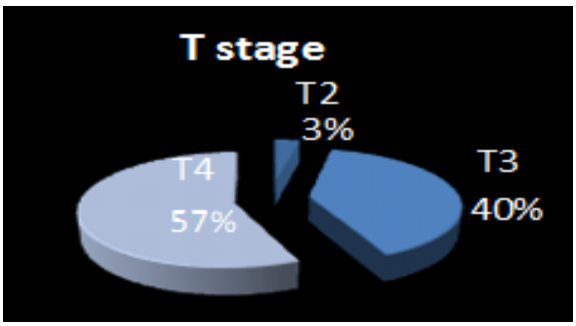


Fig 2 Primary Tumour Stage

T stage

Comparing the various subsites, the most common were in the post cricoids region, followed by the supraglottis, the posterior 1/3 tongue and the tonsil.

Tumor Stage

Most of the patients had a T4 (56.66%) disease at the time if presentation.

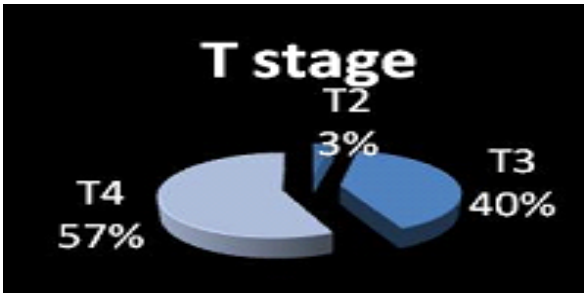


Fig 3 Primary Tumour Stage

Nodal Stage

N2 was the most common nodal presentation (70%). 10% of the patients did not have any clinically significant nodes at the time of presentation.

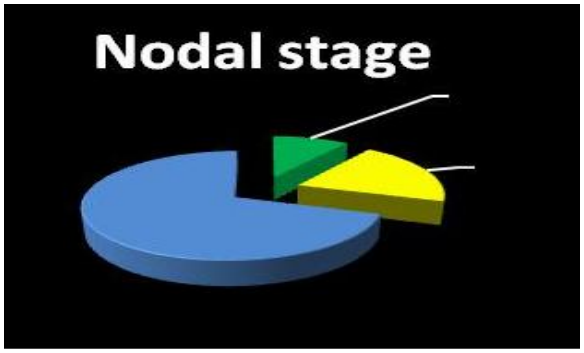


Fig 4 Nodal Stage

Stage Grouping of the Study Sample

Stage IVA was the most common stage at the time of presentation (80%).

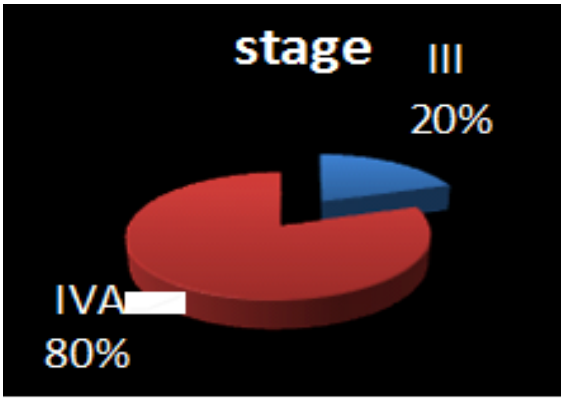


Fig 5 Stage Distribution

Histological Differentiation

Majority of the tumors were moderately differentiated (60%)

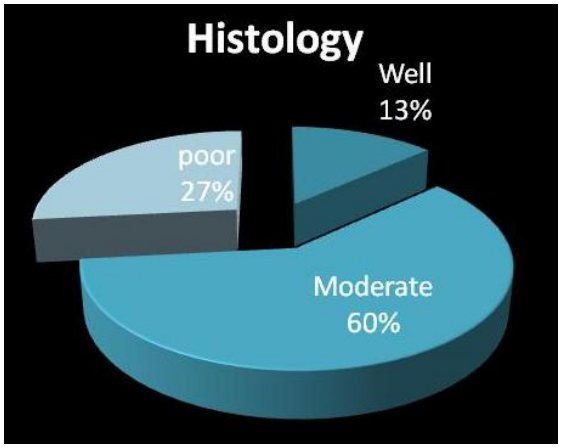


Fig 6 Histological Differentiation

Response Results

Overall response rate was 100% of which 76.6% of the patients had complete response and 23.3% had partial response. There was no static response or progressive disease in the study.

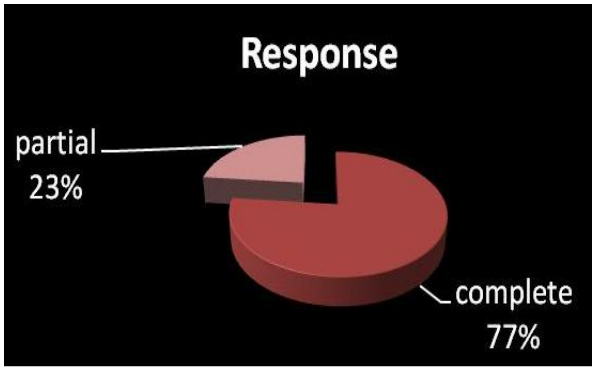


Figure no:7 Overall Response Rates

Site vs Response

Oropharynx, hypopharynx and laryngeal cancers had good response rates as compared to oral cavity cancers.

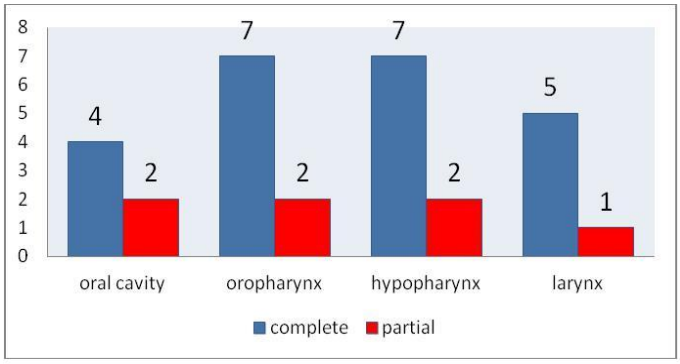


Fig 8 Site vs Response

Tumor Stage vs Response

T3 diseases had an 83.3% complete response rate as compared to T4 lesions which had 70.6% complete response rates.

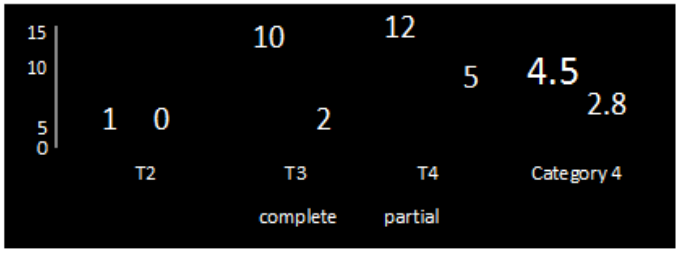


Fig 9 Tumor Stage vs Response

Nodal Stage vs Response

All N1 and N2A diseases had 100% complete response. The complete response rates for N2B and N2C diseases were 85.75% and 60% respectively

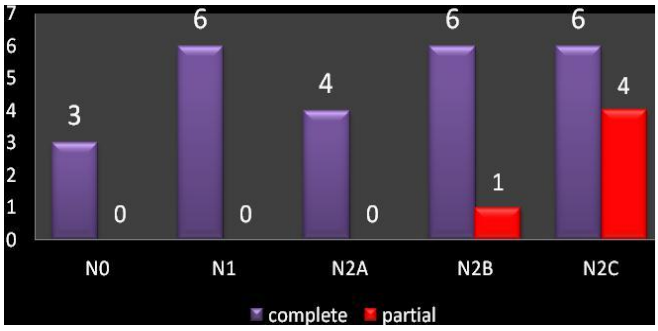


Fig 10 Nodal Stage vs Response

Histological Differentiation vs Response

The response rates correlated with the histological differentiation with poorly and moderately differentiated tumors having higher rates of

complete response as compared to the well differentiated primaries.

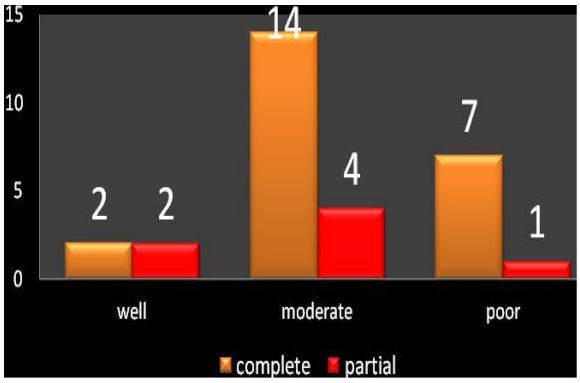


Fig 11 Histology vs Response

Stage Vs Response

Stage III patients had better complete response rates (86.66%) as compared with stage IVA disease (75%)

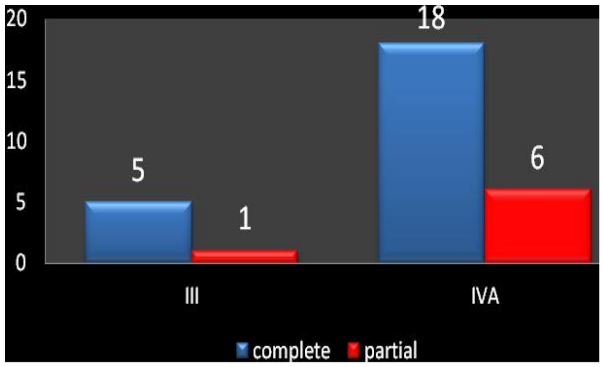


Fig 12 Stage vs Response

Treatment Break Vs Response

In this study those who had a longer duration of break in the treatment had more treatment failure rates as compared with those who completed the treatment with no breaks or had minimal breaks of 1-5 days.

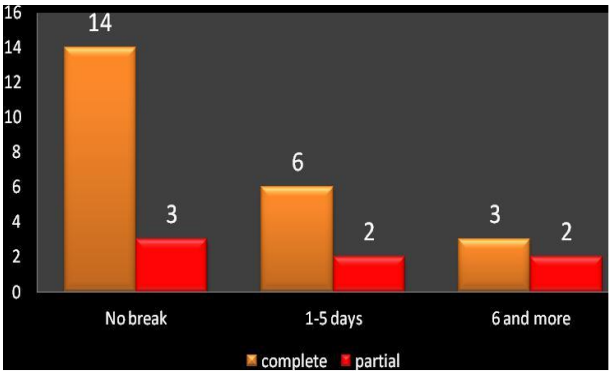


Fig 13 Treatment Break vs Response

Treatment Related Acute Toxicities

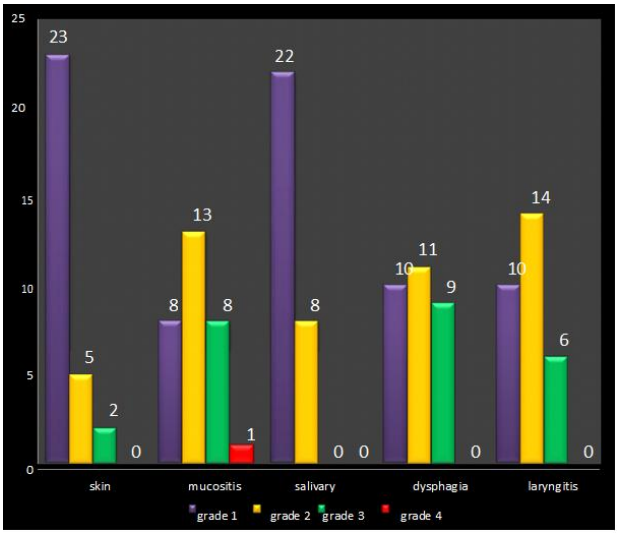


Fig 14 Acute Toxicities

Table Acute toxicity

ACUTE TOXICITY	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SKIN REACTIONS	0	23 (76.66%)	5 (16.66%)	2 (6.66%)	0
MUCOSITIS	0	8 (26.6%)	13 (43.3%)	8 (26.6%)	1 (3%)
SALIVARYGLAND	0	22 (73.3%)	8 (26.7%)	—	0
PHARYNGITIS/ DYSPHAGIA	0	10 (33.33%)	11 (36.67%)	9 (30%)	0
LARYNGITIS	0	10 (33.33%)	14 (46.67%)	6 (20%)	0

Systemic Toxicity: Managed well

Nausea: 73.3% of the patients had grade 1 nausea. Only 1 person had grade 3 nausea.

Gefitinib Related Skin Rash

Only one patient developed the classical skin rash associated with the use of gefitinib. It was a grade 1 skin reaction and did not necessitate the need for suspending the drug. It developed during the 3rd week of treatment and resolved with symptomatic treatment.

Discussion

Squamous cell carcinoma of the head and neck is one of the most prevalent cancers in India. Majority of the patients present in the locally advanced stage where surgical resection is not possible. Patients were treated with local RT alone where the local control rates were between 50-70% and the 5 year survival was a dismal 10-20%.

There was a definite rationale for the combined use of chemotherapy

1) Sensitizes tumors to radiotherapy by inhibiting tumor repopulation
2) it preferentially kills the hypoxic cells, inhibiting the repair of sublethal damage caused by radiation
3) it sterilizes the micrometastatic disease outside the radiation fields
4) Decreases the tumor mass which leads to improved blood supply and reoxygenation thus potentiating the effect of radiation.
   a) Fractionated radiotherapy, sensitizes tumors to chemotherapy by inhibiting the repair caused by chemotherapy
   b) It also decreases the size of the tumor causing improved blood supply to the tumor The improvement of outcomes by using chemotherapy along with radiation was performed. In most of the trials cisplatin was the mainstay of chemotherapy. Many meta- analyses have been conducted to show whether chemo- radiotherapy association is better than radiotherapy alone as n concerns LRC or survival· Meta- Analysis on Chemotherapy on Head and Neck cancer (MACH-NC) showed that adding chemotherapy to radiation had the following advantages
      1. The use of cisplatin as the chemotherapy has evident benefit
      2. The use of chemotherapy increased the overall survival at 5 years by 5% irrespective of the timing of association

The standard of care for all those locally advanced unresectable head and neck cancer is concurrent chemoradiation with a radiation dose of upto 70 Gy and three weekly cisplatin of 80-100mg/m^2. The weekly regimen of cisplatin is as efficacious as the three weekly regimens. This comes with a significant lesser toxicity in the weekly arm. The weekly regimen was as efficacious as the three weekly regimens with lower toxicities. Several trials are going on for the development of new drugs. One of these fields is that of molecular biology.

The EGFR pathway provides 90% of the head and neck squamous cell carcinoma over express this receptor. It plays a pivotal role in tumor growth, invasion, angiogenesis and metastasis. Preclinical trials have shown that the addition of a anti-EGFR has a synergistic effect with radiation. EGFR-directed therapy may be optimized by identifying and selecting those HNSCC patients most likely to benefit from EGFR inhibition.

TKIs like Gefitinib and Erlotinib are even less toxic than the monoclonal antibodies have proven their worth in lung cancer. By the use of TKIs significantly improves the progression free survival and the overall survival

In several phase II trials, the use of gefitinib in combination with the standard chemoradiotherapy has shown to improve the immediate response rates and the locoregional control rates. Overall survival is yet to be assessed in a large scale randomized trial. In this present study the overall response rate (CR+PR) was 100% with 76% of the patients achieving a compete response and the remaining had partial response. There was no significant association of the response to therapy when compared with the gender of the patient, the age of diagnosis, performance status of the patient. Primary tumors in the oropahrynx, hypopharynx and the larynx had a better response to treatment. Lesser volume of disease i.e. T3 diseases had better response rates as compared with the T4 diseases and the same findings were seen in the nodal disease where N1 and N2A tumors responded better than the N2B and 2C tumors. The importance of completing the treatment without any break as the problem of accelerated repopulation can lead to treatment failure. The rates of grade 3 and 4 toxicities were low. Only 6% of the patients had grade 3 skin reaction and no grade 4 reactins. The hematogical toxicity was also minimal. Only one patient developed the classical rash that is associated with the use of Gefitinib. Compared with the historical data in our department as well as the world literature the

response rates to our treatment was better with higher percentage of the patients achieving a complete response. But the sample size is small. 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.

Conclusion

The problem of head and neck cancer continues to grow. More amount of patients are presenting with locally advanced cancers. The addition of Gefitinib to the standard concurrent chemoradiation protocol seems to be a good option showing a better response rates than the standard arm. The regimen is also well tolerated with no severe increase in the toxicity and patient compliance is good.

Limitations

This study was done in a small study sample.

Acknowledgement

BARNARD INSTITUTE OF RADIOLOGY AND ONCOLOGY, Department of Surgical Oncology, Department of Medical Oncology, Madras Medical College, Chennai 3.

References

1 Horiot J-C, Le Fur R, N'Guyen T, et al.: Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. RadiotherOncol 25: 231-241, 1992

2 Overgaard .1, Sand Hansen H, Sapru W, et al.: Conventional radiotherapy as the primary treatment of squamous cellcarcinoma of the head and neck: Arandomized multicentre study of 5 versus 6 fractions per week - preliminary reportfrom the DAHANCA 6 and 7 trial. RadiotherOncol 40:S31 1996

3 Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous- cell carcinoma: Three meta - analyses of updated individual data. MACH- NC Collaborative Group. Meta- Analysis of chemotherapy on head and neck cancer. Lancet 2000;355:949- 55.

4 Homma A, Inamura N, Oridate N, Suzula S, concomitant weekly Cisplatin and radiotherapy for head and neck cancer. Jpn J Clin Oncol.2011 aug ; 41(8) ; 980-6.

5 Tejpal Gupta, Jai P Agarwal, Sarbani Ghosh Laskar, Purvish M Parikh, Radical Radiotherapy with concurrent weekly Cisplatin in loco regionally advanced squamous cell carcinomas of head and neck: a single institution experience. Head and neck oncology 2009 1 (17)

6 Traynor AM, Richards GM, Hartig GK, Khuntia D, Comprehensive IMRT plus weekly cisplatin for advanced head and neck cancer. ; The University of Wisconsin Experience, Head and neck Sept.2009 Wiley Periodicals Inc.

7 Changhu Chen 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 25:4880-4886. © 2007 by American Society of Clinical Oncology

8 Bella Pajares et al. Differential outcome of concurrent radiotherapy plus epidermal growth factor receptor inhibitors versus radiotherapy plus cisplatin in patients with human papillomavirus-related head and neck cancer. Pajares et al. BMC Cancer 2013, 13:26 http://www.biomedcentral.com/1471-2407/13/26

9 Bhattacharya et al. 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 | March-April-2014 | Vol 3 | Issue 2

10 Charu Singh. Gefitinib with concurrent chemoradiation in locally advanced head and neck cancers. J Clin ncol 32:5s, 2014.