Research Article

Chemo-radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck with or without Lapatinib – a non randomised comparison study to assess the tolerance and efficacy

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Abstract

Purpose of the study: We intend to test the efficacy of and toxicity of addition of Lapatinib to the standard of care in locally advanced squamous cell carcinoma of the head and neck (LAHNSCC). **Materials/Methods:** Between 2010 and 2012, thirty patients with histologically proven non metastatic LAHNSCC who fulfilled the inclusion and exclusion criteria for the study, stratified by disease stage and location were allocated to receive CTRT with Lapatinib or CTRT, the study approved by the institution review board and ethics committee. **Results:** Complete response was seen in 66% vs. 60% in the two arms at 3 months of follow up and this translated to 88% and 80% at 6 months of follow up (p=NS). Mucositis was seen early in the Lapatinib arm at 2nd week compared to 3rd week in the CTRT arm (p=0.04). Skin reactions developed early in the Lapatinib arm and was seen at a higher grade (p=0.02), Diarrhea was seen early and at a higher grade in the Lapatinib arm (p=0.01). Hematological toxicity was not significant between the arms. **Conclusion:** This study shows that addition of Lapatinib to the standard CTRT of LAHNSCC is efficacious and tolerable with accepted toxicity. Receptor Tyrosine kinase inhibitor mediated toxicity comparable to studies at other cancer sites. Late toxicity and long term survival with this therapy warrants a prospective stratified randomized trial.

Key words: Carcinoma, EGFR, TKI

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Introduction

Addition of chemotherapy to radiation therapy (CTRT) has improved the outlook in non metastatic locally advanced head and neck squamous cell carcinoma (LAHNSCC) and confers an overall survival benefit of 4% at 5 years [1]. Pathogenesis of LAHNSCC revolves around the over expression of epidermal growth factor receptor (EGFR) by various mechanisms [2]. EGFR targeted therapy has delivered a revolutionary pattern change in the management of these cancers [3]. Although majority of the evidence for use of EGFR targeted therapy arises from using the monoclonal antibody against EGFR, small molecules targeting the receptor tyrosine kinase (TKI) have been tested in various situations [4,5,6,7]. Predominantly these include Gefitinib, Erlotinib and Lapatinib. Lapatinib is a potent and selective inhibitor of the HER2 tyrosine kinase [8]. We intend to test the efficacy of and toxicity of addition of Lapatinib to the standard of care in LAHNSCC.

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Materials and Methods

Between 2010 and 2012, thirty patients with histologically proven non metastatic LAHNSCC who fulfilled the inclusion and exclusion criteria for the study, stratified by disease stage and location were allocated (not randomised) to receive CTRT alone versus CTRT with Lapatinib, the study approved by the institution review board and ethics committee. RT was delivered to a dose of 70Gy in 35 fractions. RT planning was done after Orfit immobilisation, CT simulation and delivered to a dose of 70Gy on the 6MV Linear accelerator (off cord shielding done after 44Gy). CT to dose of 40mg/sqm once a week. Patients randomized to Lapatinib arm received it to a dose of

1500 mg daily with RT. Before initiation of therapy, a detailed clinical evaluation, local imaging with CECT of head and neck (with MRI wherever necessary) and staging was conducted by CECT thorax. Adequate hematologic, renal, hepatic and cardiac reserve was confirmed prior to initiation of therapy. Toxicity was recorded by RTOG and CTCAE scales. At follow up, response assessment was done using WHO criteria.

1. Inclusion Criteria.

1. Patients diagnosed to have stage III, IVA or IV B squamous cell carcinoma of head and neck, including oral cavity, oropharynx, larynx and hypopharynx, with histological confirmation by biopsy or fine needle aspiration cytology.
2. Female or male patients aged 18 years and over.
3. KPS Performance Status of 70 or higher.
4. No previous surgery to the tumour except for biopsy or FNAC.
5. No previous chemotherapy or radiotherapy for any malignancy.
6. No previous anti-EGFR therapy.
7. Life expectancy ≥12 weeks.
8. Adequate bone marrow function: WBC > 4000/mm^3;Absolute Neutrophil count > 1500/mm^3 platelets > 100,000 $mm^{3.}$
9. Adequate renal function for chemotherapy (Creatinine clearance more than or equal to 50).

2. Exclusion Criteria

Any of the following is regarded as a criterion for exclusion from the study.

1. Stage I or II cancers or with metastatic disease (stage 4).
2. Nasopharyngeal, thyroid, paranasal sinus or salivary gland tumours.
3. Presence of other synchronous primary or past history of malignancy.
4. Known severe hypersensitivity to Lapatinib.
5. Inadequate bone marrow function: WBC < 4000/mm3; platelets < 100,000 mm3.
6. Serum bilirubin ≥3 times the upper limit of the reference range.
7. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 times the upper limit of the reference range.
8. Any evidence of chronic / severe or uncontrolled medical illnesses.
9. Concomitant use of CYP3A4 inhibitors or inducer.
10. Pregnancy or breastfeeding.

3. Patient Recruitment

Patients who fulfilled the inclusion and the exclusion criteria were selected for the study. All suitable subjects were explained about the study, and were provided with information regarding the proposed treatment plan in their own language. After reading the consent form and clarification of any doubts, they were enrolled into the two arms of the study in a non randomised fashion after obtaining their written informed consent before starting the treatment.

4. Pre treatment evaluation:

After obtaining a detailed history all patients are subjected to a thorough clinical examination. All patients are required to undergo the following investigations –

1. Baseline Nasophayngolaryngoscopy(NPL scopy)
2. Blood investigations included haemoglobin, total and differential blood counts, platelet counts, liver function test and serum creatinine.
3. Screening for blood borne virus (BBVS).
4. Cardiac evaluation was done with electrocardiograph and 2-D echocardiograph for patients planned for concurrent chemotherapy
5. Prior to treatment, dental clearance needs to be obtained and required extraction of unsalvageable teeth in poor condition done and prophylactic fluoride therapy initiated

5. Radiation Therapy

5.1 Patient immobilization: The patient was immobilized in the supine position using a head rest. Immobilization devices, such as customized thermoplastic ray cast was used to secure the accuracy and reproducibility of patient positioning during radiotherapy. Orthogonal laser beams were used to mark three reference coordinate systems (two laterals and one anterior) on the thermoplastic ray cast.

5.2. Planning CT scan acquisition: A set of CT slices extending at least from the level of the skull base to T4 vertebral level were acquired. Slice thickness of 3 mm was used. CT scan was performed in treatment position with a flat table top and with the immobilization device in place along with intravenous administration of 80 ml of contrast. The DICOM images of the CT were transferred onto the treatment planning system and registered.

5.3 Treatment planning: The delineation of various clinically important volumes was performed by the radiation oncologist. The Gross tumor volume (GTV), Clinical target volume (CTV), Planning target volume (PTV), Organs at risk (OAR) and other organs of interest were contoured according to the standard guidelines. The Gross Tumor Volume ***(GTV)*** is defined as all known gross disease determined from CT, clinical information, endoscopic findings and other imaging studies. The Clinical Target Volumes ***(CTV)*** is defined as the GTV plus areas considered containing potential microscopic disease, delineated by the treating physician.

The Planning Target Volume ***(PTV)*** will provide a margin around each CTV (i.e. both the primary tumor and the lymph nodes containing clinical or radiographic evidence of metastases) to compensate for the variabilities of treatment set up and internal organ motion. A minimum of 5 mm around the CTV is required in all directions to define each respective PTV. The normal tissue volume to be contoured will include the skin surface, brainstem, spinal cord, mandible, glottic larynx, parotid salivary glands and oral cavity / oral tongue in laryngeal and hypopharyngeal tumours.

Dose prescriptions for the various target volumes are specified and dose constraints are given for the organs at risk.

1. No more than 20% of any planning target volume (PTV) will receive >110% of its prescribed dose.
2. No more than 1% of any planning target volume (PTV) will receive <93% of its prescribed dose.
3. No more than 1% or 1 cc of the tissue outside the PTVs will receive >110% of the dose prescribed to the primary PTV.

Prior to the first treatment, the patient is positioned on the linear accelerator and images are obtained using the on board electronic portal imaging device (EPID). The EPID images are acquired and then carefully compared against the digitally reconstructed radiographs (DRRs) using various anatomical landmarks. The process of EPID imaging and comparison with DRRs is repeated every day for the first three days of treatment and thereafter every week. Radiation is delivered five days a week and all fields are treated every day.

6. Concurrent Chemotherapy

Patients age less than 70 years and with adequate serum creatinine clearance of more than 50 ml per minute are eligible for concurrent chemotherapy. Patients were administered Inj Cisplatin infusion 40 mg per square meter weekly after checking that the blood tests were within normal limits and if patient has no clinical evidence of infection. Cisplatin was given intravenously after adequate hydration and premedication with antiemetics (see appendix).

The first cycle of Chemotherapy was given on the day of initiation of radiotherapy. The chemotherapy was administered 1 hour prior to radiotherapy in the day care centre. Chemotherapy was continued for further cycles to a maximum of six cycles, if the weekly blood counts, liver and renal parameters were within normal limits. Cisplatin administration was delayed or discontinued in the event of grade 3 or 4 mucositis, signs and symptoms of infection, absolute neutrophil count less than 2000 cells per cu.mm or serum Creatinine clearance.

7. Concurrent Oral Lapatinib

Oral Lapatinib 1200mg was started 7 days prior to starting radiation and continued every day till the last day of radiation. It is administered at least half an hour prior to radiation and also on weekends and holidays. It is withheld in case of any drug induced grade 3 or 4 haematological or non haematological toxicities.

8. Assessment during treatment

During external beam radiation therapy (EBRT), all patients were assessed for toxicity every week by clinical examination, complete blood counts, renal parameters and liver function tests. The toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 3 (CTCAE v3.0). A nasogastric feeding procedure is advised for patients during treatment, in case of poor oral intake or serial weight loss. An ENT evaluation is obtained at the end of EBRT.

Results

A total of 30 patients referred to the radiotherapy department, meeting the study criteria were included in this non-randomised comparison study design to receive CTRT+ Lapatinib vs. CTRT alone. Median age of the entire study cohort was 50 years (23 males;7 females). All the patients recruited into the study cohort had a baseline KPS of 70 or more.

Both the arms were equally distributed with respect to stage grouping. All the patients recruited in the study received the planned dose of radiation, while 80% of the patients in both the groups received at least 4 cycles of concurrent cisplatin. Although the overall treatment time was more in both the arms, there was no statistical significant difference between the two arms. There was statistically significant weight loss in the arm receiving Lapatinib (p=0.05).

Complete response was seen in 66% vs. 60% in the two arms at 3 months of follow up and this translated to 88% and 80% at 6 months of follow up (p=NS). Mucositis was seen early in the Lapatinib arm at 2nd week compared to 3rd week in the CTRT arm (p=0.04). Skin reactions developed early in the Lapatinib arm and was seen at a higher grade (p=0.02). Diarrhea was seen early and at a higher grade in the Lapatinib arm (p=0.01). Hematological toxicity was not significant between the arms.

9. Results

9.1 Patient characteristics

Between February 2010 and November 2011, 30 patients diagnosed to have locally advanced squamous cell carcinoma of the head and neck was enrolled onto the trial. The patients either had an inoperable tumour or were unwilling to undergo surgery.

9.2 Demographics

AGE (years)	**N = 30**
Range	32 – 71
< 40	3
40 – 50	8
50 – 60	17
60 – 70	2
SEX	
Male	23
Female	7
PERFORMANCE STATUS – KPS	
80	1
70	29

9.3 Treatment characteristics and outcome analysis

CTRT +Lapatinib	15
CTRT	15

OUTCOME ANALYSIS (N = 30)

Break in Treatment

Delay in RT	N = 30
Range (days)	3 – 26
< 1 week	7
1 – 2 weeks	3
> 2 weeks	20

Reason for breaks	All patients	CTRT+ Lap	CHEMO RT
Non treatment related	15	5	10
Treatment related	15	10	5

No. of cycles of chemotherapy	Frequency
3	30
4	20
5	10
6	5

9.4 Treatment Toxicity

Weight loss and OTT.

	CTRT+ LAP	CTRT	P value
Weight loss	3.29+/-1.48	2.20+/-1.42	0.05
OTT	57.06+/-5.88	55.8+/-2.48	0.449

Response at the end of treatment.

Overall outcome	CTRT+ LAP	CTRT	P value
CR	66%	60	1
PR	33%	40%	1
CR @ 6 MONTHS	88%	80%	0.07

Overall Toxicity outcomes in both arms.

Overall outcome	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	P value
Mucositis	01	13	16	1	0	1
Skin	0	11	19	0	0	0.021
Nausea vomiting	6	20	4	0	0	0.276
Diarrhea	6	20	4	0	0	0.01
Hemoglobin	28	2	0	0	0	1
Total WBC count	28	2	0	0	0	1
ANC	28	2	0	0	0	1
Platelet	28	2	0	0	0	1
BUN	28	2	0	0	0	1
Creatinine	28	2	0	0	0	1
Total protein	25	5	0	0	0	1
Albumin	25	5	0	0	0	1
Bilirubin	13	13	4	0	0	0.7
ALP	29	1	0	0	0	0.48
AST	28	2	0	0	0	0.22
ALT	27	3	0	0	0	0.48

Discussion

The individual patient data meta-analysis of chemotherapy in head and neck cancer, MACH-NC, showed an 8% benefit at 5 years of addition of chemotherapy concomitantly with radiotherapy in non-metastatic HNSCC. Lapatinib is a potent and selective inhibitor of the HER2 tyrosine kinase. It prevents phosphorylation and subsequent signal transduction of RAS-RAF-MAPK and the PI3-AKT pathways leading to increased apoptosis and decreased cellular proliferation [9]. Phase 1 studies fixed a dose of 1500 mg for daily administration [10]. Common toxicities were anorexia, fatigue, dyspepsia and acneiform dermatitis rash. Less commonly it causes decreased left ventricular ejection fraction. Neoadjuvant therapy [11], 2-6 weeks prior to administration of CTRT and also concurrently with RT and 3-weekly cisplatin [12] showed a modest improvement in complete response rates suggesting an enhanced therapeutic benefit of this agent with chemoradiation. At the time of conduct of this study, there was no randomised or non-randomised

direct comparison of standard therapy in LAHNSCC with addition of Lapatinib. Hence this study stands one of the first in the country to test this hypothesis.

Median age of the study cohort was 50 years, slightly lower compared to Harrington et.al, while our study had more patients with stage IVA disease were higher. We used a weekly Cisplatin regimen as opposed to the comparison study. The complete response rates at 6 months post radiation are higher compared to Harrington et.al [13].

In the present study, we noted that hematological toxicity of concurrent chemotherapy with radiation therapy was not found to be aggravated. The toxicity that was more in the Lapatinib was attributable to the general toxicity of receptor tyrosine kinases in general, across various cancers. There was significant difference in the overall treatment time of completion of the planned treatment and weight loss- both of which are prognostic and have detrimental effect on the overall survival of LAHNSCC [14].

Conclusion

This prospective non-randomised study comparison shows that addition of Lapatinib to the standard CTRT of LAHNSCC is efficacious and tolerable with accepted toxicity. RTI mediated toxicity was not higher compared to other studies. The results are comparable to those studies conducted at other parts of the world. Late toxicity and long term survival with this therapy warrants a large stratified randomised study.

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