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ORIGINAL ARTICLE

Efficacy and Safety of 5-Fluorouracil Cisplatin in Comparison with Gefitinib in Advanced and Recurrent Head and Neck Cancer

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ABSTRACT

Background: The present study aimed to evaluate the efficacy and safety of Cisplatin plus 5-Fluorouracil in comparison with Gefitinib in advanced and recurrent head and neck cancer.

Methods: A quasi experimental study was undertaken at the Department of Oncology, Jinnah Postgraduate Medical Centre between 2nd April 2022 and 2nd December 2022. All patients with histologically confirmed new or recurrent cases of head and neck cancer in the advanced clinical stage were recruited. Demographic data (age, gender, body mass index, comorbidity, etc.), medical history and clinical characteristics, routine biochemical analysis, urinalysis, and tumor assessments via CT scans and MRI, adverse effects and toxicity were recorded. Patients were divided randomly into two groups. Group A received Cisplatin plus 5-Fluorouracil while group B received Gefitinib monotherapy. The primary end point of the study was the overall response rate (ORR).

Results: Complete response was demonstrated by seven (7.3%) and four (4.8%) individuals in Group A and B, respectively. Vomiting was significantly associated with Cisplatin plus 5-Fluorouracil with a frequency of 38 (39.58%) as compared to 10 (11.9%) in Group Gefitinib ($p<0.001$). Renal insufficiency was also experienced more frequently in Group A; 26 (27.1%) as compared to Group B; 2 (2.4%) ($p<0.0001$). Fever ($p=0.004$) and bone marrow suppression ($p<0.001$), loss of hearing ($p=0.012$) and skin rash ($p<0.0001$) were all significantly more frequently experienced by patients receiving Cisplatin plus 5-Fluorouracil as compared to those receiving Gefitinib.

Conclusion: Gefitinib monotherapy was found to be more favorable for patients diagnosed with advanced head and neck cancer because oral mode of administration of Gefitinib alleviates the need for a hospital admission which makes it a more feasible option as compared to the alternatives. Furthermore, Gefitinib has a better safety profile and a relatively lower incidence of adv erse effects.

Keywords: Cisplatin, Fluorouracil, Geftinib, Head Cancer, Neck Cancer, Recurrence.

INTRODUCTION

The prevalence of head and neck (HN) cancer in Pakistan is 18.74% of all new cancer cases recorded during the years 2004 to 2014. [1] The incidence recorded in Karachi is one of the highest in the world which makes it an important concern for healthcare workers and citizens alike. The rising prevalence of HN cancer can be attributed to the fact that a considerable amount of people in the city are habitual of smoking, chewing chalia and gutka.[2] A study based on South Asia has reported the five-year survival rate of HN cancer in this region to be below 40%.[3]

The care of patients with HNSCC is usually undertaken by a multidisciplinary team. The primary modalities available for treatment include head and neck surgery, chemotherapy and radiotherapy. Patient rehabilitation and quality of life are further augmented with the support of speech therapists, plastic or reconstructive surgeons, dentists and psychologists. [4-6] Patients who present with early disease (stage 1 or 2) can benefit from surgery or radiation therapy, both of which have been shown to carry a similar efficacy. For those who present with more invasive disease, a combination of modalities is recommended. In all cases where the disease is unresectable, chemoradiotherapy with cisplatin is considered to be the treatment of choice. Metastatic disease or recurrence carry a poor prognosis. [7]

When HNSCC presents with metastasis or recurrence, the management is mainly palliative with chemotherapy which classically involves platinum-based agents (Cisplatin) with 5-Fluorouracil. [8,9] Other drugs such as Methotrexate, Bleomycin, Capecitabine and Ifosfamide have also been used. [10] These drugs have shown response rates of up to 30% in some studies. [11] While trials for newer therapies are still underway, there is no single drug or combination regimen as of now that has shown a considerable improvement in the survival rate of patients with advanced head and neck cancer. [12]

Studies have established that Epidermal growth factor receptor antagonists have considerable efficacy in the treatment of HNSCC with minimal adverse effects. [13] Gefitinib is one of these EGFR-Tyrosine Kinase Inhibitors (TKI) that is highly effective against advanced head and neck cancer. In phase II clinical trials, gefitinib showed response rates ranging from 1% to 11%. Gefitinib at oral dosages of 250 mg and 500 mg was not better than methotrexate, according to a phase III study. [14] It frequently causes rashes, diarrhoea, and increased transaminases as side effects.

Our study aims to assess and compare the effectiveness and safety profile of Gefitinib with Cisplatin plus 5-Fluorouracil therapy in the treatment of advanced stage HNSCC.

METHODS AND MATERIALS

A quasi experimental study was undertaken at the Department of Oncology, Jinnah Postgraduate Medical Centre between 2nd April 2022 and 2nd December 2022. After ethical approval was procured from the institutional review board of JPMC with reference # F2-81/2022-GENL/151/JPMC, the recruitment of participants was initiated. All the patients aged >18 years, with histologically confirmed novice or recurrent cases of head and neck cancer in the advanced clinical stage, with normal renal, liver and cardiopulmonary function were eligible to take part in the study. Individuals with head and neck cancer in the clinical stage of I or II or those who were pregnant or lactating, were medically unfit for chemotherapy, or were allergic to Gefitinib, Cisplatin or 5-Fluorouracil were excluded from the study.

The sample size was calculated using WHO sample size calculator. By taking the percentage of partial survival rate as 27.3% for

Gefitinib group for patients with recurrent head and neck cancer, the margin of error as 6%, and confidence level of 90%, an estimated sample size of the Gefitinib group is 149. [15]

After informed consent was requested from all participants, the patients were randomized to one of the two treatment arms (Intervention group - Gefitinib or Control Group - Cisplatin plus 5-Fluorouracil). All data was recorded by the researchers in a predefined proforma. The recorded data included: demographic data (age, gender, body mass index, comorbidity, etc) medical history and clinical characteristics, routine biochemical analysis, urinalysis, and tumor assessments via CT scans and MRI, adverse effects and toxicity. Gefitinib was given as one dose daily for 3 months and Cisplatin for 6 cycles.

After stratification by sex, comorbidities and stage of tumor, patients were administered chemotherapy for six cycles. All the patients who fulfilled the eligibility criteria were enrolled in the study. There were two groups in the study as mentioned below:

Group A patients received (Cisplatin plus 5-Fluorouracil) which acted as the control arm. Group B patients were administered (Gefitinib) which was the intervention arm. Patients in the Intervention Arm were administered Gefitinib 250 mg tablet/ BD daily until progression.

Patients in the Group A were administered 5-Fluorouracil (1000 mg/m^2 IV on D1 & 8) plus Cisplatin (80mg/m^2 IV on D1) every 3 weeks for a maximum of 9 cycles.

The primary end point of the study was the overall response rate (ORR). The term overall response rate is defined as “the proportion of patients in the study who have a partial or complete response to the treatment”. As a secondary outcome measure, the safety profile and side effects of the drugs were also recorded.

Each patient had a thorough history review, physical examination, and clinical evaluation. As needed, a local examination and fiber optic laryngoscopy were performed to determine whether the tumor had spread locally. The head, neck, chest, and upper abdomen had baseline computed tomography (CT) scans to check for primary or metastatic illness.

Following both groups for six months, the negative outcomes and response rates were examined. Therapy was continued until the patient withdrew, the condition progressed, or the side effects lasted for more than three weeks. Throughout the trial, clinical and radiological evaluations of each patient were performed on a regular basis.

With the help of SPSS version 25, statistical analysis was carried out. Age and illness duration were two examples of quantitative data that were given as mean and standard deviation. The frequency and percentages of qualitative data (categorical data) such as gender, comorbidities, cancer type, cancer location, cancer grade, clinical stage, and therapy response were shown. A chi-square or Fisher's exact test was used to compare the two groups, with a p-value of 0.05 designating significance.

RESULTS

A mean age of 49.2 ± 12.7 years and male dominance was observed. The control group had 96 patients while the intervention group had 84 participants. The mean white blood count at presentation and at the end of the treatment was 7.26 ± 2.4 × 10^9/L and 7.52 ± 3.1 × 10^9/L , respectively. Progressive disease was observed in 33 (18.33%) patients, while stable disease was observed in 54 (30%) patients.

Table 1: Demographics and clinical characteristics of patients

Characteristics	Mean ± SD / N (%)
Age	49.2 ± 12.7
Number of drug cycle	4.37 ± 2.98
White blood count at presentation (× 10^9/L)	7.26 ± 2.4
White blood count at end of treatment (× 10^9/L)	7.52 ± 3.1
Gender	
Female	63 (35%)
Male	117 (65%)
Study groups	
Control (Cisplatin and 5-FU)	96 (53.3%)
Intervention (Gefitinib)	84 (46.7%)
Comorbidities	
Diabetes Mellitus Type 2	36 (20%)
Hepatitis	10 (5.6%)
Hypertension	28 (11.1%)
Both Hypertension and Diabetes Mellitus	10 (5.56%)
Not significant	96 (53.3%)
Mode of administration	
Oral Route	92 (51.4%)
Intravenous Route	87 (48.6%)
Stage of cancer	
III	3 (1.7%)
III A	1 (0.6%)
IV	140 (77.8%)
Grade of cancer	
1	24 (13.4%)
2	129 (72.1%)
3	24 (13.4%)
R	1 (0.56%)
Overall response rate	
Partial	82 (45.8%)
Complete response	11 (6.1%)
Progressive disease	33 (18.33%)
Stable disease	54 (30%)

Adverse effects were reported by 165 patients. Out of these, 39 (21.67%) discontinued therapy. Death occurred in 99 (55.3%) cases. In six patients, death was attributed to infection.

Table 2 illustrates the rate of overall response rates in the two study groups. Complete response was demonstrated by seven 7 (7.3%) and four 4 (4.8%) individuals in Group Cisplatin and 5-FU and Gefitinib, respectively. However, there was no statistically significant difference between the two groups in terms of overall response rates.

Table 2: Association of overall responses with study group

	Study Group		
Overall response rate	Cisplatin plus 5-Fluorouracil (5-FU) n=96	Gefitinib n=84	p-value
Partial	41 (42.7%)	41 (48.8%)	0.7436
Complete response	7 (7.3%)	4 (4.8%)	
Progressive disease	17 (51.5%)	16 (48.5%)	
Stable disease	31 (64.6%)	23 (42.6%)	

Table 3 illustrates proportions of adverse effects among the study population in both arms of the trial. In Group Cisplatin and 5-FU, 89 (92.7%) while in group Gefitinib, 76 (90.5%) patients experienced adverse effects (p=0.589). The rate of discontinuation therapy was not significantly different between the two groups.

Table 3: Association of Study group with adverse effects

	Study Group		
	Control Group (Cisplatin plus 5-Fluorouracil)	Intervention Group (Gefitinib)	p-value
Adverse effects	89 (92.7%)	76 (90.5%)	0.589
Discontinuation of therapy	33 (34.4%)	19 (22.6%)	0.083
Was death attributed to infection			0.667
No	49 (92.5%)	50 (96.2%)	
Yes	4 (7.5%)	2 (3.8%)	
Adverse effects			
Diarrhea	34 (35.4%)	32 (38.1%)	0.138
Weakness	38 (39.58%)	29 (34.52%)	0.484
Vomiting	38 (39.58%)	10 (11.9%)	<0.0001
Low blood counts	32 (33.33%)	13 (15.48%)	0.006
Mouth ulcers	26 (27.08%)	27 (32.14%)	0.601
Bleeding from wound site	9 (5%)	43 (23.8%)	< <0.0001
Renal insufficiency	26 (27.1%)	2 (2.4%)	<0.0001
Poor appetite	22 (22.92%)	11 (13.1%)	0.089
Fatigue	16 (16.67%)	11 (13.1%)	0.503
Fever	16 (16.67%)	3 (3.57%)	0.004
Liver function impairment	12 (12.5%)	8 (9.5%)	0.563
Arrhythmias	7 (7.29%)	2 (2.38%)	0.132

Hearing impairment	7 (7.29%)	0 (0%)	0.012
Hair loss	6 (6.25%)	8 (9.52%)	0.413
Skin rash	3 (3.13%)	28 (33.33%)	<0.0001
Allergic reaction	2 (2.08%)	2 (2.38%)	0.893

Vomiting was significantly associated with Cisplatin plus 5-Fluorouracil with a frequency of 38 (39.58%) as compared to 10 (11.9%) in Group Gefitinib (p<0.001). Renal insufficiency was also experienced more frequently in the control group; 26 (27.1%) as compared to the intervention group; 2 (2.4%) (p<0.0001). Fever (p=0.004) hearing impairment (p=0.012), and skin rash (p<0.0001) were all significantly more frequently experienced by patients receiving Cisplatin plus 5-Fluorouracil as compared to those receiving Gefitinib. Bleeding from the wound site was significantly associated with administration of Gefitinib (p<0.0001).

DISCUSSION

Most of the patients who came to our center with head and neck cancers had ages between 35 to 55 years. Only a handful of these patients had comorbid conditions such as diabetes and hypertension. The control group included 96 patients who were administered intravenous Cisplatin plus 5-Fluorouracil while the interventional group included 84 patients who received oral Gefitinib.

The conventional use of Cisplatin and 5-Fluorouracil combination regimen for advanced Head and neck cancer has been thoroughly evaluated by various studies. One such study has observed an overall response rate of 58% and a complete response rate of 10% in patients treated with this regimen. [16] Another study has demonstrated that both lower doses (80/800) and higher doses (100/100) of Cisplatin and 5-Fluorouracil therapy show a similar overall response rate of 30% and a 2-year survival of 16.7% with a better safety profile for the low dose regimen. [17] In our study patients treated with the conventional Cisplatin plus 5-FU, therapy showed a much-expected overall response rate of around 50% with 7% of patients showing complete response.

When explored as monotherapy for the treatment of HNSCC with metastasis or recurrent disease, Gefitinib has not been shown to demonstrate better efficacy than most other drugs in terms of an overall response rate or survival rate. [14, 15] A treatment response rate of up to 36% has been reported with Gefitinib by one study [18] and most studies have highlighted the benefit of Gefitinib as a promising drug essentially for disease recurrence. [19] In accordance with this, our study observed a significant response with Gefitinib therapy in patients with advanced disease. Furthermore, the overall treatment response rate of Gefitinib monotherapy was found to be nearly equal to Cisplatin and 5-Fluorouracil regimen with 50% of patients in each of these groups showing a response to therapy. (Table 2) Our study observed that either type of palliative care stopped the progression of disease in the majority of our patients.

Adverse effects to chemotherapy are an important consideration that affect both the compliance and the daily life quality of our patients. Overall, the most common side effects to either Gefitinib or Cisplatin plus 5-Fluorouracil therapies observed in our patients were fatigue, diarrhea and mouth ulcers. Our study noted that while patients in both the control and interventional groups experienced significant adverse effects; the occurrence and severity of certain side effects was considerably more pronounced in the control group (Table 4). We noted that nausea, vomiting and diarrhea were more prevalent in patients receiving Cisplatin plus 5-Fluorouracil therapy. Cisplatin has been known to cause severe gastrointestinal disturbances that necessitate the use of multiple anti-emetics. In addition to this, patients in this group also had a higher incidence of leukopenia and anemia which is in accordance with the previous studies. [17] Organ dysfunction is common with platinum-based agents and nephrotoxicity is a dose limiting side effect for Cisplatin. [20] In our study, this was demonstrable with renal insufficiency being seen in 26 patients taking Cisplatin therapy and only 2 patients taking Gefitinib. Hepatic dysfunction was also more common with Cisplatin and hearing loss, if any, was observed only in this group. Patients treated with Cisplatin require repeated outpatient visits and are more likely to show a higher incidence of hospital readmissions. Therefore, it is recommended for physicians to choose a dosing schedule for Cisplatin therapy that aligns better with a patient's tolerability and the feasibility of hospital visits. [21]

Gefitinib monotherapy for various cancers is associated with only mild to moderate side effects that are dependent on the dosage and are generally manageable without having to discontinue therapy.[22] Patients in our study who received Gefitinib therapy experienced less gastrointestinal disturbances compared to the control group and also reported less frequency of fever and fatigue. Another significant thing to be pointed out is that myelosuppression, a very common side effect of chemotherapy, was not observed in this group of patients. Renal and hepatic dysfunction, if any, were only mild and no hearing loss was seen. All these factors were likely responsible for better compliance in these patients and lesser rates of discontinuation. As per studies, one of the commonly reported side effects of Gefitinib therapy is a skin rash that can range from dry scaly skin to an acneiform eruption. [23] We observed a similar pattern in our study with one third of our patients on Gefitinib therapy developing a papulopustular skin rash. Another adverse effect observed significantly more in these patients compared to controls in our study was bleeding from wound sites, which resulted in earlier than scheduled outpatient visits.

In our study, a total of 39 patients discontinued therapy at some point. Discontinuation of treatment was more observable in the patients taking Cisplatin and 5-Fluorouracil compared to the patients on Gefitinib monotherapy. While the effectiveness of both these treatment regimens for the management of advanced head and neck cancer is similar, Gefitinib monotherapy has two clear advantages over Cisplatin and 5-Fluorouracil therapy. Firstly, an oral mode of administration alleviates the need for a hospital admission which makes Gefitinib a more feasible option for most of our patients. It also made Gefitinib a more practical option in the COVID-19 pandemic situation for the last few years. This observation has also been reported in other studies [15] Secondly, Gefitinib is associated with less troubling side effects. This allows for good compliance and a better quality of everyday life for our patients. We need more studies to explore the potential benefits and risks of Gefitinib as a palliative treatment for advanced head and neck tumors compared to drugs that are used conventionally but are associated with unfavorable side effects and high rates of discontinuation in our patients. Trials inculcating the use of Gefitinib in combination with radiotherapy and other chemotherapeutic agents in this patient population also need to be conducted.

CONCLUSION

Gefitinib monotherapy was discovered to be more efficient for patients with advanced stage head and neck cancer because it does not require hospitalization as it is administered orally, making it a more practical choice than the other alternatives, especially during COVID-19 pandemic. Additionally Gefitinib has a superior safety record and a considerably reduced frequency of undesired effects. However, to thoroughly investigate the effectiveness of Gefitinib against advanced stages of head and neck malignancies, multi-center and long-term trials should be carried out.

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