Journal of BUON **16:** 677-681, 2011

ORIGINAL ARTICLE

The prognostic value of thrombocytosis in newly diagnosed lung cancer patients: a retrospective analysis

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Summary

Purpose: *The importance of thrombocyte count as a prognostic factor has not been adequately investigated in patients with lung cancer. We retrospectively examined the value of thrombocytosis as a prognostic factor and investigated its relationship with other clinicopathologic factors and survival.*

Methods: *The medical records of 260 patients with lung cancer were reviewed. Pretreatment thrombocyte count, histopathological diagnosis, disease stage, gender, age, performance status (PS), thrombotic episodes, weight loss and paraneoplastic syndromes were recorded. Overall survival (OS), progression-free survival (PFS) and disease-free survival (DFS) were evaluated in all patient subgroups. Thrombocytosis was defined as platelet count >400,000/μl. We assessed statistically the possible correlation between thrombocytosis, other clinicopathologic factors and survival parameters. A two-sided p value < 0.05 was considered significant.*

Results: *There were no statistically significant differences between histological subgroups (small cell/SCLC and non-small cell/NSCLC) according to age, disease stage and gender. Sixty-six (25.38%) patients had thrombocytosis before starting treatment. We found no relationship between thrombocytosis and disease stage, gender, age, PS and thrombotic episodes. Thrombocytosis was significantly correlated only with weight loss (p=0.011) and paraneoplastic syndromes (p=0.027). OS was shorter in the thrombocytosis group, but without statistical significance. PFS and DFS did not differ between thrombocytemic and non-thrombocytemic patients.*

Conclusion: *Pretreatment thrombocytosis is not an independent prognostic factor of survival in lung cancer patients and is related with paraneoplastic syndromes.*

Key words: lung cancer, prognosis, survival, thrombocytosis

Introduction

Lung cancer ranks among the most common and lethal malignancies worldwide. Although many factors have prognostic significance in lung cancer and thrombocytosis is observed in different cancer types, recent data have not adequately clarified the importance of thrombocyte count as a prognostic factor in lung cancer patients [1,2]. In this study we retrospectively examined whether there is a correlation between thrombocytosis, other clinicopathologic factors and survival.

Methods

The medical records of 260 patients were retrospectively reviewed. Pretreatment thrombocyte counts, histopathological diagnosis, disease stage, gender, age, PS, thrombotic episodes, weight loss and paraneoplastic syndromes were recorded. OS in the whole patient group, PFS in inoperable and/or postoperative patients with residual lesions and DFS in the postoperative patients with no residual lesion were evaluated.

In order to exclude reactive thrombocytosis nonrelated to malignancy, patients with known nutritional anemia or who had a new surgical procedure (for diagnosis or treatment) in one month period, who were given chemotherapy and/or radiotherapy before their referral to our clinic were not included into the study.

The disease stage was determined by TNM classification for the whole patient group and SCLC patients were additionally classified by the Veterans Administra-

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Received 15-05-2011; Accepted 22-06-2011

tion Lung Cancer (VALC) study group staging system. PS was evaluated according to Eastern Cooperative Oncology Group (ECOG) score.

Thrombocytosis was defined as platelet count >400,000/µl. Platelet count was obtained by automatic blood count analysis (Cell-Dye Sapphire™ hematology analyzer, Abbott Diagnostics Division, Santa Clara, CA, USA).

Statistical analysis

All statistical analyses were performed using SPSS for Windows. A two-sided p-value < 0.05 was considered significant. Values were expressed as mean±standard deviation. Spearman's and Pearson's correlation coefficients were calculated to examine the correlation between the various parameters. Survival analyses were evaluated by Kaplan-Meier method.

Results

The demographic characteristics of the study groups are seen in Table 1. There was no statistical difference in the NSCLC and SCLC groups in terms of age, disease stage, and gender. Sixty-six patients (25.38%) had thrombocytosis before treatment. We found no relation between thrombocytosis and disease stage, gender, age, ECOG PS and thrombotic episodes. Thrombocytosis was significantly correlated with weight loss (p=0.011) and paraneoplastic syndromes (p=0.027) (Table 2). OS was shorter in the thrombocytosis group, but without statistical significance (Figure 1); this difference was more evident in the NSCLC group, although not statistically significant (Figure 2). PFS and DFS did not differ between thrombocytemic and non-thrombocytemic patients (Figures 3 and 4).

Table 1. Demographic characteristics of the study groups

Characteristics	*NSCLC (n=206; 79.2%) n (%)*	*SCLC (n=54; 20.8%) n (%)*	*p-value*
Gender			
Male	194 (94.1)	48 (88.8)	NS
Female	12 (5.8)	6 (11.1)	NS
Age, years (mean±SD)	61 (±9.5)	59.24 (±10.7)	NS
≤60	98 (47.5)	27 (50.0)	NS
>60	108 (52.4)	27 (50.0)	NS
Thrombocytosis at initial diagnosis	52 (25.2)	14 (25.9)	NS
Stage*			
Limited stage			
1b	15 (7.28)	3 (5.55)	NS
2a	4 (1.94)	0 (0)	NS
2b	12 (5.82)	1 (1.85)	NS
3a	9 (4.36)	7 (12.96)	NS
3b	75 (36.40)	12 (22.22)	NS
Metastatic disease			
4	91 (44.17)	31 (57.40)	NS

NSCLC: non small-cell lung cancer, SCLC: small-cell lung cancer, SD: standard deviation, NS: non significant
*Statistical analysis between limited and metastatic disease

Discussion

The role of thrombocytes has been shown in cancer metastasis and tumor angiogenesis in several studies [1,2]. Some studies claimed that thrombocyte activation occurs in cancer. β-thromboglobulin, a marker of

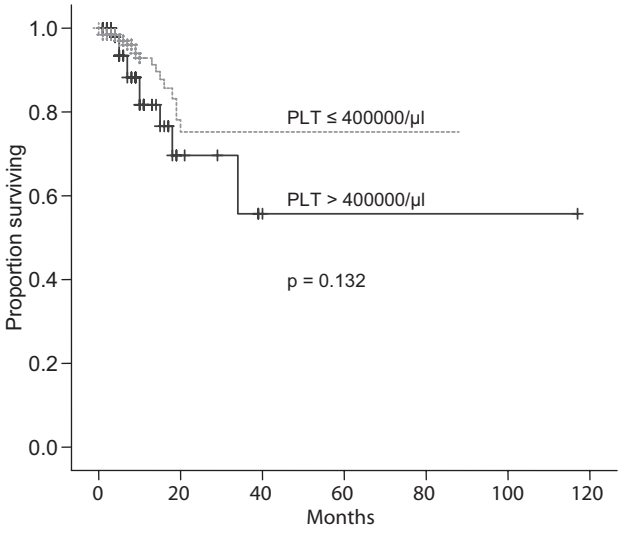

Figure 1. Overall survival in the two patient groups.

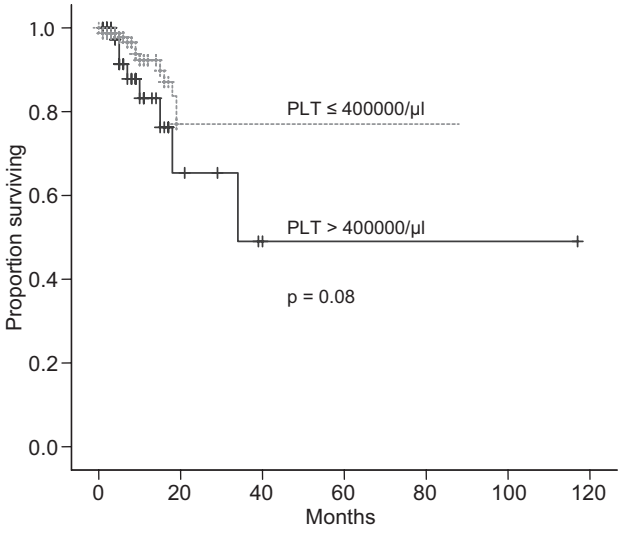

Figure 2. Overall survival in the NSCLC group.

Table 2. Parameters evaluated according to thrombocyte count groups

Evaluated parameters	*Thrombocyte count >400.000/μL (n=66) n (%)*	*Thrombocyte count ≤400.000/μL (n=194) n (%)*	*p-value*
Age (years)			
>60	28 (20.7)	107 (79.2)	NS
≤60	38 (30.4)	87 (69.6)	
Gender			
Male	60 (24.7)	182 (75.2)	NS
Female	6 (33.3)	12 (66.6)	
Disease stage*			
Limited stage			
Stage 1-2	6 (17.4)	29 (82.8)	
Stage 3a	7 (43.7)	9 (56.2)	NS
Stage 3b	20 (22.9)	67 (77.0)	
Metastatic disease			
Stage 4	33 (27.0)	89 (72.9)	
Paraneoplastic syndromes			
Absent	61 (24.2)	191 (75.8)	0.027
Present	5 (62.5)	3 (37.5)	
Types of paraneoplastic syndromes			
Hypercalcemia	1 (50.0)	1 (50.0)	NA
Inappropriate ADH secretion	1 (50.0)	1 (50.0)	NA
Hypertrophic osteoarthropathy**	3 (75.0)	1 (25.0)	NA
Weight loss			
Absent	41 (21.1)	153 (78.8)	0.011
Present	25 (37.8)	41 (62.1)	
ECOG performance status			
0	29 (21.6)	105 (78.4)	
1	24 (27.0)	65 (73.0)	NS
2	11 (36.7)	19 (63.3)	
3	2 (28.6)	5 (71.4)	
Thrombotic episodes			
Absent	61 (23.4)	183 (76.5)	NS
Present	5 (31.2)	11 (68.7)	

NS: non significant, NA: not assessable, ADH: antidiuretic hormone, *statistical analysis was done between limited and metastatic disease, **hypertrophic osteoarthropathy was diagnosed by radionuclide bone scan, carried out in all patients

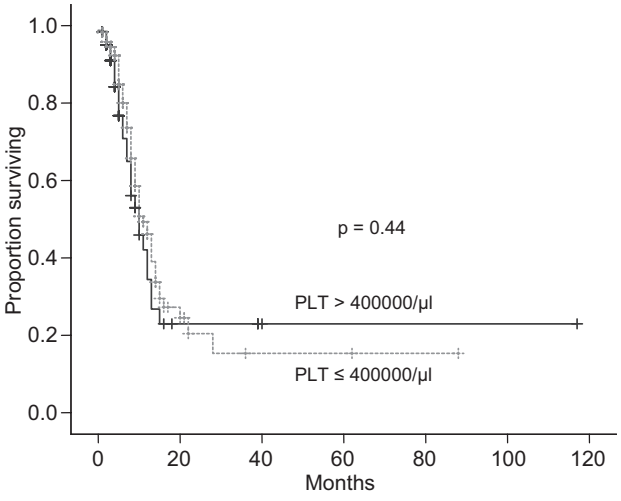

Figure 3. Progression free survival in the two patient groups.

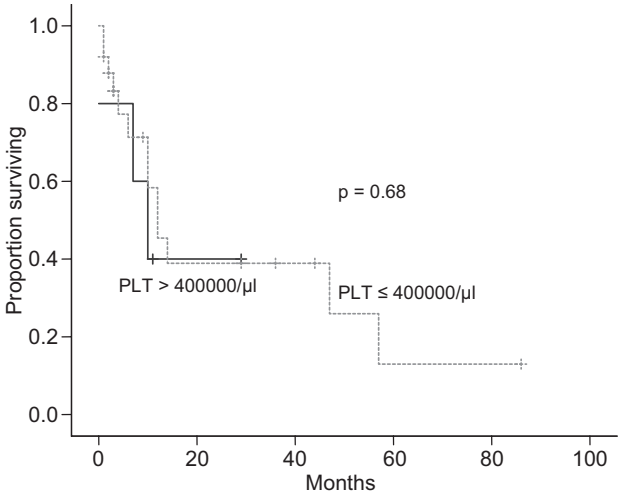

Figure 4. Disease free survival in the two patient groups.

thrombocyte activation that is expressed in α-granules of thrombocytes with VEGF, was found elevated in prostate [3], breast [4], lung [5,6], gastric [7] and colon [8] cancers. Thrombopoietin, that is the main regulator of thrombocyte production, was found at high concentrations in hepatocellular cancer [9]. On the other hand, thrombocytosis has been frequently seen in cancer. Previous studies showed that malignant cells produce several cytokines, like IL 1-β, IL-6, G-CSF and GM-CSF that might be responsible for thrombocyte activation [10-14]. Alexandrakis et al. [15] evaluated IL 1-β and IL-6 levels in benign lung disease, lung cancer patients and healthy controls and found that all of the patients with lung disease including benign and malignant lesions had higher cytokine levels, but no difference was detected in the thrombocytemic group compared to the non-thrombocytemic. This study showed that cytokines may not be the main cause of thrombocytosis in cancer. Although the pathogenesis of thrombocytosis in cancer has not been fully elucidated yet, some studies claimed that thrombocytosis is a poor prognostic factor in the renal cell [16,17], pancreas [18], esophagus [19], gastric [20], endometrium [21], breast [22], colon [23], cervix [24] and lung [25-27] cancers.

The results of previous studies investigating the association of lung cancer and thrombocytosis are controversial. Pederson et al. [26] retrospectively evaluated 1178 patients with lung cancer and 550 with benign lung disease as a control group, and found that thrombocytosis was more common (358 patients, 32%) and related with poor survival in the cancer group. They also reported that thrombocytosis was more frequent in advanced disease. However, Aoe et al. retrospectively evaluated 611 lung cancer patients and showed a relationship between thrombocytosis and survival, but did not confirm that thrombocytosis was more common in advanced stage disease [25]. On the other hand, a prospective study performed by Kotsori et al. evaluated 317 lung cancer patients (64/20.2% had thrombocytosis) and did not find a relationship with thrombocytosis and advanced stage, PFS and response to chemotherapy [28]. In this study no OS analyses were reported.

In our study, we found no correlation between thrombocytosis and survival. Our findings differ from the findings of the studies of Pederson et al. [26] and Aoe et al. [25]. However, our results are consistent with those of the study reported by Kotsori et al. [29], showing that there was no relation between thrombocytosis and PFS. The mean age in our study group was 60.6±9.81 years and was similar to other studies [25-28] and there was a strong negative correlation between advanced age and thrombocyte count (p=0.04). Thrombocytosis was more common in advanced age (>60 years) in the study of Aoe et al. [25], but in the study of Kotsori et al. [28] this was noticed in the younger age group (≤50 years). Also, in our study, no relationship between thrombocytosis and gender was noticed, as reported by previous studies [25,28]. Aoe et al. [25] stated that thrombocytosis was associated with performance status, however this relationship could not be proven in our and other studies. In our study, thrombosis was not increased in the thrombocytosis group, as in the study of Pederson et al. [26]. Literature contains only limited data on hematologic paraneoplastic syndromes in lung cancer. Takeuchi et al. showed autonomous IL-6 expression in a large cell lung carcinoma patient and claimed that thrombocytosis was related to paraneoplastic syndromes [29]. To our knowledge, our study is the first to evaluate the paraneoplastic syndromes and thrombocytosis in a patient group with lung cancer. We found that the paraneoplastic syndromes were statistically more common in the thrombocytosis group.

Although no statistically significant differences were shown from OS and PFS analysis, survival seemed to be poorer in the thrombocytosis group, particularly in NSCLC group. Of our study group, 80.38% of the patients had stage IIIb-IV disease (stage IIIb 87 patients/33.46%; stage IV 122 patients/46.92%), however, stage IIIb-IV patients were 37.26% in the study of Pederson et al. [26] and 66.61% in the study of Aoe et al. [25]. Although we had more patients with advanced-stage disease, the mortality rate (27 patients/ 10.38%) seemed to be lower compared to the studies reported by Pederson et al. (88% of the patients died in 5-year follow-up) [26] and Aoe et al. (mortality rate not stated, but the survival curves showed 50% mortality of patients in a 3-year period) [25]. This difference could be caused by terminal-stage patients taken from inpatient departments when the patients' relatives chose to take them home and also by our higher clinic turnover that resulted in large waiting lists for hospital admission. These two large groups that died but were lost to clinical follow-up could not be evaluated as dead at the end of the follow-up period and thus it might affect survival analysis results.

In conclusion, pretreatment thrombocytosis is not an independent prognostic factor of survival for patients with lung cancer and is related with paraneoplastic syndromes. There is no consensus on the role of thrombocytes in lung cancer in the literature, and it would be appropriate to prospectively study platelet activation markers and platelet counts in the same patient group to define the role of platelets.

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