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THE HEMOGLOBIN LEVEL AS A PROGNOSTIC FACTOR IN PATIENTS WITH NON- SMALL CELL LUNG CANCER TREATED WITH GEMCITABINE AND CIS- PLATINUM

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SUMMARY

Objective: Anemia is observed in various malignancies including non- small cell lung cancer /NSCLC/ and is considered to be a poor prognostic factor. The aim of this study is to investigate whether there is a correlation between anemia, other clinic- pathological factors and survival in patients with advanced NSCLC treated with Gemcitabine / cis- Platinum- containing chemotherapy.

Methods: Seventy eight consecutive patients with advanced NSCLC treated in Department of Chemotherapy, UMHAT- Dr. G. Stranski, Medical University- Pleven between 2006- 2008 were retrospectively analyzed. Of those, 27 patients /34, 6%/ had low hemoglobin /HB/ level (<120g/L for men and <110g/L for women) prior to start chemotherapy. The HB levels were obtained at the time of their first visit to the hospital. All patients received chemotherapy regimen consists of intravenous administration of Gemcitabine 1250 mg/m2 day 1 and 8 and cis- Platinum 80mg/m2 day 1 with repetition over 21 days. Survival analysis was evaluated by Kaplan- Meier test.

Results: The median survival time for all patients was 9,5 months. The median survival time for patients with low HB levels was 7,6 months versus 11,3 months in patients without anemia /$p<0.05$/. There was a significant correlation between anemia and clinical stage or performance status / $p<0.05$/.

Conclusions: These results indicate that patients without anemia have significantly higher survival rate. Pretreatment HB level appears to be a useful prognostic indicator for survival in patients with inoperable NSCLC treated with chemotherapy.

Key words: Hemoglobin, Prognostic factors, Non small cell lung cancer, Chemotherapy, Survival**.**

INTRODUCTION

Lung cancer is the leading cause of cancer deaths among both men and women in the world. Non small cell lung cancer (NSCLC) represents approximately 75- 85% of all lung cancer cases. Approximately, two- thirds of lung cancer patients have advanced or metastatic stage at diagnosis (1). Patients with stage III- IV NSCLC have a median survival time of 4- 5 months without treatment, and 1- year survival rate is only 10% to 20% (2). The treatment options for these patients are limited although platinum- based chemotherapy has been shown to provide survival and quality of life benefits. Overall 2- year survival rates for this group remain <15% (3). Newer chemotherapy combinations like Gemcitabine- Cisplatin- containing regimens showed a response rate of 19- 32% and a median survival time of 7,9 to 11,3 months (4). The difference in outcome among patients with the same clinical stage of the disease suggests that advanced NSCLC is a heterogeneous disease and the survival depend of some patients characteristics as anemia, platelet counts, weight loss, concomitant diseases etc. (5).

Anemia is a common finding in cancer patients. Up to 30% of patients with different types of tumors have been reported to suffer from anemia (6). This can be related to the disease process itself or to its treatment, whether it is chemotherapy or radiotherapy. The factors associated with anemia itself encompass disorders of iron metabolism (7), reduced numbers of erythroid progenitor cells in the bone marrow, increased levels of inflammatory cytokines (8), extracorpuscular hemolysis, catabolism of patients with tumor burden, and relative deficiency of erythropoietin (6). Generally, the anemia is considered within the category of anemia of chronic diseases as normocytic and normochromic (7). The association of decreased hemoglobin levels with decreased survival has been demonstrated by randomized, controlled trials and large, community- based studies (9).

The aim of this study was to investigate the value of pre-treatment hemoglobin (HB) level as prognostic factor for survival in patients with advanced NSCLC treated with Gemcitabine and cis- Platinum containing chemotherapy regimen.

PATIENTS AND METHODS

Seventy- eight consecutive patients with advanced or metastatic NSCLC, treated in the period 2006- 2008 in Department of Chemotherapy, UMHAT- Dr. G. Stranski,

Medical University- Pleven, were retrospectively analyzed. All patients were between 18 and 75 years of age; with morphologically documented NSCLC; advanced or metastatic disease; life expectancy of minimum three months; 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 мmol/L) and hepatic function (serum bilirubin level < 21 мmol/L); absence of active infections; no overt cardiac disease. All patients were staged by computed tomography scan and radiography of the chest.

The anemia was defined as a HB level < 120 g/L in men and < 110 g/L in women. The pretreatment HB levels were obtained at the first visit to hospital prior to start chemotherapy. HB levels were analyzed by automated complete blood cell counting devices on ethylenediamine tetra- acetic acid (EDTA) - anti- coagulated blood. In our laboratory, the 95% confidence limit (normal range) of serum hemoglobin level is defined as 120- 160 g/l for men and 110- 150 g/l for women.

Chemotherapy regimen consists of Gemcitabine of 1250 mg/m2 by intravenous infusion day 1 and 8 and cis- Platinum 80 mg/m2 with hyperhydratation on day 1. Treatments were repeated every 3 weeks up to six cycles and were stopped in the event of disease progression, serious adverse events or request by the patient. All patients received pre- medication with antiemetic drugs (5- HT antagonists) before administration of chemotherapy.

Patients were evaluated for tumor response before treatment and after every two courses of chemotherapy. Tumor response was evaluated according to WHO response criteria (10). Response was defined as complete response (CR), partial response (PR), no change (NC), or progressive disease (PD). Objective tumour response included both confirmed CR and PR. Safety was assessed using the WHO toxicity criteria (11). The duration of response was calculated from the day of the start of treatment to disease progression; overall survival was measured from study entry to death. The time to disease progression was calculated from study entry until the day of the first evidence of disease progression.

The chi- square test was used to analyze the correlations between anemia and other clinic- pathological factors. The actuarial survival was estimated by the method of Kaplan and Meier (12). Prognostic factors were analyzed using the Cox proportional hazard model. A P value <0, 05 was considered to indicate statistical significance.

RESULTS

A total of 78 patients were recruited in the study over a 24- month's period. All patients regardless of their length of treatment were included in analysis. Tumor response was evaluated for all patients who received at least one course of chemotherapy. Baseline demographic and disease characteristics are summarized in Table 1. The median age of patients was 56,8 years (range 41- 76 years) and 42% of patients were > 65 years. The male/ female ratio was 84, 3% to 15,7%. Median WHO- performance status score was 1 (range 0- 2). Median duration of treatment was 7,5 months. The follow- up period was 12 months.

The resulting antitumor effects are presented in Table 2. The overall survival was 9,5 months with overall response rate (ORR) of 32,1% (25 of 78 patients), including four complete and twenty one partial remissions. The median duration of response was 5,1 months. Median time to disease progression was 6,2 months.

Among all patients 27 (34,6%) were with low HB level (24 men and three women) prior start of chemotherapy. Survival was significantly shorter in patients with anemia (median survival time 7,6 months) compared with those without this finding (median survival time 11,3 months) ($p< 0,05$),. Furthermore, the severity of anemia significantly correlates survival (table 3). Multivariate analysis of prognostic factors using the Cox proportional hazard model revealed that anemia ($p= 0,0002$), WHO performance status ($p= 0,001$), and clinical stage ($p=0,0002$) appeared to have independent prognostic significance. Age and sex appeared to have no significant effect on survival (table 4).

The relation between HB level and other clinic- pathologic factors is shown in table 5. There was a significant correlation between anemia and clinical stage of disease ($p< 0,05$) and anemia and WHO- performance status ($p< 0,05$). Low HB levels did not correlate significant with gender, age or histological type of the tumor.

DISCUSSION

In the current study we evaluated efficacy and safety of the combination of Gemcitabine cis- Platinum as first- line chemotherapy for patients with NSCLC. Response rate- 34,2% is promising. These results are comparable with previously published data. In these studies response rate were 40- 56% with time to progression of 6- 8 months. Tumour control / CR+ PR+ SD/ was achieved in 75,6% of patients (N=59) with survival duration- 10,4 months and is similar to other reports (13,14)

The prevalence of anemia in patients with various type of cancer was reported to be 26- 86% at the time of diagnosis (15), which was comparable with the results obtained in this study. Our results also suggest that anemia is more common in patients with advanced clinical stage and with poor WHO performance status.

In addition, we demonstrated that the presence of anemia prior to start chemotherapy is an independent prognostic factor in patients with NSCLC using the Cox proportional hazard model. It has been already reported that low HB level is associated with shorter survival in patients with several types of cancer (16).

The reason for the poor prognosis in NSCLC patients

with anemia have not been clarified yet. Tumour cells are known to secrete soluble molecules such as interferon gamma, interleukin-1 and tumour necrosis factor, which may develop anemia in cancer patients by haemolysis, suppression of erythropoesis and impairment of erythropoietin response on erythroid progenitor cells. Accordingly, anemia may be regarded as a paraneoplastic phenomenon. Thus patients with anaemia might have biologically more aggressive tumour cell clones compared to patients without anemia.

In conclusion, we demonstrated that anemia was frequently observed in patients with advanced NSCLC at the first visit in the hospital and survival was significantly shorter in patients with anemia compared with patients without it. Furthermore, we showed that survival of advanced NSCLC patients was independently influenced by pre-treatment serum HB levels using multivariate analysis. These results suggest that anemia determined at the time of first presentation is a useful indicator of the prognosis in patients with advanced NSCLC treated with chemotherapy.

Table 1. Patient characteristics

Patient characteristics	Number of patients- 78
Age (years)	41 – 76
Sex	
Males	66 (84,6%)
Females	12 (15,4%)
Dominant site of metastasis	
Pleura	36 (46,1%)
LiverLung	44 (56,4%)
Bone	23 (29,5%)
Soft tissue	19 (24,4%)
Other	5 (6,4%)
	4 (5,1%)
Lost weight	
< 5%	38 (48,7%)
5-10%	28 (35,9%)
>10%	12 (15,4%)
Performance status WHO	
0	11 (14,1%)
1	45 (57,7%)
2	22 (28,2%)
Stage	
III	41 (52,6%)
IV	37 (47,4%)
Histology	
Squamous	61 (78,2%)
Adenocarcinoma	11 (14,1%)
Large- cell	6 (7,7%)
HB level	
Normal	51(65,4 %)
Anemia	27(34,6%)

Table 2. Objective responses

Patients/ Response	CR	PR	NC	PD	ORR%
78	4	21	34	16	32,1%

ORR= CR+ PR

CR, Complete response; PR, Partial response; NC, No change; PD, Progressive disease; ORR, Overall response rates;

Table 3. Relation between survival and anemia level

Anemia	N	OSS	p
Mild	11	7,7	<0,05
Moderate	12	6,3	<0,05
Severe	4	4,4	<0,05
Normal	51	11,3	<0,05

N: number of patients, MSS: overall survival time, months, Severe: <11g/L in men and <10g/L in women, Moderate: <11-12g/L in men and <10-11g/L in women, Mild: <12-13g/L in men and <10g/L in women, Normal >13g/L in men and <11g/L in women

Table 4. Multivariate analysis and prognostic factors by Cox proportional hazard ratio

Variables	HR	95% CI	P-value
Anemia	1		
Normal	1,42	1,18- 1,67	<0,001
Stage by TNM classification			
IV	1		
III	0,68	0,49- 0,96	<0,001
WHO PS			
2	1		
1	0,55	0,39- 0,86	<0,001
0	0,41	0,28- 0,69	<0,001
Sex			
Male	1		
Female	0,68	0,44- 1,02	NS
Histology			
Squamous	1		
Adenocarcinoma	0,69	0,44- 0,92	NS
Large- cell	0,55	0,36- 1,08	NS
Age years			
<60	1		
>60	0,84	0,59- 1,12	NS

HR- Hazard ratio, Ps- performance status, TNM- tumor-nodes- metastases

Table 5. Relation between anemia and other clinic-pathologic factors

Variables	Normal	Anemia	P value
Age, years	78	27	
<60	34	8	
>60	44	19	NS
Sex			
Men	66	24	
Women	12	4	NS
WHO PS			
0-1	56	17	
2	22	11	<0,001
Clinical stage			
III	41	13	
IV	37	15	<0,001
Histology			
Squamous	61	22	
Adenocarcinoma	11	4	
Large-cell	6	1	NS

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