

## Palliative low dose fortnightly methotrexate in oral cancers: Experience at a rural cancer centre from India

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### Abstract

**Context:** Palliative fortnightly chemotherapy in oral cancers. **Aims:** We present our experience with a regimen employing fortnightly (once in 2 weeks) injectable methotrexate (MTX) (40 mg/m<sup>2</sup>) in a predominantly elderly cohort of patients with carcinoma of oral cavity and oropharynx. **Settings and Design:** Retrospective chart review conducted at a rural cancer center in India. **Materials and Methods:** All patients with oral cavity and oropharyngeal cancers started on treatment with fortnightly injectable MTX (40 mg/m<sup>2</sup>) between 01/01/2011 and 31/12/2011. **Statistical Analysis Used:** The factors analyzed included the duration of disease control, pain control, overall survival and progression free survival which were evaluated using the Kaplan Meier method. **Results:** A total of 60 patients with a median age of 66.5 years were analyzed. Majority of the patients had poor nutritional status, performance status or co-morbidities. MTX was given for recurrent disease in 19 patients and after initial palliative radiotherapy in 41 patients. The median number of cycles delivered was nine. Grade 3/4 toxicities were seen in 2 patients only. Disease control rate at the end of treatment was seen in 33 (55%) patients. Median overall survival was 34 weeks (interquartile range: 17-50 weeks). **Conclusions:** The fortnightly regimen of MTX was well-tolerated and showed a good clinical activity in this elderly cohort of patients with advanced oral cavity and oropharyngeal cancers.

**Key words:** Methotrexate, oral cancer, palliative chemotherapy, squamous cell cancers

### Introduction

Low dose injectable Methotrexate at a dose of 40 mg/m<sup>2</sup> weekly is a standard palliative chemotherapy option in head neck cancer.<sup>[1]</sup> Although platinum based doublet chemotherapeutic regimens have demonstrated improved response and disease free survival they do not result in an improvement in the overall survival.<sup>[2]</sup> In view of the better response and increased symptom free duration, platinum based doublet chemotherapy remains the standard chemotherapeutic regimen of choice for patients with a good performance status and young age. The EXTREME trial reporting an unprecedented 3 months improvement in the overall survival with the addition of Cetuximab to standard Cisplatin and 5-Fluorouracil.<sup>[3]</sup>

Unfortunately the high cost of Cetuximab, as well as the greater toxicity prevents regular use of this regimen in the our setting. In patients who are having a poor performance status, advanced age and co-morbidities or those who have had failure after platinum based chemotherapy options are more limited. In these circumstances use of single agent Methotrexate gives acceptable palliation of symptoms. The present study highlights our experience with a metronomic fortnightly regimen of injectable Methotrexate in a predominantly elderly population.

### Materials and Methods

The study protocol was approved by the Institutional Review Board, which allowed a consent waiver in view of the retrospective nature of analysis. This was a retrospective audit carried for patients started on palliative fortnightly MTX between 1<sup>st</sup> January 2011 and 31<sup>st</sup> December 2011. Patients were included if they had squamous-cell carcinomas originating in the oral cavity or the oropharynx irrespective of the initial treatment status. Patients should have received at least one

cycle of MTX to be considered eligible for this study in order to get data regarding compliance with the treatment schedule in addition to efficacy. Patients who were treated for second primaries, non-squamous-cell histology or other sites of origin were excluded.

The decision to start this regimen for an individual patient was taken after a multi-specialty board meeting involving the surgical, radiation, medical oncologists and the palliative care physicians where alternative treatment approaches including surgery and re-irradiation were fully discussed. In addition, potential logistical difficulties with a weekly regimen were also discussed. The regimen was started only for patients who provided consent and who had advanced unresectable disease or with poor performance status Eastern Cooperative Oncology Group (ECOG PS 2-3) and advanced age (60 or more) which precluded surgery or those who had failed after salvage treatment. Prior to each cycle, patients had their blood counts (hemoglobin, total count, platelet count and differential count) and renal function (urea and creatinine) checked. All patients received injection MTX at a dose of 40 mg/m<sup>2</sup> on 1 day and repeated every 14 days. No premedications were given. Treatment was continued until patient refusal, disease progression and general deterioration of health or death. During each cycle, MTX was administered as a bolus intravenous (IV) infusion over 10-15 min. At each visit, patients were jointly reviewed by the palliative care specialist and the treating oncologist in order to optimize pain control and symptom management. Patients received analgesics as per the World Health Organization analgesic ladder.

For each patient, we collected the clinical and demographic data regarding the disease stage, initial treatment and treatment at relapse. Patients were defined as elderly if the age was ≥60 years. Disease regression was assessed clinically at each visit with imaging performed only where progression was suspected clinically. Pain control was also evaluated from the clinical notes and date of pain progression was noted for these patients. Patients who had improved or stable pain were censored at the last date of follow-up. Median follow-up duration was calculated from a Kaplan Meier analysis of overall survival in which the censor and deaths were reversed. Overall survival and time to progression were calculated from the date of start of palliative chemotherapy.

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The cut-off date for the analysis was 15 October 2012. Patients who had not come for follow-up for longer than 1 month were called up to determine their status. If they could not be contacted through phone calls, they were presumed as dead of progressive disease on the date of their last follow-up. In addition, patients in whom there was clear evidence of disease progression or general deterioration were presumed dead if their last date of follow-up was greater than 2 weeks from the date of analysis. Other patients were censored on the last date of follow-up or the date at which they were called up whichever was later. Actuarial survival was calculated using the Kaplan Meier method along with the log rank test to compare the survival between categorical variables. Cox regression was used for multivariate analysis of factors influencing overall survival. Descriptive statistics for continuous variables included the median, range and the interquartile range (IQR). Bonferroni correction was applied to correct for bias arising out of multiple comparisons. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS, IBM Corporation, Armonk, New York, USA).

## Results

Between 1<sup>st</sup> January 2011 and 31<sup>st</sup> December 2011, 60 patients started palliative fortnightly MTX. The median duration of follow-up was 73 weeks. The median age of this cohort was 66.5 years (range: 40-94 years; IQR: 15.75). About 77% of the patients were above the age of 60 years. The complete demographic profile of the patient population is provided in Table 1. The majority of the patients belonged to the lower socio-economic stratum, with advanced stage oral cavity carcinomas at presentation. Buccal mucosa was the commonest sub-site (48.3%) followed by oral tongue (18.3%).

The initial treatment was given with curative intent in 29 (48.3%) and with palliative intent in 31 (51.7%). All patients treated with palliative intent radiotherapy received 20 Gy in 5 fractions. The details of the initial treatment taken are presented in Table 1 stratified according to the intent of treatment. All patients with Stage I disease were treated initially with curative intent. Six patients with stage III disease were initially treated with palliative intent treatment as they were elderly (median age 80 years, range 75-85 years) and had a poor performance status (ECOG 2 or more). All of them had disease in the oral cavity and surgery could not be done in view of age and associated co-morbidities. Two of these patients had poorly controlled diabetes; one had recent history of myocardial infarction while remaining three had severe chronic obstructive pulmonary disease. None of the patients had received neo-adjuvant chemotherapy.

55 patients (91.7%) had a local-regional residual disease or recurrence prior to start of MTX. In the remaining, 2 (3.3%) patients had distant metastasis and 3 (5%) patients were started on MTX at presentation as they had refused radiotherapy or surgery. In the 19 (31.6%) patients with recurrent disease the median time to recurrence was 21 months after the initial definitive treatment. 11 of these 19 (57.8%) patients with recurrent disease had in addition received some form of salvage treatment prior to starting MTX [Table 2]. However, by the

**Table 1: Details of initial treatment, patterns of recurrence and salvage treatment other than methotrexate**

Variable	Factor	Initial treatment intent (%)		Total (%)
		Curative	Palliative	
Initial treatment site	In reporting institute	11 (18.3)	26 (43.3)	37 (61.7)
	Outside	18 (30)	5 (8.3)	23 (38.3)
Surgery done	Yes	12 (20)	0 (0)	12 (20)
	No	17 (28.3)	31 (51.7)	48 (80)
Initial radiation type	Not given	4 (6.7)	3 (5)	7 (11.7)
	Definitive	18 (30)	0 (0)	18 (30)
	Adjuvant	7 (11.7)	0 (0)	7 (11.7)
Concurrent chemoradiation	Palliative	0 (0)	28 (46.7)	28 (46.7)
	No	22 (36.7)	31 (51.7)	53 (88.3)
Residual disease after radiotherapy	Yes	7 (11.7)	0 (0)	7 (11.7)
	No (recurrent disease)	10 (16.7)	31 (51.7)	41 (68.3)
Recurrence site (n=19)	Local	19 (31.7)	0 (0)	19 (31.7)
	Locoregional	13 (21.7)		
	Nodal only	2 (3.3)		
	Distant metastasis	2 (3.3)		
Salvage for recurrence other than methotrexate (n=19)	None	8 (13.3)		
	Palliative radiation	2 (3.3)		
	Definitive radiation	2 (3.3)		
	Surgery	5 (8.3)		
	Chemotherapy	2 (3.3)		

Percentages of the total number of patients (n=60) is provided in parentheses

**Table 2: Multivariate analysis of various prognostic factors influencing overall survival in the study population using cox regression method**

Variable	Category (n)	Hazard ratio	95% confidence intervals		P value
			Lower	Upper	
Age (<60)	≥60 (31)	0.942	0.48	1.87	0.87
Gender (female)	Male (33)	0.70	0.34	1.46	0.34
Income (BPL)	APL (8)	1.11	0.41	3.04	0.84
Initial stage (I)	III (9)	0.81	0.15	4.41	0.81
	IVA (37)	0.78	0.19	3.13	0.73
	IVB (11)	0.85	0.15	4.84	0.86
ECOG PS (2)	3 (23)	0.46	0.24	0.90	0.02
Co-morbidities (no)	Yes (37)	1.30	0.59	2.85	0.51
Nutritional status (good)	Fair (30)	0.59	0.23	1.56	0.29
	Poor (21)	0.63	0.24	1.69	0.36
Site (oral cavity)	Oropharynx (7)	3.04	1.01	9.20	0.04
Initial treatment at hospital (no)	Yes (37)	0.55	0.26	1.16	0.11
Methotrexate given for (initial treatment)	Recurrence (19)	1.26	0.25	6.36	0.78
	Residual (36)	1.88	0.35	10.13	0.46

The reference category for each variable is given inside parentheses.  $P=0.005$  taken as statistically significant after Bonferroni correction. Figures in parentheses in 2<sup>nd</sup> column represent the number of patients for each category. ECOG PS: Eastern cooperative oncology group performance status, BPL: Below poverty line, APL: Above poverty line

time of start of MTX all patients had recurred. Pathological confirmation of recurrence was obtained in all these patients prior to initiation of therapy.

Prior to starting MTX, severe pain requiring step III analgesics was present in all patients. In addition to this, mucosal ulceration due to disease was present in 54 (90%) patients. Eight patients (13.3%) had fungating local or nodal disease while severe trismus was present in 14 patients (23.3%).

The median durations between starting MTX after recurrence or palliative radiotherapy were 56 and 50.5 days respectively. The median number of MTX cycles delivered was 9 (range: 1-30, IQR: 9.75). The median total MTX dose delivered was 425 mg (range 50-1500 mg; IQR: 437.5 mg). Dose reductions in MTX were required in five patients due to toxicity and in these patients the median total dose delivered was 90% of the planned dose (range: 84-98%; IQR: 10%). Five patients had an interruption in the treatment with MTX. In these patients, the median duration of treatment interruption was 17 weeks (range: 1-29 weeks; IQR: 21 weeks). These treatment interruptions were due to treatment related toxicity in 3 patients while in two patients treatment was stopped on patient request after complete clinical regression. Nine patients wanted to continue treatment at a local palliative care center as they were unable to commute every 2 weeks. In the remaining patients, treatment was stopped because of disease progression in 22 (36.7%) and patient refusal in 12 (20%). 23 (38.3%) patients stopped treatment without informing us of the reason. Follow-up telephone calls in these patients revealed that two patients were still alive but not willing to continue further treatment while remaining 21 patients had died with a median time to death of 3 weeks after the last visit.

At the end of treatment, the disease control was maintained in 33 (55%). Complete clinical regression was seen in 2 (3.3%) patients, whereas partial regression and static disease were seen in 9 (15%) and 22 (36.7%) patients respectively. In these patients, both the size and the ulceration of the disease reduced or remained static. In one patient with a good regression salvage surgery was done and the patient is presently disease free at last follow-up (13.5 months post-surgery). In the remaining 27 (45%) patients, there was documented disease progression at the end of the last cycle for which MTX was stopped. Pain was controlled without requiring increasing doses of morphine till the last follow-up in 34 patients (56.7%). The median duration of pain control without increased opiates was 57 weeks (IQR: 21-85 weeks) from start of palliative MTX [Figure 1]. While good relief in pain ulceration and fungation was noted in the responding patients none of the patients had any improvement in trismus.

At the end of last follow-up, 8 (13.3%) patients were alive out of which 2 patients who had a complete clinical regression

were also disease-free. The median overall survival for the entire population was 34 weeks (IQR: 17-50 weeks). The proportion of patients surviving at the end of 6 months and 1 year were 65% and 19% respectively. The median progression free survival after starting MTX was 25 weeks (IQR: 11-40 weeks) [Figure 1].

Multivariate analysis with Cox regression showed that the initial performance status and disease site were significant predictors of overall survival [Table 2]. After Bonferroni correction, none of the variables were found to have a statistically significant influence on the survival.

Treatment was generally well-tolerated with Grade 3-4 toxicity limited to neutropenia in two patients. None of the patients had derangement of hepatic or renal function during treatment. Table 3 details the various toxicities experienced by the patients. All toxicities were graded following the Common Terminology Criteria for Adverse Events version 4.02 grading schema. None of the patients required hospitalization for any toxicity.

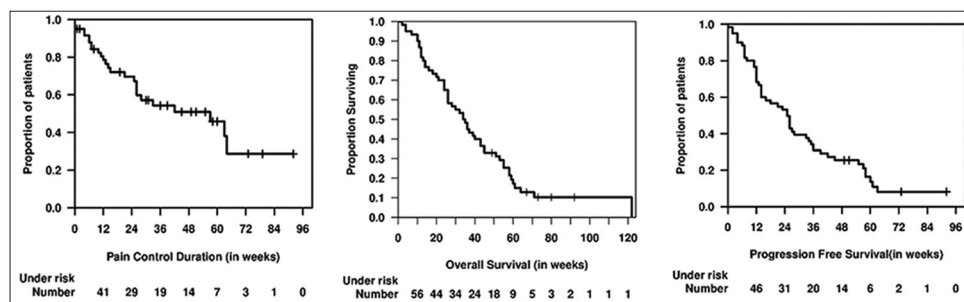
## Discussion

Results from various prospective studies [Table 4] show that IV Methotrexate is associated with an overall response rate in the range of 15%-25% and a disease stabilization rate of 40-60%. The median overall survival reported in these studies is less than 30 weeks.<sup>[1,2,4-8]</sup> All these studies were phase II/III trials comparing Methotrexate against a variety of other chemotherapeutic agents and combination chemotherapy. None of the studies demonstrated a clinically significant improvement in the overall survival over and above that produced by Methotrexate alone.

The skewed distribution of major cancers centres concentrated in and around urban centres results in several logistical and financial challenges for the patients hailing from rural areas when weekly treatments are advised. In the present study around 40% patients stopped coming to the hospital for treatment once their disease started progressing or when they became asymptomatic. Hence the present fortnightly regimen was given in these patients.

**Table 3: Frequency of various toxicities experienced by the patients during treatment with methotrexate**

Toxicity	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Anaemia	49 (81.7)	1 (1.7)	10 (16.7)	0 (0)	0 (0)
Neutropenia	57 (95)	0 (0)	1 (1.7)	1 (1.7)	1 (1.7)
Thrombocytopenia	59 (98.3)	0 (0)	1 (1.7)	0 (0)	0 (0)
Mucositis	57 (95)	0 (0)	2 (3)	0 (0)	0 (0)



**Figure 1: Kaplan Meier Survival curve of duration of pain control (panel A), overall survival (panel B) and progression free survival (panel C) in weeks. Numbers in the bottom of the figure represent the number at risk**

**Table 4: Results of single agent methotrexate based chemotherapy arms from various randomized studies**

Author	Year	Number (% MTX)	Median age (years)	PS 0-1 %	OC %	1° Rx by MTX %	Disease control rate %	Median* survival (weeks)
Deconti <i>et al.</i> <sup>[1]</sup>	1981	237 (34)	58	67	36	3	52	22
Hong <i>et al.</i> <sup>[4]</sup>	1983	44 (50)	60	23	41	0	41	24.4
Forastiere <i>et al.</i> <sup>[2]</sup>	1992	277 (88)	60	72	NR	9	60	22.4
Schornagel <i>et al.</i> <sup>[5]</sup>	1995	264 (50)	NR	95	32	6	47	25.6
Pivot <i>et al.</i> <sup>[14]</sup>	2003	139 (33)	62	NR	24	0	41	12.4
Guardiola <i>et al.</i> <sup>[7]</sup>	2004	57 (40)	56	NR	5	NR	40	15.6
Stewart <i>et al.</i> <sup>[15]</sup>	2009	486 (33)	NR	76	32	0	48	26.8
Present study	2012	60 (100)	66.5	0	88	5	55	34

MTX=Methotrexate, % MTX=Percentage of total patient receiving methotrexate alone, PS=Performance status, % OC=Percentage of patients with oral cavity primaries, 1° Rx by MTX=Initial treatment with methotrexate, Disease control rate=Complete response, partial response plus static disease, NR=Not recorded. \*Median survival extrapolated from survival curve

One study published by Campbell *et al.* in 1987 compared such a fortnightly regimen with cisplatin, cisplatin -5FU and Methotrexate and 5-FU.<sup>[9]</sup> In this study of 200 patients divided in four arms showed that the fortnightly regimen of Methotrexate results in a disease control rate of 38% and a median overall survival of around 4 months (extrapolated from the survival curve). However only 28% of the patients had oral cavity disease in this cohort with a mean age of 65 years.

In the present study fortnightly Methotrexate gave encouraging results in a cohort of mainly elderly patients with oral cavity cancers. The overall survival and disease control rates are comparable to other studies despite the low dose density achieved due to fortnightly administration. In a small study Patil *et al.* have reported a disease control rate of 67% and PFS of 21 weeks with low dose methotrexate based metronomic chemotherapy.<sup>[10]</sup> Conversely studies employing a higher dose of Methotrexate have failed to show an improvement in the overall survival as compared to standard weekly Methotrexate.<sup>[11]</sup> The biological reason for this apparent difference may be related to the finding that the dihydrofolate reductase content in human squamous-cell carcinomas is low and easily saturable by even low doses of Methotrexate.<sup>[12,13]</sup>

The present study has several weaknesses inherent in its retrospective design. Systematic evaluation of quality of life or pain scores was not done. Most of the disease regression is noted clinically which gives a more generous estimate of the response. Also due to the retrospective nature of data analysis toxicity is likely to be underestimated. The better survival experienced by patients may also be due to large majority of these patients had non metastatic disease and oral cavity cancers, both factors known to be associated with a better survival in some studies.<sup>[1,9]</sup>

In order to minimize the potential of a selection bias for this study we have analysed the results of all patients with oral cavity and oropharyngeal tumors who had started Methotrexate within a one year period irrespective of the number of treatments taken. However given the retrospective nature of the study selection bias cannot be ruled out.

The strength of the present study is that the study patients are representative of head neck cancers encountered in our country with a preponderance of buccal mucosal cancers. Fortnightly Methotrexate has encouraging activity along with a low toxicity profile in such patients. Given the high incidence of these cancers in our country this cheap, well tolerated and effective palliative chemotherapy regimen merits further evaluation in well designed prospective trials.

## Conclusion

Fortnightly Methotrexate shows good clinical activity in this subset of oral cavity cancers in a predominantly elderly patient cohort from the Indian subcontinent. The cheap and easily administered regimen has good disease control rates as well as low levels of toxicity. In addition the fortnightly nature of visits has logistical and economic benefits for a rural population with limited financial resources. We do intend to test this schedule against other metronomic schedules in our population in the coming months.

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## News

### Warning / Breaking News

#### CT Scans in NHL Surveillance Causes More Cancers

Abstract BSSUB-3488 presented on 30<sup>th</sup> June 2014 at the 19<sup>th</sup> Congress of the European Hematology Association (EHA) showed that patients with non-Hodgkin's lymphoma who have received 8 or more CT scans have a 2-fold risk for secondary primary malignancies (hazard ratio, 2.23; 95% confidence interval, 1.60 - 3.11;  $P < .001$ ). Notably, the risk appeared to be dose-dependant. With each additional CT scan, the risk for a secondary primary malignancy increased 3%.

Data was based on nationwide population-based study evaluated 4874 patients with non-Hodgkin's lymphoma who received curative-intent treatment from January 1997 to December 2010 wherein 180 secondary primary malignancies were identified.

“The incidence of secondary-cancer origin from breast, stomach, and liver is higher in patients with more CT scans,” according to Sheng Hsuan Chien, Taipei Veterans General Hospital, Taiwan.

#### Sites of Secondary Primary Malignancies

Cancer	Hazard Ratio	95% Confidence Interval	P Value
Breast	11.22	1.47–85.64	.02
Stomach	5.22	1.17–23.23	<.03
Hepato-Biliary Tract	2.18	1.00–4.73	.049

Physicians must assess the timing of CT scans more carefully and avoid the overuse of CT scans in cancer patients. “I certainly do fewer CT scans now than I did 10 years ago, based on a better understanding of radiation exposure issues,” Dr. Kahl noted.

James O. Armitage, MD, Joe Shapiro Distinguished Chair of Oncology at the University of Nebraska Medical Center in Lincoln, says there is no convincing evidence supporting the use CT imaging in the surveillance of lymphoma patients. “Our team doesn't do routine surveillance imaging because there's simply no benefit from it,” he said.

The potential drawbacks extend beyond unnecessary radiation exposure. An abnormal reading on a surveillance image is often more likely a false positive, and that can lead to biopsies that don't need to be done, or even worse — therapy for disease that's not even there.

Rita Redberg, MD, MSc, director of Women's Cardiovascular Services at the University of California, San Francisco Medical Center, summed up, “... we need to evaluate every test — and in particular imaging tests that use ionizing radiation — such that the benefits of this test will outweigh the risks, and we've considered alternatives ...”.