EFFICACY OF METHOTREXATE IN THE MANAGEMENT OF LOCALLY ADVANCED AND METASTATIC HEAD AND NECK CANCERS

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ABSTRACT

Objective: To evaluate the efficacy of single agent methotrexate in locally advanced and metastatic head and neck cancer.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Oncology, Combined Military Hospital (CMH), Rawalpindi from Jan 2017 to Jul 2017.

Methodology: Fifty patients were enrolled with locally advanced or metastatic head and neck cancers, which were unfit for further treatment with curative radical surgery, radiotherapy and/or double agent chemotherapy. All the patients were treated with metronomic chemotherapy methotrexate 50mg weekly intravenously and the dose was escalated as tolerated up to a maximum of 200mg/week. Patients were followed up fortnightly for clinical response using Response Evaluation Criteria in Solid Tumors (RECIST). Imaging was performed on suspicion of progression.

Results: Out of 50 patients, two (4%) patients have shown complete clinical response, 16 (32%) patient with partial response and 19 (38%) patients with stable disease. Disease progression was observed in 13 (26%) patients. Subset analyses revealed thirty-two (64%) patients with improvement in quality of life in terms of symptomatic control. Only 9 (18%) patients were observed with Grade 2 neutropenia, 4 (8%) patients with grade 2 anemia.

Conclusion: Single agent methotrexate was an effective alternative regimen for patients with locally advanced or metastatic head and neck cancers.

Keywords: Head and neck cancer, Methotrexate, Palliative chemotherapy.

INTRODUCTION

The head and neck cancers form the sixth most common cancer, globally, and is the most common cancer in developing countries[1]. Approximately 95% of head and neck cancers (HNC) are squamous cell carcinoma. Rare histologies include adenocarcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma[2]. In Pakistan, squamous cell carcinoma of oral cavity is the most frequently occurring malignancy in head and neck region[3]. Surgery or radiotherapy is the standard of care for early-stage head and neck cancers, whereas for advanced staged tumor usually both are required[4]. Adding of chemotherapy with other treatment modalities improve survival in patients treated with curative intent[5]. Locoregional recurrences or metastatic disease is the main reason of treatment failure[2]. Metastatic or locally advanced HNC are usually treated with palliative intent with single agent or combination chemotherapies, targeted therapies or supportive care only[6]. Optimal Treatment is based on performance status, prior treatment, symptoms, comorbidities, and logistics[7]. Low dose single agent methotrexate intravenously is an acceptable palliative chemotherapy option for recurrent, locally advanced or metastatic head and neck squamous cell carcinoma (HNSCC) particularly in patients with poor performance status and unfit for double agent chemotherapy[8]. Methotrexate is usually administered at 50 mg weekly and the dose is escalated up to 200mg/week as tolerated[9].

The Objective of this study was to evaluate the efficacy of single agent methotrexate in locally advanced and metastatic head and neck cancer[10]. It is also imperative to remember that

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palliative systemic therapy has not been appropriately demonstrated to improve overall survival. The recent meta-analysis suggested that methotrexate single agent appears to be a good choice, in view of ease of administration and lesser hospital visits.

METHODOLOGY

Fifty patients from Oncology outpatient department (OPD) at CMH, Rawalpindi, from January 2017 to July 2017, were selected after informed consent and permission from concerned authorities and Hospital Ethical review Committee in this quasi experimental study. Sample size of 50 was calculated using WHO sample size calculator with 95% confidence level, and 89% anticipation population. Non-probability consecutive sampling technique was adopted. All patients had locally advanced or metastatic head and neck cancers that were unfit for treatment with curative intent radical surgery, radiotherapy and/or double agent chemotherapy based on disease extent and/or general medical condition. All Patients with other concomitant malignant disease or who have already received any single agent chemotherapy were excluded. Cancer staging was done according to 7th edition of American Joint Committee of Cancer (AJCC) TNM classification. All the data were recorded and compared with pre-intervention data fortnightly commencing after first two cycles of methotrexate. Response assessment was done using Response Evaluation Criteria in Solid Tumors (RECIST). Minimum six cycles of methotrexate were received by a patient and the average number of cycles received by patients in the study was nine. Parameters used to measure efficacy included shrinkage/progression in tumor size and pain relief. Shrinkage/ progression in tumor size was assessed by clinical examination and/or imaging. Pain relief/ aggravation was measured on numerical rating scale. Imaging was performed on suspicion of progression[11,12]. Quality of life was measured using Eastern Cooperative Oncology Group performance status (ECOG PS) scale and frequency of hospital visits.

Patient Complete history, physical examination and clinical evaluation were done. Local examination and fiber optic laryngoscopy was conducted for the local extension of tumor as required. CT scan head, neck, and chest with upper abdomen were done for primary or metastatic disease at baseline and on suspicion of disease progression. Patients were given palliative chemotherapy with Methotrexate 50mg as a single agent intravenously weekly and dose was escalated up to a maximum of 200mg. Chemotherapy was continued until disease progression, un-acceptable toxicity and/or deterioration of general health. Median follow up time was 3 months. Symptoms of pain and any adverse events during chemotherapy were also recorded as per National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0-pain scale[13]. Before starting the regimen, the adverse effects of the methotrexate were explained to the patients. Clinical examination and complete blood counts were done before giving every infusion of metronomic chemotherapy. Pain management treatment given in the form of analgesics. Data analy-sis was done SPSS-19. Outcome was stratified in two groups i.e. patients achieving palliation (Complete response, partial response or stable disease) and those failing to achieve palliation with therapy. McNemar's test applied to post therapy outcomes related to pre-therapy status and results (fig-1 & table-II) were found to be statistically significant (p-value ≤0.05).

RESULTS

Fifty patients 42 (84%) males and 8 (16%) females) were selected for palliative weekly chemotherapy Methotrexate. Mean age was 66.5 ± 4.1 years (range: 32-76 years). Eighteen (36%) patients were smokers and 8 (16%) were smokeless tobacco (snuff) addicts. In the study Oral cavity was the primary site in 28 (56%) patients, whereas 10 (20%) patients with hypopharyngeal, 7 (14%) with oropharyngeal, 3 (6%) with laryngeal and two (4%) with maxillary sinus primaries. All the patients were histologically diagnosed squamous cell carcinoma, 44 (88%) patients had a

locally advanced residual or recurrent disease prior to start of single agent methotrexate. In the remaining, 6 (12%) patients had distant metastasis (table-I). Majority of the patients were associated with mild to moderate pain requiring analgesics before starting chemotherapy. Twelve (24%) patients had fungating local or nodal disease while trismus was present in 7 (14%) patients. Five patients had an interruption during treatment with Methotrexate. These treatment

Table-I: Patient and treatment characteristics.

Number of patients	50
Age (range)	32-76 years
Mean age	66.5 ± 4.1 years
Male	42 (84%)
Female	8 (16%)
Primary tumor site	
Oral Cavity	28 (56%)
Hypopharynx	10 (20%)
Oropharynx	7 (14%)
Larynx	3 (6%)
Maxillary sinus	2 (4%)
Histopathological Diagnosis	Squamous cell carcinoma
Locally Advanced	44 (88%)
Metastatic disease	6 (12%)
Previous treatment	
Surgery	11 (22%)
Chemoradiation	31 (62%)
Chemotherapy	14 (14%)

Table-II: Results of McNemar's test.

Pre Chemotherapy	Post Chemotherapy		*p*-value
	No Palliation	Palliation	
No Palliation	13	37	<0.001
Palliation	-	-	

interruptions were due to poor performance status. At completion of study period complete clinical regression was seen in two (4%) patients where as partial regression in tumor mass was recorded in 16 (32%) patients. Nineteen (38%) patients had stable disease. In these patients, both the size and the ulceration of the disease reduced or showed stable disease process. In the remaining 13 (26%) patients, there was documented disease progression for which methotrexate was stopped (fig-1). There was a good relief in pain was noted in 32 (64%) patients. None of the patients had any improvement in trismus. Speechand diet symptomatic improvement was observed in 19 (38 %) patients.

Treatment was generally well tolerated. Only nine (18%) patients developed grade 2 neutropenia, 4 (8%) patients experienced grade 2 anemia and 8 (16%) patients were observed with grade 2 Mucositis (fig-2). All the toxicities were effectively treated with supportive care management

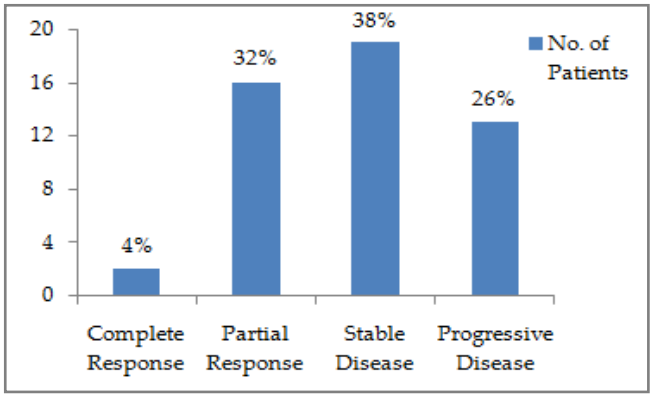

Figure-1: Treatment response of methotrexate.

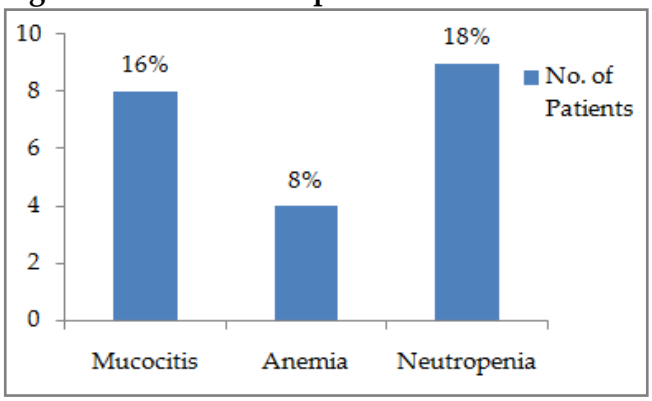

Figure-2: Toxicity of methotrexate.

and no hospitalization was required for any toxicity.

DISCUSSION

The limited treatment option, treatment-related toxicities, high incidence of recurrences and high morbidity makes head and neck cancers an attentive disease in our subcontinent. The management options for persistent or recurrent HNC in the previously treated patients with concurrent chemoradiation or chemotherapy are

limited[11-13]. Salvage surgery in selected patients is done resulting in a 2-year disease free survival of 36% (range 23%–55%)[9]. Re-irradiation in HNC has been occasionally explored because of fear of severe adverse effects[14]. Chemotherapy alone is considered an alternative treatment for residual or recurrent inoperable patients[15]. Response rate of palliative chemotherapy is 10%-40% and median survival rates are less than six months[16]. Multiple metronomic cytotoxic drugs have shown activity in head and neck cancer comprising methotrexate and 5-fluorouracil, as well as others, which shows overall response rate only of 22%[17]. There is a recent shift in focus on disease stabilization with single agent metho-trexate due to disease control comparable to the other therapies with better quality of life. Patil *et al* have reported a disease control rate of 67% and PFS of 21 weeks with low dose methotrexate based metronomic chemotherapy[18]. In contrary to these, our study revealed 36% over all response rate. Conversely, studies employing a higher dose of Methotrexate have failed to show any improvement in the overall survival as compared to standard weekly Methotrexate[19]. Combination chemotherapy has shown significant improvement in tumor response as compared to single agent therapy but with high-grade toxicity and no overall survival benefit has been demonstrated, thus sacrificing the quality of life of such patients[20]. In a phase II trial single agent methotrexate in recurrent HNC has shown high grade toxicities with Mucositis (16.6%), anemia (11.1%) and Neutropenia (11.1%)[21]. The toxicities observed with methotrexate chemotherapy in current study are Mucositis (16%) anemia (8%) and Neutropenia (18%), which were managed adequately. In the present study the most impressive finding is lack of any serious adverse reactions which makes it an ideal option.

CONCLUSION

Weekly methotrexate as single agent may be considered an effective alternative regimen in locally advanced or metastatic head and neck cancer patients particularly for elderly patients and those with poor performance status.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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