

# Retrospective study of metronomic chemotherapy in advanced NSCLC at a tertiary centre in south India

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## Abstract

**Background:** Chemotherapy and immunotherapy are the backbone for treatment of most NSCLC (non small cell lung cancer). But many patients are not able to tolerate chemotherapy and not able to afford immunotherapy in our scenario.

**Objective:** The aim of this retrospective study was to assess the clinical activity and toxicity profile of metronomic therapy with cyclophosphamide and etoposide in advanced NSCLC.

**Material and methods:** Fifty patients were treated (20 treatment naive patients, 10 as second line therapy and 20 as maintenance therapy) between Feb 2015 and Feb 2018. Patients were given tab cyclophosphamide 50 mg once daily and Cap. Etoposide 50 mg alternate days continuously till disease progression. Patients were assessed for treatment response in the form of progression free survival.

**Results:** The median age was 65 years. The median duration of treatment was 6 months. Response was seen in form of stable disease only, in 16 patients. Median progression free survival was 4 months in treatment naive, 7 months in setting of maintenance therapy and 3 months in second line setting.

**Conclusion:** In resource limited setting, metronomic chemotherapy is useful in advanced NSCLC. This is an affordable regimen which has minimal toxicity with promising survival.

**Keywords:** NSCLC, metronomic therapy

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## 1. Introduction

Lung cancer is the leading cause of cancer mortality worldwide [1]. Nearly 70% are diagnosed with advanced disease at presentation [2]. Approximately 85% of lung cancers are NSCLC (non small cell lung cancer). Intravenous chemotherapy and immunotherapy are now the standard treatment regimes for advanced NSCLC. The problem with intravenous chemotherapy is that many elderly patients do not tolerate platinum doublet and immunotherapy is too expensive for most patients. Hence the need for non toxic, affordable regimen arises. Metronomic chemotherapy has been studied extensively in multiple cancers; however studies in lung cancer are lacking [3].

Our study aimed to study the effect of metronomic therapy in advanced lung cancer patients.

## 2. Materials and methods

This retrospective study was done at the department of medical oncology, Yenepoya medical college Mangalore. Data of cases of advanced NSCLC on metronomic chemotherapy during a period of three years from Feb 2015 to Feb 2018 was collected from the medical case records. Histologically confirmed cases of advanced NSCLC on metronomic chemotherapy, over the age of 18 years of either gender were included. The age, sex, epidermal growth factor receptor (EGFR) status, anaplastic lymphoma kinase (ALK) status, co morbidities, eastern cooperative oncology group performance status (ECOG PS), number of metastatic sites and whether treatment was in first line setting or maintenance therapy or recurrent setting was noted. Metronomic chemotherapy consisted of combination of tablet cyclophosphamide 50 mg given once

daily with Capsule Etoposide 50 mg given on alternate days continuously till disease progression. A semi-structured Performa was used to collect information from the medical case records. Records were checked for any evidence of toxicity and response to the treatment regimen. Patients were assessed for treatment response in the form of progression free survival and also assessed for drug toxicities.

## 2.1 Statistical analysis

Data was entered in Microsoft Office Excel worksheet and analyzed using statistical software SPSS version 17.0. For qualitative data, Chi square test was used and  $P$  value  $<0.05$  considered statistically significant.

## 3. Results

Case records of NSCLC patients admitted during a period of Feb 2015 to Feb 2018 revealed that 50 cases were eligible for this study after satisfying the inclusion and exclusion criteria. Of these twenty patients were treatment naive, ten patients were treated as second line therapy and twenty patients received metronomic therapy as maintenance therapy. The patient characteristics are shown in Table 1. The median age of study population was 65 years (range 51-82 years). Majority of the study population were males (40 out of 50). Adenocarcinoma and squamous cancer accounted for 64% and 20% respectively. EGFR testing was done in 12 patients and 5 patients (nearly 41%) were positive, these patients received first line tyrosine kinase inhibitors and on progression received metronomic therapy. ALK testing was done in 5 patients all of them were negative.

### 3.1 Survival

The median duration of treatment was 6 months. Response was seen in form of stable disease only, in 16 patients. Median progression free survival was 4 months in treatment naive, 7 months in setting of maintenance therapy and 3 months in second line setting (Figure 1).

### 3.2 Toxicities

The median number of months of treatment for all patients was 5 months (Range 1-24 months). The most common toxicities were hematologic. 6 patients developed neutropenia (Grade 1-2 in 5 patients and Grade 3-4 in one patient). No treatment discontinuation was seen due to toxicity; no treatment-related death was reported.

## 4. Discussion

This study assessed the clinical efficacy and toxicity of metronomic therapy in patients with advanced NSCLC. The use of standard chemotherapy in elderly lung cancer patients is associated with significant toxicities resulting in poor quality of life. Metronomic chemotherapy works by antiangiogenic mechanism. These regimens usually use lower dose of chemotherapy agents, lower than their maximal tolerable dose [4].

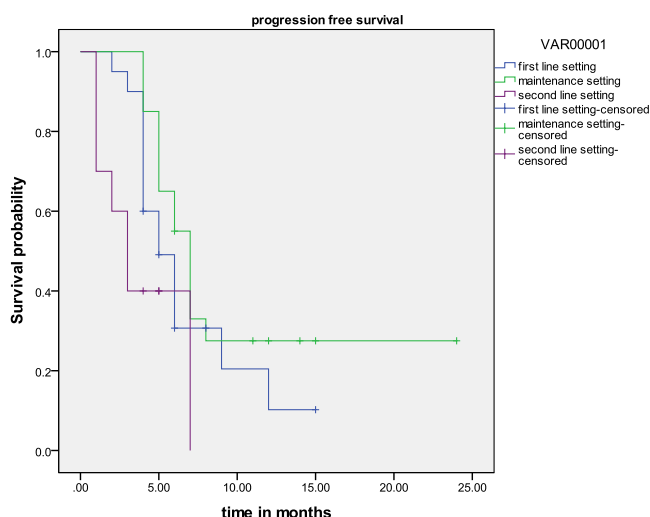
Different regimens of metronomic therapy have been tried in lung cancer. These include drugs like etoposide, cyclophosphamide, vinorelbine and paclitaxel [5]. Metronomic paclitaxel is associated with significant anemia (8%) neutropenia (5.4%) and sensory neuropathy (5.4%)[6]. Metronomic vinorelbine is associated with significant anemia (44%), fatigue (32%) and diarrhea (10.5%) [7]. These are not seen with the above regimen. Compared to other regimens which are intravenous, this regimen has less frequent admission, lesser side effects making it desirable for elderly patients who have to travel long distance for health care facility and being very affordable[4].

There are several studies looking at survival with metronomic therapy. Most studies have compared it in first line and second line setting, resulting in a progression free survival of 3-6 months [8],[9]. We also looked at role this combination in maintenance regimen. Compared to other regimens, this had better results than most single agent (4.8 months in FLEX study, 4.4 months in PARAMOUNT study)[12],[13] but inferior survival than combination maintenance regimen like bevacizumab with pemetrexate (10.2 months PFS in AVAPERL study and 12.8 months PFS in POINTBREAK study)[10],[11].

Metronomic chemotherapy is not a standard treatment protocol for lung cancer patients due to lack of prospective randomised clinical trials. In resource limited setting, metronomic chemotherapy is useful in advanced NSCLC. This is an affordable regimen which has minimal toxicity with promising survival.

**Table 1: Patient characteristics**

	Number of patients
Age:	Median
Sex	
Male	40
female	10
EGFR status	
Not known	38(76%)
Test done in (positivity)	12(41%)
ALK status	
Test done in (positivity)	5(0%)
Performance status	
PS:0-1	41(82%)
PS: 2 and above	9(18%)
Line of therapy	
First line	20(40%)
Maintenance setting	20(40%)
Recurrent setting	10(20%)
Smokers	35(70%)
Histology	
Squamous	10(20%)
Adenocarcinoma	32(64%)
Poorly differentiated cancer	8(16%)

**Figure 1: Survival with metronomic therapy**

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