http://dx.doi.org/10.5272/jimab.2014206.560

Journal of IMAB
ISSN: 1312-773X
http://www.journal-imab-bg.org

OPEN ACCESS

Journal of IMAB - *Annual Proceeding (Scientific Papers)* 2014, vol. 20, issue 6

THROMBOCYTOSIS AS PROGNOSTIC FACTOR FOR SURVIVAL IN PATIENTS WITH ADVANCED NON SMALL CELL LUNG CANCER TREATED WITH FIRST- LINE CHEMOTHERAPY

Deyan Davidov,
Department of Medical Oncology, Oncological Center - UMHAT "Dr Georgi Stranski", Medical University, Pleven, Bulgaria

SUMMARY:

Objective: The aim of this study was to evaluate elevated platelet count as a prognostic factor for survival in patients with advanced (stage IIIB/ IV) non- small cell lung cancer (NSCLC) receiving first- line chemotherapy.

Methods: From 2005 to 2009 three hundreds forty seven consecutive patients with stage IIIB or IV NSCLC, treated in Department of Medical Oncology, UMHAT- Dr. G. Stranski entered the study. The therapeutic regimens included intravenous administration of platinum- based doublets. Survival analysis was evaluated by Kaplan- Meier test. The influence of pretreatment thrombocytosis as prognostic factor for survival was analyzed using multivariate stepwise Cox regression analyses.

Results: Elevated platelet counts were found in 78 patients. The overall survival for patients without elevated platelet counts was 9,6 months versus 6,9 months for these with thrombocytosis. In multivariate analysis as independent poor prognostic factors were identified: stage, performance status and elevated platelet counts.

Conclusions: These results indicated that platelet counts as well as some clinicalpathologic characteristics could be useful prognostic factors in patients with unresectable NSCLC.

Key words: Prognostic factors, Thrombocytosis, Non small cell lung cancer, Survival

INTRODUCTION

Lung cancer remains the most common cause of cancer death worldwide for both men and women. NSCLC constitutes about 75%- 85% of all lung cancer cases [1]. Despite recent improvements of diagnostic technologies, approximately 50% of patients diagnosed with NSCLC present at diagnosis with advanced (stage III or IV) disease. The prognosis and overall survival (OS) in these patients still remain poor because local and distant failures are common [2]. Although can be curative at the early stages of NSCLC, the majority of patients with advanced stage NSCLC is not amenable to curative resection at diagnosis [3]. The median survival time for patients with untreated advanced or metastatic NSCLC is only 4- 5 months, with a survival rate at one year of only 10% [4]. The treatment options for these patients are limited although platinum-based chemotherapy has been shown to provide survival and quality of life benefits, but overall 2- year survival rates for this group remain <15% [5]. Newer chemotherapy combinations showed a response rate of 19- 32% and a median survival time of 7,9 to 11,3 months [6]. The difference in outcome among patients with the same clinical stage of the disease suggests that advanced NSCLC is a heterogeneous disease. Additionally, some patients experience weight loss and some have a significant number of comorbidities. This wide spectrum of clinical features of patients with advanced NSCLC probably contributes to disparities in outcomes seen in different chemotherapy regimens and the survival depends of some patients and tumor characteristics [7]. These patients's heterogeneity leading to the need for the identification of prognostic factors for survival. The analysis of these factors may define a subgroup of NSCLC patients with similar survival potential. They will be helpful advising individuals, choosing treatment, understanding the disease and optimizing the results of chemotherapy. Prognostic factors are a variables, assessed before any treatment, correlated to an evaluation criterion (i.e. survival), that are useful in estimating the patient's future, independently of the treatment that will be applied [8].

More recently, significant attention has been given to the association between malignancies and coagulation [9]. A hypercoagulability state is one of the signs of a more aggres-sive disease, while a thromboembolism is one of the major causes of mortality in cancer patients [10]. A prognostic significance between the platelet count and lung cancer has been identified [11 - 16]. However, the majority of these studies included patients with only small cell lung cancer.

The estimation of platelet counts before any treatment is easy, readily available and economical, and is used routinely. The aim of this study is to investigate the correlation between thrombocytosis, some clinicopathological characteristics and overall survival in patients who are undergoing first- line chemotherapy for advanced or metastatic NSCLC.

PATIENTS AND METHODS

The present study enrolled three hundreds forty seven consecutive patients with stage IIIB or IV NSCLC, treated from 2005 to 2009 in Department of Medical Oncology, UMHAT "Dr G. Stranski", Medical University-

Pleven. All patients were between 18 and 76 years of age; with freshly and pathologically confirmed diagnoses of NSCLC; advanced or metastatic disease; World Health Organisation (WHO) performance status 0 to 2; no prior chemotherapy or radiotherapy; adequate bone marrow function (absolute granulocyte count > $1,5x10^9$/L, platelet count > $140x10^9$/L) as well as normal renal (serum creatinine level < 1,5 mcrmol/L) and hepatic function (serum bilirubin level < 21 mmol/L). The patients with the following characteristics were excluded from the present study: patients who had any coexisting or previous cancer other than NSCLC; patients with concomitant diseases suspected of increasing the serum platelet concentration, including severe hypertension, splenic diseases and blood coagulation disorders; and patients who had taken acetylsalycilic acid drugs one month prior to the treatment. Histological typing of tumors was made according to the recommendations of the WHO [17]. Clinical stages were determininated according to the international TMN classification for lung cancer [18].

The diagnostic investigation included physical examination, full peripheral blood count, blood biochemistry, urinanalysis, chest radiography, abdomen ultrasound (all patients). Computer tomography of the thorax and bone scans was performed if necessary. The diagnosis of NSCLC was made with fiberoptic bronchoscopy with biopsies and brushing in 228 patients, mediastinoscopy in 4 patients, peripheral lymph node biopsy in 67 patients, transthoracic needle biopsies in 14 patients, cytological examination of sputum and when existing, of pleural fluid in 34 patients. Patients with uncertain histology and with small cell lung cancer were excluded from the study.

Data on the following variables were collected: patients age, gender, TNM stage, morphology, WHO performance status, haemoglobin level, total leukocyte count, platelet count, history of significant weight loss (more than 10% in three months preceding diagnosis), type of first- line chemotherapy and survival. Follow- up information, including cause of death, was ascertained through a review of clinical notes.

Peripheral venous blood for the platelet enumeration was drawn before chemotherapy was given. Platelet counts were analysed using an electronic particle counting device on blood using ethyllenediamine tetra- acetic acid (EDTA) as anticoagulant. In agreement with other studies, thrombocytosis was defined as a platelet count of > $400x10^9$/L [13].

All patients were treated with cisplatin or carboplatin based first- line chemotherapy regimens. Chemotherapy regimens could be divided in two groups: new third- generation regimens and conventional regimens. New third-generation regimens included cisplatin or carboplatin given with either paclitaxel or docetaxel or gemcitabine. Conventional regimens were cisplatin or carboplatin given with vinorelbine or ifosfamide plus mitomycin C. All patients were assessed for tumor response after the end of chemotherapy. Response was defined as complete response (CR), partial response (PR), no change (NC) or progressive disease (PD) according RECIST criteria [19]. The OS was measured from the date of the start of chemotherapy treatment to date of death from any cause or date of last patient contact.

All 347 patients were included in statistical calculations. The OS was estimated by the method of Kaplan and Meier [20]. Variables were studied for influence on survival in a univariate analysis by using the log- rank test, and in a multivariate analysis using the Cox proportional hazard regression analysis [21]. The results were considered statistically significant at the p< 0, 05 levels.

RESULTS

Patient's characteristics

A total of 347 patients with advanced NSCLC, treated with platinum derivates based first- line chemotherapy from January 2005 till December 2009 were analysed regardless of their length of treatment. Baseline demographic and disease characteristics are summarized in Table 1. The median age of patients was 62,7 years (range 39- 76 years) and 51% of patients were > 60 years. The male/ female ratio was 83,8% to 16,2%. Median WHO- performance status score was 1 (range 0- 2). The most common histology was squamous cell carcinoma- 277 patient (74,2%), the patients with adenocarcinoma were 56 (18,1%) and 14 of tumors were large- cell carcinoma (7,7%). One hundred and sixty cases were categorized as stage 3B and 187 cases were in stage IV. Forty five patients (13%) reported a history of significant weight loss- more than 10% for three months. Standard chemotherapy used was as follows: conventional regimens in 158 (45,5%) patients and new regimens in 189 (54,5%) patients. The median duration of treatment was 5, 3 months. The median follow- up period was 12 months (2- 38 months).

Platelet count and clinicopathological factors

Mean pretreatment platelet count for the whole group was 245,39 x 10^9/L ± 88,23 (range 109- $678x10^9$/L). Thrombocytosis was detected in a total of 78 patients (22,3%). The correlation between the clinicopathological factors of the patients and their platelet count is shown in Table 2. Elevated platelet count was associated with several factors, including advanced stage, WHO performance status 2 and weight loss more than 10% for three months. Thrombocytosis did not correlate with age, gender and histological type of tumor.

Platelet counts and survival

Patients with thrombocytosis had a significantly shorter OS than patients without thrombocytosis. For whole group OS was 8,4 months, but for patients without thrombocytosis OS was 9,6 months versus 6,9 months for patients with elevated platelet count (p< 0,001).

The results of univariate analysis are summarized in Table 3. The tumor stage, performance status at presentation, weight loss more than 10% and platelet count prior the start of chemotherapy were all significant predictors for the OS. The results of multivariate analysis including all variables for which p< 0, 05 on univariate analysis are summarized on Table 4. Of the variables that were included in

the multivariate analysis tumor stage, PS at presentation and initial thrombocytosis were independent prognostic determinants for OS.

DISCUSSION

Identifying prognostic factors in non- small cell lung cancer has been the focus of many investigators. They are helpful advising individuals, choosing treatment, understanding the disease and optimizing the results of chemotherapy. Because of the heterogeneity of this disease and the variation in the chemotherapy regimens as well as the patient's characteristics, these prognostic factors vary from one study to another. Factors proven to be significant in predicting for outcome in one study may not be reproduced in another study.

In this study we examined 347 consecutive patients with inoperable NSCLC and found 78 patients (22,3%) who had thrombocytosis at the time of their first evaluation in our hospital. In previously published studies, the prevalence of thrombocytosis in patients with lung cancer varies widely between different series, ranging from 13% to 60% [22]. A great deal of this variance is apparently due to the considerable disagreement of published studies about the correlation of thrombocytosis with the various histological types of lung cancer [11, 16]. On the other hand since the vast majority of published data derive from retrospective studies, any conclusions about the real prevalence of thrombocytosis in NSCLC are debatable. From this point of view, the finding of our study, comprising a sizeable number of patients, provide useful information on the subject.

The prevalence of thrombocytosis did not differ significantly between ages, sex and histology. On the contrary, in the present study we identified significant association between elevated platelet counts and advanced stage, worse PS and weight loss more than 10% for three months. Univariate analysis revealed that OS was shorter in patients with thrombocytosis than in patients without it. On multivariate analysis thrombocytosis remained a significant prognostic factor. Although thrombocytosis is associated with other risk factors, pretreatment platelet count predicts poorer survival in patients with advanced NSCLC. These results are with agreement with previous published findings. High circulating levels of platelets are found in patients with metastatic disease and have been related to extensive disease and poor prognosis in patients with NSCLC [11]. Tomita et al. described that the preoperative platelet count was a prognostic factor for resectable NSCLC patients. The 5- year survival probabilities of patients with normal or elevated platelet counts were reported as 26,87% and 63,73%, respectively [23]. Pedersen et al. reported that patients with elevated platelet counts had a significantly poorer survival rate than those with normal platelet counts (p< 0, 0001) [11].

Platelets play various significant roles in the physiological pathways, including homeostasis and inflammation. Also, platelets correlate with the progression of malignancies. The precise reason for association between an elevated platelet count and the worse outcome for NSCLC remains unknown. Firstly the increase in platelet count may promote tumor cells growth and angiogenesis. Platelets release various cytokines, including vascular endothelial growth factor (VEGF) and platelet- derived growth factor (PDGF), during blood clotting. The VEGF and PDGF family of proteins has a significant role in regulating angiogenesis. The invasiveness of the cancer cells may be enhanced by the plasma components in stored platelets [24]. Additionally, bevacizumab, an inhibitor of VEGF, is able to reduce this promotive effect. Moreover, platelets promote the formation of capillary- like structures by endothelial cells, via integrins mediating cell- cell adhesion [25]. Secondly, platelets enhance tumor metastasis by protecting the tumor cells from the host's immune system. Platelets expressing immunoregulatory proteins, including glucocorticoid- induced tumor- necrosis factor receptor- related protein, may protect the cancer [26].

In conclusion, in our study the frequency of thrombocytosis in patients with advanced NSCLC at first presentation was 22,3%. Survival in these patients was significantly shorter compared with patients without thrombocytosis. These results indicated that an elevated platelet count could be a useful prognostic factor for survival in patients with advanced NSCLC treated with chemotherapy.

Table 1. Baseline patient's characteristics

Characteristics	Number of patients 347
Age (years)	39 - 78
Gender	
Males	291 (83,8%)
Females	56 (16,2%)
Histological type	
Squamous	277 (74,2%)
Adenocarcinoma	56 (18,1%)
Large- cell	14 (7,7%)
Stage	
IIIB	160 (52,6%)
IV	187 (47,4%)
Performance status WHO	
0	38 (10,9%)
1	132 (38,1%)
2	177 (51,0%)
Weight loss	
<5%	245 (70,6%)
5-10 %	57 (16,4%)
>10%	45 (13,0%)
Platelet count	
Normal	269 (67,7%)
Elevated	78 (22,3%)

Table 2. Assotiation of platelet count with the parameters of patients

Thrombocytosis				
Parameters	Patients, n (%)	≤300, n (%)	>300, n (%)	P- value
Gender Male Female	 291 (83,8) 56 (16,2)	 225 (77,3) 42 (78,6)	 66 (22,7) 12 (21,4)	 NS
Age (years) >65 <65	 202 (58,2) 145 (41,8)	 153 (75,7) 116 (80,0)	 49 (24,3) 29 (20,0)	 NS
Histologycal type Squamous Adenocarcinoma Large-cell	 277(74,2) 56 (18,1) 14 (7,7)	 218 (78,7) 45 (78,6) 11 (78,6)	 59 (21,3) 11 (19,6) 3 (21,4)	 NS NS
Stage IIIB IV	 160 (52,6) 187 (47,4)	 131 (82,1) 138 (73,8)	 29 (17,9) 49 (26,2)	 p<0,001
Performance status WHO 0 1 2	 38 (10,9%) 132 (38,1%) 177 (51,0%)	 38 (78,7) 101 (76,5) 121 (68,4)	 8 (21,1) 31 (23,5) 56 (31,6)	 p<0,001
Lost weight <5% 5- 10% > 10%	 245 (70,6) 57 (16,4) 45 (13,0)	 189 (77,1) 41 (71,9) 37 (82,2)	 56 (22,9) 16 (28,1) 8 (17,8)	 p<0,001

NS- Not significant

Table 3. Results of univariate survival analysis.

Factor	Favorable	Unfavorable	HR	95% CI	P- value
Age	<65	≥65	1,15	0,69 -1,12	NS
Gender	Female	Male	1,44	1,26 -1,88	NS
Stage	IIIB	IV	1,88	1,43 -2,49	<0,001
WHO PS	Others	2	1,58	1,39 -1,76	<0,001
Weight loss	Others	> 10%	1,63	1,34 -1,82	<0,001
Histology	Squamous	Others	1,23	0,94 -1,66	NS
Platelet count	$<400x10^9$/L	$\geq 400x10^9$/L	1,65	1,12 - 2,48	<0,001

HR- Hazard ratio, CI- Confidence interval, PS- performance status, NS-Not significant

Table 4. Results of multivariate survival analysis.

Factor	Favorable	Unfavorable	HR	95% CI	P-value
Age	<65	≥65	1,84	0,59 -1,12	NS
Gender	Male	Female	1,68	1,34 -1,96	NS
Stage	IIIB	IV	1,73	1,29 -2,16	<0,001
WHO PS	Others	2	1,65	1,28 -1,88	<0,001
Weight loss	Others	> 10%	1,45	1,08 -1,93	NS
Histology	Squamous	Others	1,27	0,88 -1,54	NS
Platelet count	$<400x10^9$/L	$\geq 400x10^9$/L	1,84	1,36 -2,23	<0,001

HR- Hazard ratio, CI- Confidence interval, PS- performance status, NS- Not significant

REFERENCES:

1. Siegel R, Siegel R, Naishadham D, Jemal A. Cancer statistics. *CA Cancer J Clin.* 2012 Jan-Feb; 62(1):10- 29. [PubMed] [CrossRef]

2. Kim DN, Nam TK, Choe KS, Choy H. Personalized combined modality therapy for locally advanced non-small cell lung cancer. *Cancer Res Treat.* 2012 Jun;44(2):74-84. [PubMed] [CrossRef]

3. Lee DS, Kim YS, Kang JH, Lee SN, Kim YK, Ahn MI, et al. Clinical responses and prognostic indicators of concurrent chemoradiation for non- small cell lung cancer. *Cancer Res Treat.* 2011 Mar;43(1):32-41. [PubMed] [CrossRef]

4. Rapp E, Pater JL, Willan A, Cormier Y, Murray N, Evans WK, et al. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer- report of a Canadian multicenter randomized trial. *J Clin Oncol*. 1988 Apr;6(4);633- 641. [PubMed]

5. Bunn PA Jr, Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non- small cell lung cancer: a review of the literature and future directions. *Clin Cancer Res*. 1988 May;4(5);1087- 1100. [PubMed]

6. Schiller JH, Harrington D, Belani, CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non- small- cell lung cancer. *New Eng J Med*. 2002 Jan;346(2);92-98. [PubMed] [CrossRef]

7. O'Connell JP, Kris MG, Gralla RJ, Groshen S, Truat A, Fiore JJ, et al. Frequency and prognostic importance of pretreatment clinical characteristics in patients with advanced non-small- cell lung cancer treated with combination chemotherapy. *J Clin Oncol.* 1986 Nov;4(11);1604- 1614. [PubMed]

8. Berghmans T, Paesmans M, Sculier JP. Prognostic factors in stage III non-small cell lung cancer: a review of conventional, metabolic and new biological variables. *Ther Adv Med Oncol.* 2011 May;3(3):127- 138. [PubMed] [CrossRef]

9. Unsal E, Atalay F, Atikcan S, Yilmaz A. Prognostic significance of hemostatic parameters in patients with lung cancer. *Respir Med.* 2004 Feb;98(2):93 98. [PubMed]

10. van Doormaal FF, Raskob GE, Davidson BL, Decousus H, Gallus A, Lensing AW, et al. Treatment of venous thromboembolism in patients with cancer: subgroup analysis of the Matisse clinical trials. *Thromb Haemost.* 2009 Apr;101(4):762 769. [PubMed] [CrossRef]

11. Pedersen L, Milman N. Prognostic significance of thrombocytosis in patients with primary lung cancer. *Eur Respir J.* 1996 Sep;9(9):1826- 1830. [PubMed] [CrossRef]

12. Gonzalez Barcala FJ, Garcia Prim JM, Moldes Rodriguez M, Alvarez Fernandez J, Rey Rey MJ, Pose Reino A, et al. Platelet count: association with prognosis in lung cancer. *Med Oncol.* 2010 Jun;27(2):357 362. [PubMed] [CrossRef]

13. Aoe K, Hiraki A, Ueoka H, Kiura K, Tabata M, Tanaka M, et al. Thrombocytosis is a useful prognostic indicator in patients with lung cancer. *Respiration,* 2004 Mar-Apr;71(2):170-173. [PubMed] [CrossRef]

14. Tomita M, Shimuzu T, Hara M, Ayabe T, Onitsuka T. Impact of preoperative haemoglobin level on survival of non- small lung cancer patients. *Anticancer Res.* 2008 May-Jun;28(3B):1947- 1950. [PubMed]

15. Engan T, Hannisdal E. Blood analyses as prognostic factors in primary lung cancer. *Acta Oncol.* 1990; 29(2): 151 154. [PubMed]

16. Constantini V, Zacharski L, Moritz T, Edwards R. The platelet count in carcinoma of the lung and colon. *Thromb Haemost*. 1990 Dec;64(4):501- 505. [PubMed]

17. Brambilla E, Travis WD, Colby TV, Corrinz B, Shimosato Y. The new World Health Organization classification of lung tumours. *Eur Respir J.* 2001 Dec;18(6):1059-1068. [PubMed] [CrossRef]

18. AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 6th ed, Greene FL, Page DL, Fleming ID, et al. (Eds). Springer-Verlag, New York, 2002.

19. Therrase P, Arbuch S, Eisenhauer E, Wanders J, Kaplan R, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst.*. 2000 Feb;92(3):205- 216. [PubMed] [CrossRef]

20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958 Jun;53(282);457- 481. Published online: 12 Apr 2012. [CrossRef]

21. Peto R, Pike MC, Armitage P, Breslow N, Cox D, Howard S, et al. Design and analysis of randomized clinical trials requiring prolonged observations in each patient II. Analysis and examples. *Br J Cancer*. 1977 Jan;35(1);1- 39. [PubMed]

22. Diehl WL, Mandelbaum I, The significance of thrombocytosis in patients with carcinoma of the lung. *Surg Gynecol Obstet.* 1983 Feb;156(2):187- 188. [PubMed]

23. Tomita M, Shimuzu T, Hara M, Ayabe T, Onitsuka T. Prognostic impact of thrombocytosis in resectable non- small lung cancer. *Interact Cardiovasc Thorac Surg.* 2008 Aug;7(4):613- 615. [PubMed] [CrossRef]

24. Dineen SP, Roland CL, Toombs JE, Kelher M, Silliman CC, Brekken RA, et al. The acellular fraction of stored platelets promotes tumor cell invasion. *J Surg Res.* 2009 May;153(1):132-137. [PubMed] [CrossRef]

25. Pipili-Synetos E, Papadimitriou E, Maraqoudakis ME. Evidence that platelets promote tube formation by endothelial cells on matrigel. *Br J Pharmacol*. 1998 Nov; 125(6):1252-1257. [PubMed] [CrossRef]

26. Placke T, Kopp HG, Salih HR, Modulation of natural killer cell anti-tumor reactivity by platelets. *J Innate Immun.* 2011; 3(4):374-382. [PubMed] [CrossRef]

Please cite this article as: Davidov DN. Thrombocytosis as Prognostic Factor for Survival in Patients with Advanced Non Small Cell Lung Cancer Treated with First- Line Chemotherapy. *J of IMAB*. 2014 Oct-Dec;20(6):560-564. doi: http://dx.doi.org/10.5272/jimab.2014206.560

Received: 28/09/2014; Published online: 23/12/2014

Address for correspondence:
Dr. Deyan Nikolov Davidov,
Department of Medical Oncology, Oncological Center, Medical University,
1 "St. Kliment Ohridsky" Str., 5000 Pleven, Bulgaria
Phone: +359/64/886 317, Fax: +359/64/888 246
e-mail: dean_davidov@abv.bg