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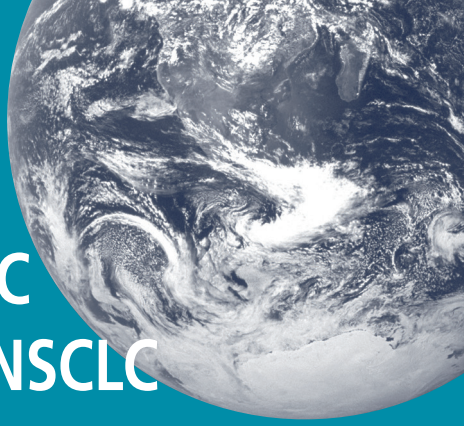

EFFICACY STUDY OF METRONOMIC CHEMOTHERAPY IN METASTATIC NSCLC AND CORRELATION WITH VEGF AND THROMBOSPONDIN LEVELS

S. BJ[1], B.P. LALKOTA[1], V.H. VELDHORE[2], R. RAO[3], R.NAIK[1]

[1]Medical Oncology, HCG Cancer Speciality Centre, Bangalore, India.
[2]Molecular Pathology, HCG Cancer Speciality Centre, Bangalore, India.
[3]Statistics and Research; HCG Cancer Speciality Centre, Bangalore, India.

Abstract – *Objective:* *The best treatments for metastatic lung cancer patients are palliative.We evaluated the effects of metronomic chemotherapy on survival outcomes in this population.*

Patients and Methods: *Thirty-four subjects with treatment refractory (n=26) and treatment naïve (n=7) metastatic lung cancer were included in an open-label single arm efficacy study of metronomic chemotherapy. Patients were given a chemotherapy regimen of Tab. Cyclophsophamide 50 mg once daily and Cap. Etoposide 50 mg once daily, 3 weeks on and one week off in 28 day cycle over a minimum period of 3 months or until the progression of their disease whichever was earlier. Patients were assessed for treatment response using RECIST Criteria (version 1.1) and duration of progression-free survival and overall survival. Data were analyzed using Kaplan Meir survival analysis.*

Results: *The mean age of the study population was 63.4±11.2 years. The mean duration of metronomic chemotherapy was 94.9±60.4 days. Overall 64.7% had progressive disease and 26.5% had stable disease. There was a significant improvement in overall survival in those with ECOG performance status of 1 compared to ECOG status of 2 (median survival=240* vs. *52 days, Log Rank Mantel Cox=11.32,* p=*0.001) and pathology grade 2 compared to grade 3 (median survival=200* vs. *37 days, Breslows Wilcoxon=5.76,* p=*0.02) and stable disease on RECIST compared to progressive disease following metronomic chemotherapy (median survival=360* vs. *50 days, Log Rank Mantel Cox=8.68, =0.003). There was also a significant improvement in progression-free survival in those with ECOG performance status of 1 compared to ECOG status of 2 (median survival=98* vs. *52 days, Log Rank Mantel Cox=6.62,* p=*0.001) and in grade 2 compared to grade 3 disease (mean survival=97* vs. *32 days, Log Rank Mantel Cox=4.73,* p=*0.03). Tumor load and multiple organ sites of disease did not seem to influence survival.*

Conclusions: *The results suggest stable response in about one third of study population, favorable progression-free and overall survival rates following metronomic chemotherapy. Performance status is an important predictor in this category of population. VEGF and TPS levels don't correlate clinically.*

KEYWORDS: *Metronomic Chemotherapy, Cyclophosphamide, Lung Cancer, Etoposide, VEGF, Thrombospondin.*

INTRODUCTION

Conventional chemotherapy is given once in every three weeks or two weeks at maximum tolerated dose. Drug-free interval is given to allow normal proliferating cells to recover. Metronomic chemotherapy is a continuous or frequent administration of cytotoxic agents at low doses. Extended breaks are not given in between[1]. Generally, metronomic chemotherapy is said to have low or no toxicity to normal proliferating cells. They have selective activity against tumor vasculature.

Corresponding Author: Srinivasa BJ, MD; e-mail: sripav77@yahoo.co.in

Tumor angiogenesis is inhibited, mainly by selective inhibition of tumor endothelial proliferation. It induces increase in endogenous angiogenesis inhibitor-thrombospondin levels. It also prevents mobilization of circulating endothelial progenitor cells from bone marrow. Another mode of action is by immunomodulation, that is selective depletion of T_{REG} cells. Tumor dormancy or direct cytotoxicity is other postulated mechanism of action of metronomic chemotherapy. Many cytotoxic drugs have this property of anti-angiogenesis including drugs used in this study[2]. Preclinical[3-6] and clinical studies[7-9] have established the benefits of metronomic chemotherapy in metastatic lung cancer. Oral chemotherapy drugs used in our study- cyclophosphamide and etoposide in lung cancer, cause selective inhibition of endothelial proliferation and induce apoptosis. Studies with oral cyclophosphamide and etoposide combination are limited. Hence, efficacy of this combination is addressed in this study. Combination of cyclophosphamide and etoposide used in this study is based on southwest oncology group[9]. Daily oral cyclophosphamide at 50 mg and etoposide at 50 mg for 21 day once in 28 days is used, which is slightly different from the dose and schedule of original study. Toxicity of this therapy is mild and will not give treatment interruptions as in conventional dosing. Various biomarkers of angiogenesis for response, predicting or to prognosticate the disease have been described, but no validated surrogate markers exist. Lung cancer is the most common leading cause of cancer deaths in both males and females worldwide. Non-small cell lung cancer (NSCLC) constitutes around 80% of lung cancer cases[10]. About half of them present more with stage IIIB or IV, where curative surgery is not possible. It comprises of adenocarcinoma, squamous, large cell, small cell and other not specified with increased frequency of adenocarcinoma[11]. Smoking is estimated to be the strongest risk factor in approximately 90% of patients[12] TNM stage at presentation has strong impact on prognosis. Survival decreases from median of 59 months in stage I disease to 4 months in stage IV disease[13]. Performance status (PS) and smoking are two independent risk factors of overall survival[14]. Prognosis depending on histopathology and degree of differentiation is uncertain[15]. Moreover, treatment is complicated by associated comorbidities such as coronary artery disease, hypertension, diabetes and chronic obstructive pulmonary disease. Stage IIIB and IV disease are generally treated with systemic chemotherapy or symptom based palliation if PS is poor[12]. Cytotoxic chemotherapy with platinum doublets is recommended as standard treatment for these patients[16]. Patients with metastatic NSCLC, visiting or referred to our center, were offered metronomic chemotherapy.

PATIENTS AND METHODS

Study design

It is a prospective, single arm, efficacy study of metronomic chemotherapy drugs in metastatic NSCLC patients. After Ethical Committee clearance, 34 patients with NSCLC were enrolled in the study from May 2011 to December 2012.

Study population

Inclusion criteria:

1. Patients ≥18 years of age;
2. Histologically confirmed NSCLC;
3. Metastatic disease;
4. Measurable disease, as defined by RECIST criteria;
5. ECOG PS 0-2 (Karnofsky PS 60-100%);
6. Life expectancy > 6 months;
7. Leukocytes ≥ 3,000/μL, absolute neutrophil count ≥ 1,500/μL, platelet count ≥ 100,000/μL, hemoglobin ≥ 9.0 g/dL;
8. Adequate hepatic function, defined as follows: total bilirubin ≤ 1.5 x ULN; aspartate aminotransferase (AST) ≤ 3 × ULN (or ≤ 5 x ULN if liver metastases); alanine aminotransferase (ALT) ≤ 3 x ULN (or ≤ 5 x ULN if liver metastases);
9. Creatinine normal OR creatinine clearance ≥ 60 mL/min.
10. Women of childbearing potential must agree to use adequate contraception (as per institutional standard of care) during treatment and until 6 months after the last administration of investigational drugs.

Exclusion criteria:

1. Women who are pregnant or breastfeeding or patients of childbearing potential without being tested for pregnancy at baseline or with a positive test;
2. Those on other antiangiogenic therapies;
3. Presence of exclusively non-measurable disease (i.e.: exclusive bone disease with non-representative tumor markers);
4. Unwillingness or inability to comply with study requirements;
5. Other concurrent investigational agents within 3 months of starting the therapy;
6. Concurrent combination anti-retroviral therapy for HIV-positive patients.

Medicinal product (dose/route/regimen)

Capsule Etoposide 50 mg/day for 3 weeks on and one week off. Tablet cyclophosphamide 50 mg/day daily.

Statistical Analysis

Data were analyzed using SPSS version 16 for windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics using proportions were analyzed by frequencies and percentage. Pearson X^2 analysis was used to analyze the effect of predictor variables such as T size, stage on response rates. Kaplan Meier survival analysis was carried out with predictor variables such as stage, tumor load, PS, pathologic grade for disease-free and overall survival. Paired *t*-test was used to analyze VEGF and thrombospondin levels within lung and breast groups and independent samples test was used to analyze changes in VEGF and thrombospondin levels, following metronomic chemotherapy between responders and non-responders.

RESULTS

Thirty-four patients were enrolled for the study from May 2011 to December 2012. The mean age of the study population was 63.4 ± 11.2 years. Thirteen patients were more than 70 years old (Table 1).

Response: the mean duration of metronomic chemotherapy was 94.9 ± 60.4 days. Overall 24 patients (70.5%) had progressive disease and 10 patients (29.4%) had stable disease. There was no complete or partial response. Response rates in different subpopulation of study patients are summarized in Table 2.

Survival: median overall survival of all study population was 150 days (95% CI, 65 to 234 days). Ten patients (29.4%) were alive and 21 patients (61.8%) were dead at the end of 20 months of follow-up with 3 patients lost to follow-up. Median overall survival in stable disease patients is 360 days (95% CI, 177 to 542 days) and 50 days (95% CI, 23 to 76 days) in progressive disease patients (p = 0.03). Median overall survival of ECOG PS of 1 is 240 days (95%CI, 160 to 390 days) and 52 days (95% CI, 0 to 120 days) in patients with ECOG status of 2 (p = 0.001). Median overall survival in pathology grade 2 patients is 200 days (95%CI, 106 to 293 days) and 37 days (95% CI, 19 to 54 days) in pathological grade 3 patients (p = 0.02). Progression-free survival in patients with ECOG PS of 1 is 98 days (95% CI, 61 to 134 days) and 52 days (95% CI, 11 to 92 days) in ECOG 2 status (p = 0.001). Median progression-free survival in pathological grade 2 patients is 97 days (95% CI, 84 to 109 days) and 32 days (95% CI, 26 to 37 days) in grade 3 (p = 0.03). Median overall survival in patients with tumor load <10 cm was 160 days (95% CI, 37 to 282 days) and 95 days (95% CI, 1 to 189 days) in patients with tumor load > 10 cm (p = 0.366) (Figure 1).

TABLE 1. Base line characteristics.

Strata	*N° of patients (n)*	*Percentage*
No of patients	34	
Age in years (range)	63.25 (35-82)	
Gender		
– Male	25	73.5
– Female	9	26.9
ECOG performance status		
– 1	21	61.8
– 2	13	38.2
Smoking		
– Yes	22	64.4
– No	11	32.4
Previous chemotherapy		
– No	7	20.5
– Yes	27	79.4
No. of lines of chemotherapy		
– 1st line	24	70.5
– 2 or more lines	10	29.4
Histology		
– SCC	11	32
– Adenocarcinoma	21	61
– Poorly differentiated	2	5.8
Pathological grade		
– 2	7	79.4
– 3	27	20.6
N° of metastatic lesion		
– <2	14	41.1
– >2	20	58.8
Site of metastasis		
– Bone	14	41.1
– Brain	7	20.5
– Pleural effusion	13	38.2
Total tumor burden		
– >10 cm	20	58.8
– <10cm	14	41.2
Co morbidities		
– Yes	17	50
– No	17	50
EGFR mutation status		
– Not known	26	76.5
– Positive	6	17.6
– Negative	1	2.9

TABLE 2. Responses in different subpopulation of study patients in metastatic NSCLC; SD: Stable disease; PD: Progressive disease.

Category	*N*	*Stable disease (SD) n (%)*	*Progressive disease (PD) n (%)*	*Chisquare value*	*p-value*
Overall response	34	10 (29.4)	24 (70.5)		
Chemo naïve	7	0 (0)	7 (100)	2.727	0.09
Chemo refractory (received one or two lines of chemotherapy)	27	10 (37)	17 (63)		
Adenocarcinoma	19	6 (19.4)	13 (41.9)	1.09	0.58
Squamous cell carcinoma	7	1 (3.2)	6 (19.4)		
Poorly differentiated	5	2 (6.5)	3 (9.7)		
No tobacco consumption	11	5 (13.3)	6 (23.3)	0.835	0.36
Tobacco consumption in any form	21	5 (13.3)	16 (14.3)		

Toxicity: overall toxicity was observed in a total of 9 patients (25.6%). Hematological toxicity was observed in 8 patients (22.84%), with grade 1 and 4 (one patient each) and grade 2 and 3 (3 patients each). There was no anemia or thrombocytopenia. One patient developed asymptomatic hyperpigmentation of palms and soles, which gradually resolved.

BIOMARKERS OF ANGIOGENESIS

Serum VEGF and thrombospondin levels in metastatic NSCLC at baseline and 3 months after treatment are summarized in Tables 3, 4, and 5.

DISCUSSION

Treatment of metastatic NSCLC with daily oral cyclophosphamide 50 mg and capsule etoposide 50 mg for 3 weeks on, and one week off, was given to 34 patients. Results suggest stable disease as the main response rate in 29.4% of study population. There was no complete CR or PR. No single stable response was observed in chemo naïve patients but 37% of pre-treated patients had stable disease. There was no significant response difference in patients on histology, PS and tumor load. Median overall survival of the study population was 150 days. There was a significant improvement in overall survival in stable disease patients compared to progressive disease patients. Patients with ECOG 1 PS had both improved overall and progression-free survival compared to ECOG 2 patients. Patients with pathological grade 2 also had improved overall and progression-free survival compared to grade 3 histology. Tumor load did not influence survival rates. There is no significant correlation of serum VEGF levels TSP levels before and after chemotherapy. There is no significant decrease in VEGF levels and increase in TSP levels after therapy. Also, there is no significant correlation of biomarker levels in

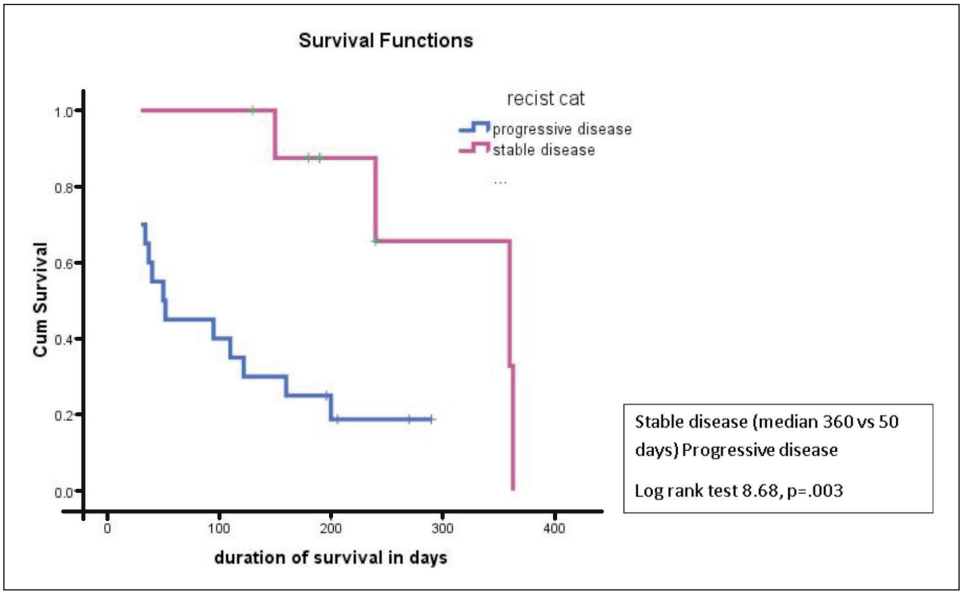

Fig. 1. Overall survival and response rates.

TABLE 3. Results of VEGF and thrombospondin (TSP) levels.

Serum biomarker	*n*	*Pre chemo-therapy (Mean ±SD)*	*Post chemo-therapy (Mean ±SD)*	*Difference (Mean ± SD)*	*t Test*	*p-value*
VEGF	11	145.8±90	144.9±116	.94± 70.3	-.044	.96
TSP	11	77.6±37.9	60.7±37.9	16.9± 55.1	1.02	.33

TABLE 4. Results of VEGF and thrombospondin (TSP) levels.

Response category	*N*	*Pre chemo VEGF levels in pg/ml (Mean ±SD)*	*Post chemo VEGF levels in pg/ml (Mean ±SD)*	*Percentage of change*	*t Test*	*p-value*
Progressive disease	6	150±34	116±53	33.8800	-.2.01	0.07
Stable disease	4	163±147	213±170	-49.5850		

TABLE 5. Results of VEGF and thrombospondin (TSP) levels.

Response category	*N*	*Pre chemo VEGF levels in pg/ml (Mean ±SD)*	*Post chemo VEGF levels in pg/ml (Mean ±SD)*	*Percentage of change*	*t Test*	*p-value*
Progressive disease	6	84±36	45±35	38.6317	-1.06	0.31
Stable disease	4	78±43	75±39	3.2125		

responding and non-responding patients. SWOG[9] observed complete response in 3% patients and partial response in 9% patients giving objective response of 12% in 64 patients treated with above combination. All patients were chemo naïve in this study, compared to only 7 patients (20%) in our study. Hence, stable response of 29.4% observed in our study is comparable. Median survival was 5 months, which is encouraging in heavily pre-treated patients in our study compared to 6 months in chemo naïve patients. The dose intensity of both drugs for a single cycle in our study is more compared to the original study, which is justifiable in these pre-treated patients (Figure 2). Waits et al[17] observed partial response rate of 23% with single agent etoposide in 22 patients of chemo naïve NSCLC. Saxman et al[18], observed only 4% partial response in advanced chemo naïve NSCLC patients. Our study used two drugs combination and had stable disease as main response in chemo refractory patients. Toxicity profile observed in our regimen is mild with asymptomatic grade 4 and grade 3 neutropenia observed only in 1 and 3 patients, respectively, without anemia and thrombocytopenia. This is comparable to above studies and is in contrast to the regimen of oral etoposide and intravenous carboplatin combination, which had more thrombocytopenia as reported by Walls et al[19]. Limitations of the study are a smaller sample size, no control arm and failure to assess quality of life. Platinum agents are not used in metronomic dosing as a backbone, which is the current standard of treatment in patients with metastatic NSCLC using conventional doses. There are conflicting reports of VEGF[20-21] levels and limited reports on thrombospondin[22] levels that it correlates with anti-angiogenic effect of metronomic chemotherapy in metastatic NSCLC patients. This study also was not able to draw any firm conclusion. It requires larger sample size to observe small difference in serum levels, which our study is lacking. It is suggested that stable disease or time to progression should be the clinical endpoint in targeted therapy. Therefore, they do not kill the tumor cells and tumor shrinkage may not be observed[23]. Hence, stable response observed in this study suggests that the treatment effect is on tumor microenvironment, especially tumor angiogenesis. Both strategies (bevacizumab targeting VEGF and metronomic chemotherapy targeting tumor endothelium) are not comparable as the mechanism of action is different, but the outcome of the tumor anti-angiogenesis is similar. This necessitates the requirement of studies on incorporation of metronomic chemotherapy into conventional dosing regimens.

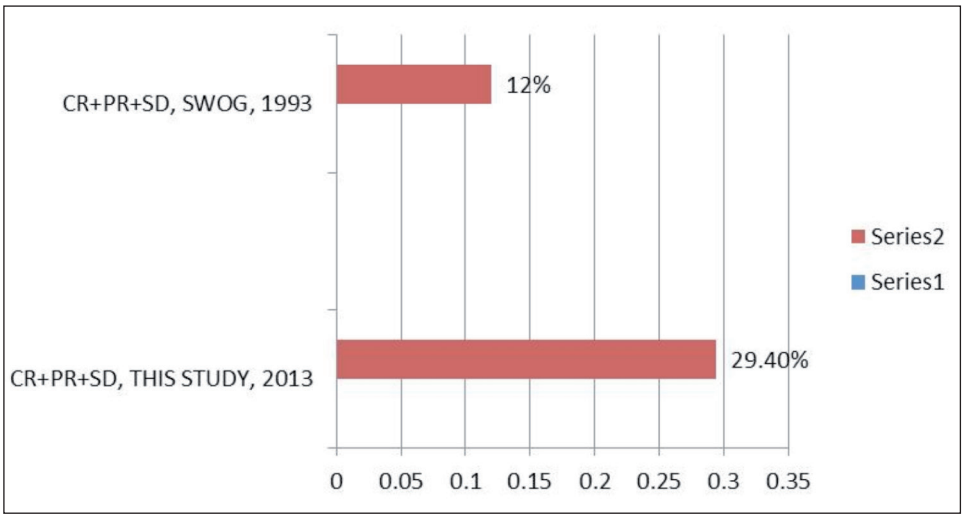

Fig. 2. Comparison with different study.

CONCLUSIONS

Metronomic chemotherapy in metastatic NSCLC can be considered as an effective option. PS and pathological grade is important predictors in this category of population with improved progression-free and overall survival. Tumor load and multiple organ sites of disease did not influence survival. Serum VEGF levels and thrombospondin levels did not correlate with response and anti-angiogenic effect of metronomic chemotherapy in study population.

Metronomic chemotherapy approach is safe with no or minimal toxicity in study population.

As the sample size is small, above results need validation in randomized control clinical studies.

Conflict of interests

The Authors declare that they have no conflict of interests.

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