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GEFITINIB ALONG WITH METHOTREXATE AS PALLIATIVE METRONOMIC CHEMOTHERAPY IN PATIENTS WITH ADVANCED AND METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA: A SINGLE INSTITUTE EXPERIENCE FROM A TERTIARY CANCER CENTER.

Oncology

Dr A H Rudresha	Associate Professor, Dept. of Medical Oncology, KMIO.
Dr Kavi Sankar K V*	Final Year Resident, Dept. of Medical Oncology, KMIO. *Corresponding Author
Dr Linu Abraham Jacob	Professor, and HOD, Dept. of Medical Oncology, KMIO.
Dr Suresh Babu M C	Professor, Dept. of Medical Oncology, KMIO.
Dr Lokesh K N	Associate Professor, Dept. of Medical Oncology, KMIO.
Dr Rajeev L K	Associate Professor, Dept. of Medical Oncology, KMIO.
Dr Smitha Saldanha	Associate Professor, Dept. of Medical Oncology, KMIO.
Dr Sindhusha K	Final Year Resident, Dept. of Medical Oncology, KMIO.

ABSTRACT

Background: In patients with recurrent or metastatic squamous cell carcinoma of the head and neck, who have already received prior chemotherapy with platinum-containing regimens combined with fluorouracil or taxanes either as induction treatment or as part of chemoradiation, there are very few effective second line options. This study analyzed the safety and efficacy of gefitinib and methotrexate combination metronomic chemotherapy in patients with advanced head and neck cancers. **Materials and Methods:** This was a single center, prospective observational study conducted in our hospital over a period of 2 years (September 2021-April 2023). 131 patients were included in our study. They received Gefitinib 250mg daily plus methotrexate 15mg once a week orally on D1, D8, D15 and D22 of a 28-day cycle. The primary objective was to determine the progression free survival. **Results:** The median follow-up was 9.6 months (range, 0 to 18.6 months). The median progression-free survival was 4.3 months (95% CI, 4 mon to 4.5 mon). The median overall survival was 6.4 months (95% CI, 5.9 mon to 6.5 mon) and the response rate was 64% (95% CI, 43% to 77%). The median improvement in quality-of-life score was 42 points on a scale of 100. **Conclusions:** Gefitinib with methotrexate was well tolerated and found to have a positive impact in terms of response rates and quality of life improvement in patients with advanced or metastatic or recurrent head and neck squamous cell cancers.

KEYWORDS

Advanced Head And Neck Squamous Cell Cancer, Oral Metronomic Chemotherapy, Quality Of Life

INTRODUCTION:

In India, Head and neck squamous cell carcinomas constitute a major health burden. Owing to exposure to tobacco in various forms, the incidence and associated mortality due to head and neck cancers are increasing year by year. Based on the GLOBOCAN 2020 data, there were 219722 new cases of Head and Neck cancers and 121096 patients died due to head and neck cancers in one year [1]. This data illustrates the magnitude of social and economic burden caused by head and neck cancers in the country. Treatment of patients with recurrent head and neck cancers pose a significant challenge to oncologists despite the advancements in the fields of head and neck surgery, radiotherapy and chemoimmunotherapy. This is mainly because of the reason that despite adequate treatment, the incidence of recurrence is high in patients with head and neck cancers (nearly 50%) [2] and treating patients with recurrent head and neck cancers that are not amenable to further local treatment is difficult as these patients would have already received chemotherapy with multiple agents including platinum, fluorouracil and taxanes either as induction treatment or as part of chemoradiation [3]. In such patients, further effective second-line chemotherapy options are limited. EGFR targeted therapy and immunotherapy have made significant advances in treatment of patients with advanced recurrent or metastatic but the responses seen with these agents are also not sustained and most of the patients on these agents eventually have progressive disease [4]. Also, the cost factor associated with these agents is significant and many patients are not affordable for same especially in developing nations [5]. Since there are no further available options, most of these patients are started on metronomic chemotherapy and palliative supportive care. Metronomic chemotherapy, a concept initially coined by Douglas Hanahan, involves administration of low doses of chemotherapy agents over an extended period of time without any gaps.[6] This is unlike the traditional method of chemotherapy administration wherein rest periods are given for recovery of normal tissues. This approach was based on the fact that the rest period that is given during the chemotherapy cycles would be leading to the development of re growth of tumor cells and also resistant clones. Metronomic chemotherapy exerts its anti-cancer activity by also inhibiting tumor angiogenesis, stimulating anticancer immune response and inducing tumor dormancy.[7] Metronomic chemotherapy has been used in patients with recurrent or metastatic head and neck cancers and has been widely studied by various researches.[8][9][10] Many different combination metronomic chemotherapy regimens have been used in head and neck cancers. However, none of them have showed clear superiority over each other as found in various studies. This study reports the safety and efficacy of Gefitinib and methotrexate combination metronomic chemotherapy in patients with advanced recurrent and metastatic head and neck cancers.

METHODS:

Patient Selection:

This is a Prospective Observational Study done at our institute in patients with metastatic and/ or, recurrent locally advanced head and neck squamous cell cancers during the period September 2021 to April 2023.

Inclusion Criteria:

- Age at presentation 18 years or older
- ECOG (eastern cooperative oncology group) PS 0-3
- Histologically or cytologically confirmed advanced or metastatic Head and neck squamous cell carcinoma (oral cavity oropharynx, hypopharynx& larynx).
- Not eligible for Platinum or 5 Fluorouracil or Taxane based IV chemotherapy due to poor performance status (or) already received palliative IV chemotherapy and progressed on same.
- Adequate hematopoietic, hepatic, and renal function defined as:Absolute neutrophil count >1.5x109cell/ml, Platelets >100,000 cells/mm3, Haemoglobin >9.0g/dL, concentrations of total serum bilirubin within upper limit of normal, Aspartate aminotransferase

(AST) and alanine aminotransferase (ALT) within 2.5xULN
- No history of interstitial lung disease (ILD)

Exclusion Criteria:
- Non-Squamous histology.
- People with known or suspected hypersensitivity to methotrexate/ Tyrosine kinase inhibitors.
- Severe Cardiac, renal or hepatic illness.
- Breastfeeding or Pregnant women.
- Patients who do not give written informed consent.

AIMS AND OBJECTIVES: To study the efficacy and safety of Oral Metronomic Chemotherapy combination with Gefitinib and methotrexate in patients with Recurrent, Residual and/or Metastatic Head & Neck Cancers

Study Conduct And Design With Treatment Protocol: All patients with Biopsy confirmed Recurrent, Residual and Metastatic Head & Neck cancers were counselled regarding option of Metronomic chemotherapy and were included in the study for treatment after obtaining informed consent. A total of 131 patients were included in the study.

Metronomic Chemotherapy Regimen Used: Oral Methotrexate: 15mg once weekly with Oral Gefitinib: 250mg once daily. Given continuously until disease progression or unacceptable toxicity.

Response Assessment: All the patients were assessed clinically fortnightly. Improvement in clinical symptoms such as decrease in pain and swelling, improvement in physical activity or clinical signs such as decrease in tenderness and size of tumor, improvement in performance status was considered under clinical response. Worsening of these signs or symptoms was denoted as clinical progression of disease. Radiological assessment with Contrast enhanced CT scan of head, neck and thorax was done every 3 monthly. The responses were graded according to the Response Evaluation Criteria in Solid Tumors criteria version 1.1.[6] The disease response was graded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Any response other than disease progression was considered as objective/clinical response. Quality of Life assessment was done before starting treatment and then every 3 monthly with The European Organisation of Research and Treatment of Cancer Quality of Life Core Questionnaire, version 3.0 (EORTC QLQC30) and EORTC head and neck module (EORTC QLQ-HN35). The toxicities during the treatment were assessed according to the Common Terminology Criteria for Adverse Events, version 5.0. In case of Grade III/IV (CTCAE) toxicities, the drug dose was adjusted or stopped.

Study End Points: The primary end was progression free survival. PFS was defined as the time in months from the date of enrollment to the date of progression or death, whichever was earlier. Progression-free survival (PFS) was evaluated from the initiation of oral metronomic chemotherapy till documented clinical/radiological progression of disease. The secondary end points were response rate (RR), adverse event rate, quality of life, and OS. Overall survival (OS) was defined as the duration between the initiation of oral metronomic chemotherapy till the last follow-up or the death of patient.

Statistical Analysis: Statistics Data was recorded on a pre-designed proforma using Microsoft excel spread sheet. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) software version 23. Survival curves were plotted with Kaplan–Meier product limit method. General linear model repeated-measures analysis of variance with appropriate sphericity correction was used for comparison of quality-of-life parameters at different time periods.

RESULTS:
One hundred and thirty-one patients with recurrent locally advanced or metastatic head and neck squamous cell carcinoma who satisfied the study eligibility criteria were enrolled in the study and were started on metronomic chemotherapy with Gefitinib methotrexate combination. The baseline characteristics of the patients are shown in Table 1.

SAFETY: The main toxicity observed was grade 1/2 mucositis, was observed in 31 % of the patients. Grade 1/2 neutropenia was seen in 8% of the patients, however none of the patients developed febrile neutropenia. Anemia of grade 1/2 developed in 9% of the patients and grade 3/4 requiring blood transfusions developed in 3% of the patients. Nausea was seen in 7% of patients and 3% of patients had vomiting. Skin rash was seen in 4% of patients. No patient required any dose reduction due to toxicity. There were no treatment related mortalities. All deaths were due to disease progression. The major adverse events are shown in Table 2.

Table 1: Table 1. Patient characteristics

S No	Category	Subset	Number	%
1	Age	<31 years	7	5.3
		31-40 years	9	6.8
		41-50 years	34	25.9
		51-60 years	52	39.6
		>60 years	29	22.1
2	Sex	Male	95	72.5
		Female	36	27.5
3	ECOG PS at presentation	0	3	2.2
		1	33	25.2
		2	68	51.9
		3	27	20.6
4	Exposure to tobacco	Yes	112	85.4
		No	19	14.6
5	Primary site	Oral cavity	63	48
		Oropharynx	24	18.3
		Hypopharynx	32	24.4
		Larynx	12	9.1
6	Stage	III	1	0.7
		IVA	34	25.9
		IVB	78	59.5
		IVC	18	13.7
7	Prior treatment	Surgery & chemo& RT	57	43.5
		Surgery & RT alone	18	13.7
		Chemo & RT alone	45	34.3
		RT alone	11	8.3

Table 2: Adverse events

Adverse event	No	%
Diarrhea	9	6.8
Rash	6	4.5
Fatigue	34	25.9
Oral mucositis	41	31.2
Nail changes	16	12.2
Pneumonitis	1	0.7
Anemia	13	9.9
Neutropenia	11	8.3
Thrombocytopenia	4	0.3
Raised AST	18	13.7
Raised ALT	16	12.2
Raised creatinine	2	0.15
Raised bilirubin	5	3.8
Nausea	10	7.6
Vomiting	5	3.8

Efficacy:
Survivial: The median follow-up was 9.6 months (range, 0 to 18.6 months). Objective response (Stable Disease + Partial Response) was observed in 64% of patients in the form of SD (41%) and PR (23%). Disease progression was observed in 36% of patients.

The best clinical response rate post oral MCT was observed in the 3rrd month. The median overall survival was 6.4 months (95% CI, 5.9 mon to 6.5 mon). The median progression-free survival was 4.3 months (95% CI, 4 mon to 4.5 mon). The Kaplan–Meier graphs for estimated OS and PFS are depicted in Figure 1 and Figure 2, respectively.

Global Health Status/quality Of Life:
The Quality-of-life score was calculated using the European Organisation of Research and Treatment of Cancer Quality of Life Core Questionnaire, version 3.0 (EORTC QLQC30) and EORTC head and neck module (EORTC QLQ-HN35).

The median Global Score (GS) at baseline was 25. This increased to 42 at 3 months (p=0.002) and to 67 at 6 months(p=0.014). The QOL improvement is shown in Figure 3.

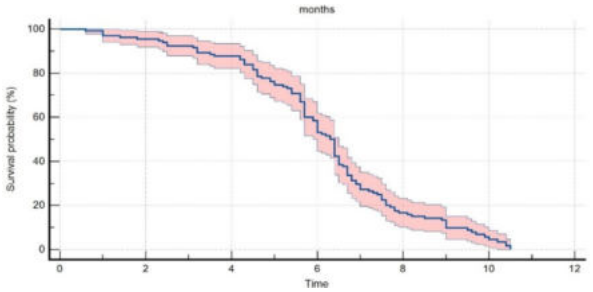

Figure 1. Kaplan-Meier of overall survival.

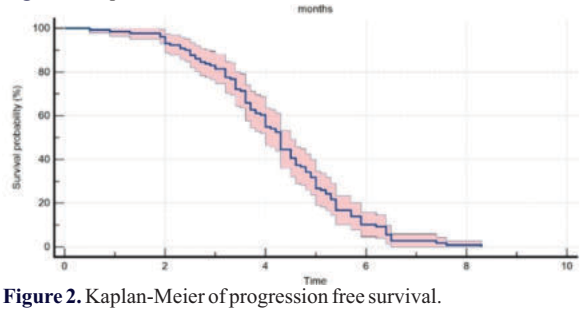

Figure 2. Kaplan-Meier of progression free survival.

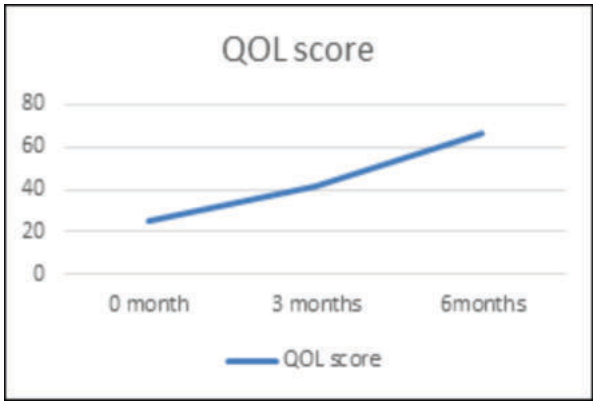

Figure 3. QOL score.

DISCUSSION:

Patients with advanced and metastatic squamous cell carcinoma of Head and neck have a poor prognosis with mean survival of about 6 months and are often not eligible beyond palliative care.[11] Oral metronomic chemotherapy has been widely used in many centers across the world in patients who have received prior lines of chemotherapy. However, there are no randomized control trials and head on head comparison between various oral metronomic chemotherapy regimens. Based on available data and research articles, combination metronomic chemotherapy has proven efficacy in patients with advanced head and neck cancers. Some of the combination metronomic chemotherapy regimens have efficacy rates comparable with other chemoimmunotherapeutic agents. Our study emphasizes the fact that Gefitinib methotrexate combination chemotherapy has good efficacy and safety profile for use in patients with advanced recurrent and/or metastatic squamous cell carcinoma of Head and neck. The main advantages of OMCT are its easy availability, accessibility, low financial burden and easy to administer. In developing countries like ours, where not all patients have access to immunotherapy due to logistic issues, we recommend that randomized control trials have to compare the efficacy of metronomic chemotherapy over other chemoimmunotherapy agents and if proven efficacious, they can be of much benefit especially in countries like India where the burden of Head and neck cancer is very much high than the western world.

CONCLUSION:

Oral metronomic therapy with methotrexate and Gefitinib is a feasible option for patients who are unable to afford the immunotherapy drugs or targeted agents. Gefitinib along with methotrexate was well tolerated and was found to have a positive impact in terms of efficacy rates and the quality of life of patients with advanced Squamous cell carcinoma of head and neck.

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