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ORIGINAL ARTICLE

Thrombocytosis in primary lung cancer

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ABSTRACT

BACKGROUND The prevalence of thrombocytosis in lung cancer has been variably reported from 13% to 60%. The vast majority of published data derive from retrospective studies and therefore the estimation of the real prevalence is difficult.

PATIENTS AND METHODS We prospectively enumerated platelets in the peripheral blood of 317 consecutive, untreated lung cancer patients. Thrombocytosis was defined as a pletelet count >400.000/mm3. Tumours were histopathologically classified according to the WHO classification and staging was performed according the 2002 version ISS for NSCLC and to the VALSG two stage system for SCLC.

RESULTS Thrombocytosis was present in 64 (20.2%) patients and it was unrelated to gender and extent of disease but it was age related: 29/91 (31.8%) in patients ≤50 yrs versus 35/226 (15%) in patients >50yrs old (p=0.001). The distribution of thrombocytosis in the two major histological types was 54/165 (32.7%) for NSCLC and 10/152 (6.6%) for SCLC (p<0.001). Thrombocytosis did not differ (p=0.13) between NSCLC subtypes: adenocarcinomas (37/95, 39%), squamous cell carcinomas (11/48, 23%) and large cell carcinomas (6 22, 27%). Time to progression (TTP) did not differ (p=0.2) between thrombocytemic and non-thrombocytemic patients. On the contrary, 142/253 (56%) non-thrombocytemic patients responded to chemotherapy versus 21 of 64 (32.8%) thrombocytemic patients (p=0.001).

CONCLUSIONS Thrombocytosis is rather uncommon in untreated patients with SCLC while it is present in about one third of patients with NSCLC and it is unrelated to clinical stage or gender but related to age. In SCLC, it is unrelated to stage, gender or age. The presence of thrombocytosis in NSCLC and SCLC does not affect TTP. It is inversely related to response to chemotherapy but only in NSCLC.

KEY WORDS: *Thrombocytosis, Lung cancer, NSCLC, SCLC, Chemotherapy, Platelets*

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INTRODUCTION

Thrombocytosis, defined as a platelet count of more than 400.000/mm^3 is a well known paraneoplastic manifestation in a variety of malignant neoplasms, including lung cancer[1-5]. Nevertheless, the reported prevalence of thrombocytosis varies widely between different series, ranging from as low as 13%[6] to as high as 60%[7]. Likewise, there is considerable disagreement, in the literature, about the correlation of thrombocytosis with the various histological types of lung carcinoma[2,3,8,9]. More importantly, the vast majority of published, so far, data derive from retrospective studies making conclusions about the real prevalence of thrombocytosis difficult.

We, therefore, thought that a prospective estimation of platelets number in untreated patients with lung carcinoma would provide interesting information on the topic.

STUDY AIM

The primary endpoint of the present study was to estimate, in a prospective manner, the prevalence of thrombocytosis in patients with primary lung carcinoma before the administration of any treatment for their tumour.

Secondary endpoints were: a) the comparison of thrombocytosis between the various histological types and subtypes, b) the evaluation of the potential prognostic value of thrombocytosis in terms of response to treatment and c) the evaluation of the potential effect of thrombocytosis on the time to progression (TTP).

To this effect, we determined, in a prospective way, platelets count in the peripheral blood of all lung cancer patients consecutively admitted in the Department of Medical Oncology between 1999 and 2005 if they fulfilled the study's eligibility criteria.

PATIENTS AND METHODS

ELIGIBILITY AND EXCLUSION CRITERIA

In order to be included in the study patients had to fulfill all the inclusion and exclusion criteria shown in table 1.

LABORATORY INVESTIGATIONS

The following investigations were performed:
History and detailed clinical examination
Haemoglobin, white blood count, differential count, platelets
Urea, creatinine, liver function tests, electrolytes
Chest X-ray and CT scan of the thorax
Bronchoscopy and biopsy of any abnormal findings
CT scan of the abdomen
CT scan of the brain
Bone scintigraphy

TABLE 1. Eligibility criteria

Inclusion criteria
• Histologically or cytologically confirmed carcinoma of the lung
• No previous therapy for their tumour of any kind
• Stages I-IV
• Availability for follow up
• Informed consent
Exclusion criteria
• Suggestive or proven bone marrow involvement
• Known or suspicious myeloproliferative or myelodysplastic syndrome
• Prior splenectomy for any reason
• Idiopathic thrombocytopenic purpura
• Cirrhosis

STAGING

Patients with NSCLC were staged according to the current 2002 version of the International Staging System (ISS)[1]. Patients with SCLC were staged according to the two stage system introduced by the Veterans' Affairs Lung Study Group (VALSG) into Limited Disease (LD) and Extensive Disease (ED)[2].

METHODS

Peripheral venous blood for platelets enumeration was drawn before any specific therapy i.e. surgery, irradiation or chemotherapy was given. Platelet counts were analysed using an electronic particle counting device on blood using EDTA as anticoagulant. Thrombocytosis was defined as a pletelet count >400.000/mm^3

Histopathology was assessed using morphological and immunohistochemical criteria. Tumours were histopathologically classified according to the WHO classification[3].

EVALUATION OF RESPONSE TO TREATMENT

WHO criteria were used to evaluate response to treatment. More specifically:

Complete Response (CR) was defined as complete disappearance of all tumour lesions for a duration of at least three weeks

Partial Response (PR) was defined as decrease of >50% in the sum of the product of cross-sectional diameters of well outlined lesions or >50% decrease of poorly outlined lesions for at least three weeks, in the absence of progressive disease elsewhere or occurrence of new lesions elsewhere.

Progressive Disease (PD) was defined as >25% increase in the product of cross-sectional diameters of one or more outlined lesions or the occurrence of new lesions irrespectively of response elsewhere

STATISTICAL CONSIDERATIONS

Comparative analysis of the prevalence of thrombocytosis between the different groups was performed using Pearson chi-square test. The same test was used for comparative analysis of response rates between thrombocytemic and non-thrombocytemic patients.

Time to progression was separately estimated for thrombocytemic and non-thrombocytemic patients, using the Kaplan-Meier method and comparison of the two curves was performed by the logrank test.

All statistical analyses were carried out in SPSS v 13.0

RESULTS

Between 1999 and 2005, 317 consecutive patients with

primary lung cancer were included in the study. Their demographic, clinical and laboratory characteristics are shown in table 2. There were 165 (52%) NSCLC and 152 (48%) SCLC patients. The distribution of the different histological subtypes among NSCLC histology were: 95 (58%) adenocarcinomas, 48 (29%) squamous cell carcinomas and 22 (13%) large cell carcinomas. Expressed as a percentage of the whole group of 317 lung cancer patients, adenocarcinomas represented 30%, squamous cell carcinomas 15% and large cell carcinomas 7% of cases, respectively. Of 317 patients, 274 (86%) were males and 43 (14%) were females. The corresponding figures for NSCLC were 143 (87%) and 22 (13%), respectively and for SCLC 131 (86%) and 21 (14%), respectively. Median age of the whole group was 61 years with a range from 29 to 82. One hundred and twenty five (39%) patients had localized disease while the corresponding figures were 66 (40%) and 59 (39%) for NSCLC and SCLC, respectively. Table 3 summarizes our findings. Of the 317 patients, 64 (20.2%) had platelet count above 400.000/mm^3. Separate analysis of our results according to the two major histological types, demonstrated that 54 of 165 (32.7%) patients with NSCLC were thrombocytemic compared with 10 of 152 (6.6%) patients with SCLC and this difference is highly significant (p<0.001). The distribution of stage among the 54 thrombocytemic NSCLC patients was as follows: one patient had stage IIA, 4 patients stage IIB, 7 patients IIIA, 4 patients IIIB and 38 patients stage IV. In the whole group of 317 patients, analysis according to the disease extent, demonstrated that among 125 patients with localized disease, 21 (16.8%) had thrombocytosis compared with 43 of 192 (22.4%) patients with metastatic disease (p=0.225). When these results were further analyzed according to the two major histologies (table 4), 16 of 66 (24.2%) patients with localized NSCLC were thrombocytemic compared with 5 of 59 (8.5%) patients with localized SCLC (p=0.019). The corresponding figures for metastatic disease were 38 of 99 (38.4%) patients with NSCLC compared with 5 of 93 (5.4%) patients with SCLC (p<0.001). Of the 274 male patients (table 3), 55 (20%) had thrombocytosis compared with 9 of 43 (20.9%) women (p=NS). The corresponding figures for NSCLC (table 4) were 48 of 143 (33.6%) males versus 6 of 22 (27.3%) females (p=NS) and for SCLC, 7 of 131 (5.3%) males versus 3 of 21 (14.3%) females (p=NS). When the prevalence of thrombocytosis in males and females was compared between the two major histological types (table 5), it was found that 48 of 143 (33.6%) NSCLC male patients were thrombocytemic versus 7 of 131 (5.3%) SCLC males (p=<0.001). The corresponding figures for females were 6 of 22 (27.3%) in NSCLC versus 3 of 21 (14.3%) in SCLC (p=0.29). Analysis according to age (table 3), demonstrated that 29 of 91 (31.8%) patients aged ≤50 years were thrombocytemic compared with 35 of 226 (15%) aged >50 years (p= 0.001). When aged related thrombocytosis was separately analyzed in the two major histopathological types (table 4), 24 of 52 (46.2%) NSCLC patients aged ≤50 years demonstrated thrombocytosis compared with 30 of 113 (26.5%) NSCLC patients aged >50 years (p=0.013). The corresponding figures for SCLC were 5 of 39 (12.8%) patients aged ≤50

TABLE 2. Patients Characteristics

	NSCLC	SCLC	Total
Patients No (%)	165 (52)	152 (48)	317 (100)
Male (%) Female (%)	143 (87) 22 (13)	131 (86) 21 (14)	274 (86) 43 (14)
Median age (range)	61 (29-81)	61 (33-82)	61 (29-82)
Localised (%) Metastatic (%)	66 (40) 99 (60)	59 (39) 93 (61)	125 (39) 192 (61)
Adenocarcinoma (%) Squamous cell carcinoma (%) Large cell carcinoma (%)	95 (58) 48 (29) 22 (13)	NA NA NA	

TABLE 3. Results

	Patients No	Thrombocytosis (%)	P value
All patients	317	64 (20)	
Male Female	274 43	55 (20) 9 (20.9)	P=NS
Age ≤50 years Age >50 years	91 226	29 (31.8) 35 (15.5)	P=0.001
NSCLC SCLC	165 152	54 (32.7) 10 (6.6)	p<0.001
Localised Metastatic	125 192	21 (16.8) 43 (22.4)	P=NS

TABLE 4. Prevalence of thrombocytosis in NSCLC and SCLC patients according to demographic and clinical characteristics

	NSCLC		SCLC	
Male Female	48/143 (33.6) 6/22 (27.3)	p=NS	7/131 (5.3) 3/21 (14.3)	p=NS
Age ≤50 years Age >50 years	24/52 (46.2) 30/113 (26.5)	p=0.013	5/39 (12.8) 5/113 (4.4)	p=NS
Localised Metastatic	16/66 (24.2) 38/99 (38.4)	p=NS	5/59 (8.5) 5/93 (5.4)	p=NS
Adenocarcinoma Sqamous carcinoma Large cell carcinoma	37/95 (39) 11/48 (23) 6/22 (27)	p=NS	NA NA NA	

TABLE 5. Comparative prevalence of sex-related and age-related thrombocytosis between the two major histological types of lung cancer

Parameter	NSCLC	SCLC	P value
Male	48/143 (33.6%)	7/131 (5.3%)	P <0.001
Female	6/22 (27.3%)	3/21 (14.3%)	P = 0.29
Age ≤50 yrs	24/52 (46.2%)	5/39 (12.8%)	P = 0.001
Age >50 yrs	30/113 (26.5%)	5/113 (4.4%)	P =0.001

years versus 5 of 113 (4.4%) patients aged >50 years (p=NS). A comparison of age related thrombocytosis between the two major histological types (table 5) demonstrated that 24 of 52 (46.2%) NSCLC patients aged ≤50 years were thrombocytemic versus 5 of 39 (12.8%) SCLC patients of similar age (p=0.001). The corresponding figures for patients >50 years were 30 of 113 (26.5%) in NSCLC versus 5 of 113 (4.4%) in SCLC (P <0.001). The distribution of thrombocytosis in the various histological subtypes of NSCLC are shown in table 4. Of 95 patients with adenocarcinoma 37 (39%) were thrombocytemic, of 48 patients with squamous cell carcinoma 11 (23%) were thrombocytemic and of 22 patients with large cell carcinomas 6 (27%) were thrombocytemic. These figures were not significantly different (p=0.13). In the whole group of patients, median time to progression (TTP) was 8.5 months (95% CI, 7 – 9.9) for patients with platelets count ≤400.000/mm^3 compared with 6 months (95% CI, 4.7 – 7.3) for patients with platelets count >400.000/mm^3. The corresponding figures for the two major histological types were 5 months (95% CI, 3.6 – 6.4) and 7 months (95% CI, 5.2 – 8.7) for NSCLC and 6 months (95% CI, 0 – 13) and 10 months (95% CI, 8 – 12) for SCLC. TTP curves of thrombocytemic and non-thrombocytemic patients are plotted in figure 1 for the whole group of patients and in figures 2 and 3 for NSCLC and SCLC, respectively. The logrank test demonstrated no significant difference in TTP for any comparison (p=0.2, p=0.3 and p=0.7, respectively) between thrombocytemic and non-thrombocytemic patients. We then proceeded to evaluate any possible correlation between platelets number and response to chemotherapy (table 6). The chemotherapeutic regimens used were platinum-based triplets for NSCLC and a combination of Vincristine and Doxorubicin day 1, Cyclophosphamide and Methotrexate day 2 and VP- 16 days 1-5 q3W for SCLC. One hundred forty two of 253 (56%) non-thrombocytemic patients responded to chemotherapy versus 21 of 64 (32.8%) thrombocytemic patients (p=0.001). A separate analysis for the two major histological types demonstrated that 49 of 111 (44%) NSCLC non-thrombocytemic patients responded to chemotherapy versus 15 of 54 (27.7%) thrombocytemic patients, a significant (p=0.043) difference. The corresponding figures for SCLC were 93 of 142 (65%) non-thrombocytemic patients versus 6 of 10 (60%) thrombocytemic patients and this difference is not significant (p= 0.48).

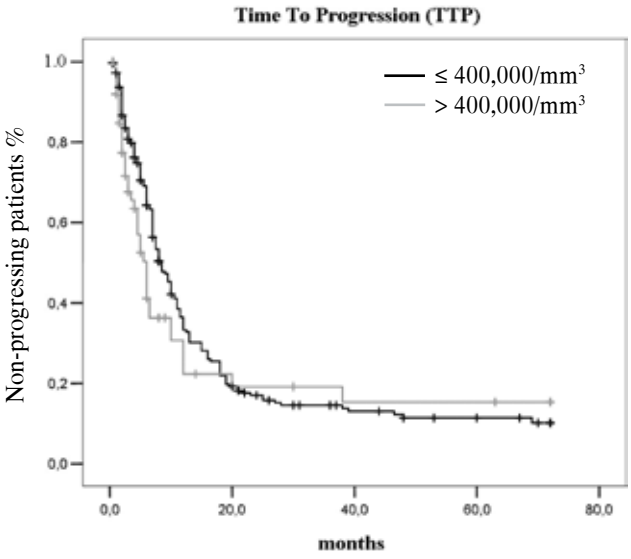

FIGURE 1. Actuarial time to progression (TTP) curve for the whole group of patients.

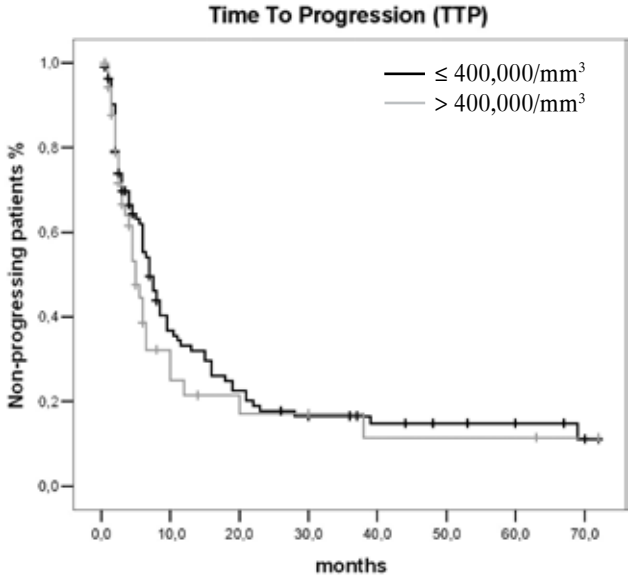

FIGURE 2. Actuarial time to progression (TTP) curve for NSCLC patients.

DISCUSSION

Although the association of thrombocytosis and lung cancer has been previously described[4-10,12], its prevalence varies widely between different series, ranging from 13%[9] to 60%[10]. 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

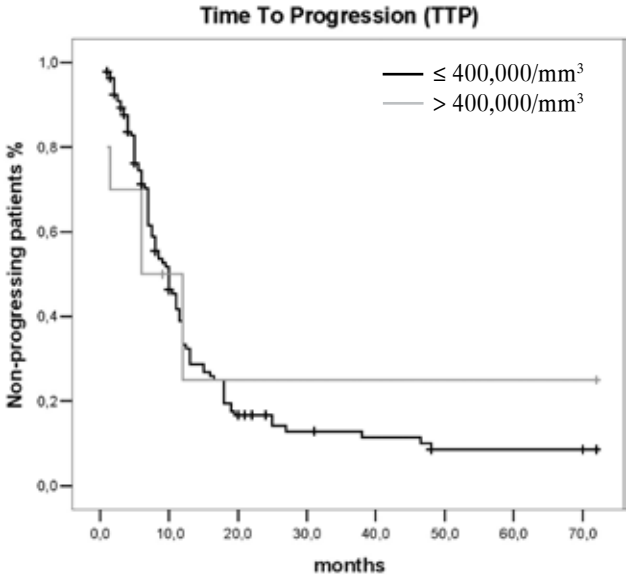

FIGURE 3. Actuarial time to progression (TTP) curve for SCLC patients

TABLE 6. Correlation between thrombocytosis and response to chemotherapy

	Responders/Nonresponders (%)		
	Nonthrombocytemic	**Thrombocytemic**	**P value**
All patients	142/253 (56)	21/64 (32.8)	P= 0.001
NSCLC	49/111 (44)	15/54 (27.7)	P= 0.043
SCLC	93/142 (65)	6/10 (60)	P= 0.48

carcinoma.[5,6,11,12] On the other hand, since the vast majority of published data derive from retrospective studies any conclusions about the real prevalence of thrombocytosis in primary lung cancer are debatable. From this point of view, we think that the findings of our prospective study, comprising a sizeable number of patients, provide useful information on the subject. Prior to discussing our findings a comment seems necessary explaining the unusual distribution of the two major histological types in our patients population. The high representation of SCLC in our series is due to the referral pattern of patients to our department. Since our main source of referrals is the department of thoracic surgery, almost all SCLC patients, irrespectively of stage, are referred to our department for medical treatment in contrast to the majority of early stage NSCLC patients who are treated surgically.

We observed thrombocytosis in 20.2% of the whole group of patients studied, a prevalence closer to the lower end of published series[7-9,12]. The prevalence of thrombocytosis did not differ significantly between localized and extensive disease and this is at variance with the findings of Pedersen et al[5]. Likewise, no difference was found according to sex. On the contrary, thrombocytosis was significantly more frequent in patients younger than 50 years compared with patients 50 years and older. It is of interest that a correlation of thrombocytosis with age was observed only in the group of NSCLC patients. Significant correlation between thombocytosis and age has been previously reported by Aoe although there is no mention in his report of a possible interaction with histology[8].

Comparison of the prevalence of thrombocytosis between the two major histological types of lung cancer demonstrated a highly significant difference, with thrombocytosis occurring in almost one third of patients with NSCLC while only a small percentage of SCLC patients had platelets count above 400.000/mm^3. It is worth of notice that the difference remained significant when comparison between NSCLC and SCLC patients was performed according to age and the extent of the disease. As far as sex is concerned, the difference between NSCLC and SCLC remained significant only in male patients. To our knowledge, the aforementioned findings have not been previously reported.

No significant differences in prevalence of thrombocytosis were observed among the various histological subtypes of NSCLC and this observation is in agreement with the findings of other studies.[5,6,8] In order to discern any prognostic or predictive significance of thrombocytosis, we compared TTP and response rate between thrombocytemic and nonthrombocytemic patients. We found that TTP was not affected by the presence of thrombocytosis either in the whole group of patients or in the two major histological types, separately. On the contrary, thrombocytosis was found to be inversely associated with response rate. In a separate analysis of the two major histological types, this negative association was restricted to NSCLC patients.

CONCLUSIONS

Thrombocytosis is rather uncommon in untreated patients with SCLC while is present in about one third of patients with NSCLC. In NSCLC, it is not related to clinical stage or gender but it is age related. In SCLC, thrombocytosis is unrelated to stage, gender or age. The presence of thrombocytosis does not affect TTP. However, in NSCLC, its presence seems to constitute an unfavourable factor for response to chemotherapy.

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