ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 3.4
IJAR 2014; 1(1): 585-589
www.allresearchjournal.com
Received: 21-04-2014
Accepted: 26-05-2014

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To study head and neck squamous cell carcinoma patients undergoing concurrent chemoradiotherapy

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Abstract
Background and Objectives: To evaluate the toxicity profile and rate of immediate Loco regional response in patients with locally progressed squamous cell carcinoma of the head and neck who were treated with daily Gefitinib and weekly Cisplatin.
Materials and Methods: 20 participants who met the inclusion criteria were included in this Phase II single arm research. This study was conducted at Department of Pharmacology, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram, and Andhra Pradesh, between September 2013 to August 2014 After 6 weeks, the clinical examination and radiological imaging were used to evaluate the immediate locoregional response. This treatment's toxicity profile was evaluated using RTOG acute morbidity grading criteria.
Results: The study included 20 patients, 15 of whom were male. The most prevalent subsites were the oropharynx and hypopaharynx. Every single patient made it through their whole radiation and chemotherapy regimen. Assessment was conducted 6 weeks after therapy ended, and 76.6% of patients had a complete response, while 23.3% had a partial response. Patients with malignancies of the oropharynx, hypopharynx, and larynx responded well to the treatment. Although all patients experienced mucositis during treatment, the incidence of severe cases was minimal. The characteristic skin toxicity that is linked to gefitinib was only experienced by one patient.
Conclusion: When treating locally advanced head and neck cancer, concurrent chemoradiotherapy with cisplatin and Tablet gefitinib offers a viable alternative with tolerable toxicity, excellent patient compliance, and good therapeutic response. For gefitinib to be included to the standard treatment protocol and show a meaningful benefit, a large-scale trial is required.

Keywords: Cefitinib, cisplatin, and chemoradiation, concurrent

Introduction
A cancer diagnosis, no matter the site, is devastating for the patient and their loved ones. The disease impacts not just the patient's physical and mental health, but also their community. Head and neck cancer is the sixth most frequent disease globally, and it causes a huge and noticeable burden. The rate is significantly greater in India, where it ranks among the most prevalent cancers. Geographic dispersion and local habits also affect the incidence. Tobacco use, in all its forms, and the additive effects of combining it with alcohol are strong predictors of its prevalence [1-3].
Around the world, the number of cancer cases is on the rise. The vast majority of newly diagnosed cancer cases occur in developing nations like ours. Western Europe, South Africa, India, and Australia all have very high rates of cancers of the mouth and throat.1. Among the SAARC countries, India has the highest cancer incidence rate. The majority of patients are treated with a combination of surgery, chemotherapy, and radiation when they are in the locally advanced stage of cancer. Overall, 5-year survival among this population is roughly 50% even with the finest treatment, and it is much lower in a developing nation like ours. Furthermore, the survival rate has not changed noticeably despite the fact that there have been recent advancements in treatment across all three domains [2-4].

Cancer of the head and neck is among the top four malignancies in women in India, while it ranks among the top two in men. After lung illness, TB, and cardiovascular disease, head and neck cancer ranks as the fourth leading cause of mortality among people aged 25 to 69. Since head and neck cancers disproportionately affect a demographic that contributes much to the nation's economy and social fabric, this is hardly surprising. A World Health Organization study estimates that 2.5 million people in India are living with cancer at any one time, with one-third of those people afflicted with head and neck cancer. Tobacco, in its many forms, is a major carcinogen, and the local population's habits expose them to it. As a result, the cancer incidence varies by region and by demographic [5-7].

In comparison to non-infectious diseases, cancer and other non-communicable illnesses such as cardiovascular disease, diabetes, and hypertension now account for the majority of deaths and illnesses. A major issue in public health nowadays is the prevalence of cancer and other non-communicable diseases. As a result, our disease prevalence pattern is rapidly approaching that of the Western population [6-8].

Unfortunately, our healthcare system is still behind the times, and many areas still lack the resources to offer the same level of treatment as in the West, particularly for cancer. The government has launched several initiatives to address cancer prevention and its causes, with a focus on tobacco usage. Tobacco products and advertisements for them are no longer shown on television, and all products containing tobacco now carry warning labels that state that smoking causes cancer. Tobacco use causes cancer, and the media is helping spread the word.

There has been a concerted effort to reduce tobacco use, but despite this, more and more people are becoming addicted to the drug, particularly young people. This has led to an upsurge in cases of cancer associated with tobacco use, including head and neck cancer. Tobacco use is particularly rampant among young adults, which is reflected in the rising cancer incidence rate in this demographic [7-9].

The purpose of this research was to assess the efficacy of treating locally progressed head and neck squamous cell carcinoma with a combination of conventional radiotherapy, Gefitinib, and weekly Cisplatin.

Materials and Methods

20 participants who met the inclusion criteria were included in this Phase II single arm research. This study was conducted at Department of Pharmacology, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram, and Andhra Pradesh, between September 2013 to August 2014 After 6 weeks, the clinical examination and radiological imaging were used to evaluate the immediate locoregional response. This treatment's toxicity profile was evaluated using RTOG acute morbidity grading criteria.

Inclusion Criteria

- Squamous cell carcinoma of the head and neck was confirmed by biopsy.
- The primary tumor sites include the oral cavity, oropharynx, hypopharynx, and larynx.
- Stage III illness without any indication of distant metastases.
- Under 70 years old.

Exclusion Criteria

- Histology that is not squamous.
- Nasal cavity tumors.
- Prior therapy for any other cancerous condition.

Results

After completing their entire course of treatment, all 20 of the study's patients were accessible for analysis. We gathered the results as follows. Males outnumbered girls, as was to be expected. This illustrates how risk factors for alcohol and tobacco use are more common in the male population than in the female one.

Table 1: Sex distribution

Sr. No.	Sex	Patients	%
1	Male	15	80.0
2	Female	5	20.0

Age Distribution

Almost half of the patients were in the 51 -60 years age group. The percentage of patients in the younger age group is also high. The oldest patient included in the study was 68 years old. The youngest was 32 years. Both were males associated with the use of tobacco.

Table 2: Age wise distribution

Sr. No.	Age	Patients	%
1.	31- 40yrs	2	13.33
2.	41 -50yrs	4	26.66
3.	51-60yrs	12	46.66
4.	61-70yrs	2	13.33

Personal Habits

Majority of the patients had history of use of tobacco in its various forms. 14 of them had concomitant use of alcohol. Only 4 of them did not give any history of use of tobacco or alcohol, all of whom were females.

Table 3: Personal Habits

Sr. No.	Habits	Patients	%
1.	Tobacco (Smoking)	10	50
2.	Tobacco (Smokeless)	6	30
3.	Alcohol	2	10
4.	None	2	10

Symptoms and signs

Majority of the patients presented with the complaint of pain and an equal number with the complaint of dysphagia. 2 (10%) patients presented with the complaint of neck swelling.

Table 4: Symptoms and signs

Sr. No.	Presenting symptoms/signs	Number	%
1.	Pain	5	25
2.	Ulcer/ Growth	4	20
3.	Dysphagia	3	15
4.	Odynophagia	5	25
5.	Neck swelling	2	10
6.	Voice change	1	05

Duration of symptoms according to site wise

Mean duration of the presenting symptoms were similar amongst the different subsites. Longest duration of symptom was a laryngeal cancer where patient presented with a history of hoarseness of voice for 6 months associated with progressive dysphagia for the past 2 months

Table 5: Duration

Sr. No.	Site	Mean Duration
1.	Oral cavity	2.9
2.	Oropharynx	3.1
3.	Larynx	3.2
4.	Hypopharynx	3.3

Discussion

The social and economic effect of squamous cell carcinoma of the head and neck is substantial, and it ranks among the most common cancers in India. When most patients arrive, the disease has progressed to an advanced local stage, making surgical excision either impossible or very dangerous. Local radiation therapy alone used to be the gold standard for these patients, but the results were pitiful: A 5 year survival rate of 10-20% and a local control rate of 50-70% [8-10].

Using radiation and chemotherapy simultaneously was a well-thought-out strategy for treating locally advanced head and neck cancer. Radiation therapy is most effective when administered to tumors that have already undergone chemotherapy. This is because chemotherapy stops tumor repopulation, kills hypoxic cells first, sterilizes micrometastatic disease outside of radiation fields, and reduces tumor mass, which improves blood supply and reoxygenation and makes radiation more effective [11-13]. By blocking the repair that chemotherapy causes, fractionated radiation makes cancers more sensitive to chemotherapy. Additionally, it reduces tumor size, which improves blood flow to the tumor and increases the cytotoxic effect of chemotherapy by making it easier for the drug to reach tumor cells.

The use of chemotherapy in conjunction with radiation was the subject of multiple trials that sought to determine its viability and potential to improve outcomes. Cisplatin, either alone or in combination with other drugs, was the chemotherapeutic mainstay in the majority of the trials. Several meta-analyses validated the anticipated theoretical benefit of combining radiation with chemotherapy, another cytotoxic treatment. This benefit was amply proven in the trials [14-16].

There have been a lot of meta-analyses looking at LRC and survival rates to see if chemo-radiotherapy is better than radiotherapy alone. Perhaps the most prominent and influential of these meta-analyses is the Meta-Analysis of Chemotherapy for Head and Neck Cancer. The current gold standard for treating locally advanced, non-resectable head and neck cancer is concurrent chemoradiation with cisplatin doses of 80-100 mg/m2 given three times weekly and radiation doses of up to 70 Gy. Unfortunately, there are a lot of toxicities and low compliance rates linked to the three-week regimen. Assuming a cumulative dose of 200 mg/m2 is reached, there is literature suggesting that the weekly regimen of cisplatin is just as effective as the three weekly treatment. The weekly arm experiences much reduced toxicity as a result of this. The weekly treatment was just as effective as the three-weekly regimen with reduced toxicities, according to a study done in our department. Presently, the gold standard for treatment is the use of concomitant chemoradiation in locally advanced settings [17-19].

The best case scenario survival rate with this treatment is now in the 50-60% range. Unfortunately, overall survival has not improved much despite the use of multiple therapeutic techniques. New medications that may increase overall survival are currently the subject of multiple trials. The study of molecules is one of these areas. Someone once said that in order to win, you had to know your enemy [20, 21]. It will be easier to fight with better knowledge. Oncology is another area that can benefit from this same idea. Beginning with the understanding that different types of cancer exhibit distinct morphologies, behaviors, and histologies, our understanding has now grown to encompass the field of molecular biology. Thanks to advancements in cancer research, we now know which proteins are involved in certain pathways and mechanisms that cause the disease, and we can target these processes with a variety of medications. Instead of the mass nonspecific cytotoxicity afforded by traditional chemotherapies, they provide an appealing possibility of targeting the tumor cells preferentially [20-22].

A total of 100% of patients responded in this trial; 76% had a complete reaction and the other patients had a partial response. When looking at patient performance status, age at diagnosis, and gender, there was no statistically significant correlation between treatment response and any of these variables. Treatment efficacy was higher for primary tumors located in the oropahrynx, hypopharynx, and larynx than in the oral cavity, according to this study. This could be because the majority of cancers found in the mouth were well-differentiated and did not respond well to treatment. This jibes with the observation that tumors with less differentiation had higher treatment response rates than those with more differentiation.

Nodal disease showed a similar pattern, with N1 and N2A tumors responding better than N2B and 2C tumors, and tumors with a smaller volume of disease, or T3, had higher response rates than tumors with a larger volume, or T4. Thirty percent of cases of pharyngitis and twenty percent of cases of laryngitis were grade 3. Nobody reacted at the fourth grade level. Patients also had other systemic toxicities, such as nausea, vomiting, and diarrhea, which were all controllable with standard antiemetic treatment. Among all patients, just one experienced severe nausea. Grade 3 diarrhea and vomiting did not occur in any of the patients. There was no occurrence of grade 3 or 4 hematogical toxicity, and the total amount was small. Transfusions of blood were necessary to treat grade 2 anemia in 6% of patients. Patients did not experience thrombocytopenia or febrile neutropenia. Neither renal nor liver damage occurred in a single patient [21-23].

The brief follow-up time and relatively small sample size were the study's main drawbacks. One of the reasons why Gefitinib is being considered for this condition is because the majority of SCCHN over-express EGFR. The high expense of doing an EGFR expression investigation meant that it could not be afforded for all patients. Therefore, it was not feasible to conduct a subgroup analysis using parameters corresponding to EGFR wild type, mutant, or over-expression. Current treatment for locally progressed SCCHN involves concurrent cisplatin-based chemo-radiation and Gefitinib; however, larger multi-centric trials are required to

confirm and validate these promising results [24-28].

Conclusion

To sum up, it's safe to say that head and neck cancer is becoming an increasingly serious concern, and that prevention attempts have been mostly ineffective. This means that a greater number of individuals are arriving with cancers that have progressed outside the local area. Patients in this category may benefit from adding Gefitinib to the conventional concurrent chemoradiation regimen, since this strategy outperforms the control arm in terms of response rates. Along with a marked rise in toxicity, the regimen is well-tolerated, and patients are generally compliant. However, due to the small sample size, statistical significance could not be achieved in this investigation. To confirm these promising results and further understand Gefitinib's function in the treatment of locally advanced head and neck cancer, larger trials are required.

Funding: None

Conflict of Interest: None

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