The Effect of Cisplatin-Etoposide Chemotherapy on Platelet Parameters in Lung Cancer Patients

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Abstract
The aim of this study was to investigate the effect of cisplatin etoposide chemotherapy on platelet indices in advanced stage lung cancer patients. Twenty advanced stage lung cancer patients who received cisplatin and etoposide chemotherapy and 35 healthy subjects were enrolled. The platelet indices (platelet count, mean platelet volume (MPV), plateletcrit (Pct) and platelet distribution width (PDW)) and other blood count parameters were recorded in baseline, before second cycle and after sixth cycle of chemotherapy. In baseline analysis, white blood cell count, but not other blood parameters, were different in patient group compared with control group. After six cycles of chemotherapy, PDW values were elevated than baseline analysis in lung cancer patients. Other platelet parameters were not changed after chemotherapy. This study showed that MPV, platelet count, or Pct don’t change after cisplatin-etoposide chemotherapy in lung cancer patients.

Introduction
Thromboembolic events are common in cancer patients. There are several factors: clotting alteration, previously atherosclerotic or cardiovascular disease, tumor embolism, or tumor related thrombotic factors (1). In addition, increased risk of thromboembolism has been reported after chemotherapy in cancer patients (1-6).

In chemotherapy induced thromboembolism, platelets play role (7). It is known that larger platelets are more reactive, highly aggregable (8-10). High mean platelet volume (MPV), a marker of platelet size, has been associated with ischemic stroke (11). Platelet size is also independent risk factor for myocardial infarction, and large platelet is one predictor of recurrent myocardial infarction and death (10).

The predictive parameters of chemotherapy induced thromboembolic events have not been exactly determined in cancer patients. Since the platelet indices might change after chemotherapy, this alteration might be predictive for thromboembolic events. In this regard, we aimed to investigate the effect of cisplatin etoposide chemotherapy on platelet indices in advanced stage lung cancer patients.

Materials and Methods
Data collection:
In this retrospective study, 20 advanced stage lung patients (18 small cell lung cancer and 2 non-small cell lung cancer) who received six cycles of cisplatin and etoposide chemotherapy (Patient group) and 35 healthy subjects (Control group) were enrolled. All of them were smoker. Patients with autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus), chronic infections (human immunodeficiency virus infection, tuberculosis), previous thromboembolic diseases (coronary artery disease, stroke), anticoagulant and antithrombotic drug use (previously or during follow up), or those who had received continuous non-steroidal anti-inflammatory drugs were excluded. The patients having initial or later metastasis to bone marrow were not enrolled.

The platelet indices (Platelet count, MPV, platelet...
crit (Pct) and platelet distribution width (PDW)) and other blood count parameters were recorded. Data were obtained from archive of the Medical Oncology Clinic. Automated blood counter (Coulter Gen-S, Minnesota, MN, USA) had been used for complete blood count (CBC). Patients whose all CBC analyses were from this analyzer were included. CBC parameters before first and second cycles and after sixth cycles of chemotherapy were documented in patients. CBC values of control subjects were also recorded.

**Statistics:**

For exploration of initial difference, hematological data, including platelet parameters, were compared in between patient group and control group by Mann Whitney U test. Then, changes in the platelet parameters during chemotherapy were investigated for the effect of one chemotherapy cycle and six chemotherapy cycles. These parameters were statistically analyzed comparing baseline and second cycle and comparing baseline and sixth cycle by Wilcoxon test. SPSS software was used.

**Results**

None of patients had any thromboembolic event. All of them completed six cycles of chemotherapy. Ages of patients and healthy subjects were matched (median:59, (range:48-80) vs. 59 (35-82), respectively; p>0.19). Three of patients (15%) and 8 of controls (23%) were female (p=0.37).

White blood cells (WBC) were elevated in patient group compared with control group (8770/µL ± 2635/µL vs. 7209/µL ± 1331/µL, respectively; p: 0.005). Hemoglobin, hematocrit, and platelet parameters (Platelet count, Pct, PDW and MPV) were not different between groups (Data have not been demonstrated).

In CBC analysis after sixth chemotherapy, PDW values were elevated more than those of baseline analysis in lung cancer patients. Other platelet parameters were not different between in baseline and before second chemotherapy cycle and between in baseline and after sixth chemotherapy cycle (Table 1).

**Discussion**

In this study, we aimed to investigate the effect of cisplatin etoposide chemotherapy on platelet indices in advanced stage lung cancer patients. We found that platelet parameters did not change after chemotherapy (excluding PDW) when baseline and after sixth cycle compared. This study has several limitations. This is a retrospective study. The number of patients was small. Platelet morphology and functions have not been investigated. The relation between platelet parameters and thromboembolic events has not been demonstrated in our study nevertheless, to the best of our knowledge; this is the first study in which the effect of chemotherapy in platelet parameters is investigated.

Anticancer drugs can associate with thrombotic complications (1-6,12,13). One of the anticancer drugs more known related to thrombosis is cisplatin. Some other complications such as myocardial infarction (12), cerebrovascular accident (2), thrombotic microangiopathy (14,15) and Reynaud’s phenomena have been reported after cisplatin treatment. The mechanisms are not clear. The pathophysiology involve vasospasm due to hypomagnesemia, hyper-reninemia or hyper-aldosteronemia, monocyte procoagulant hyperactivity, increased fibrinopeptide A, decreased tissue activators, endothelial dysfunction and elevation of serum cholesterol (1,17). Cisplatin induced vascular and thrombotic complications are mediated also by platelet activation and aggregation (1,7). Thus, urinary thromboxane A2 and its degradation products have increased after cisplatin treatment (18,19). A study also showed that cisplatin may trigger platelet aggregation and thromboxane formation of platelet (17). Furthermore, active and aggregable platelets are larger (8-10). Several studies have shown that high MPV, a marker of large platelets in lung cancer patients were recorded. Data were obtained from archive of the Medical Oncology Clinic. Automated blood counter (Coulter Gen-S, Minnesota, MN, USA) had been used for complete blood count (CBC). Patients whose all CBC analyses were from this analyzer were included. CBC parameters before first and second cycles and after sixth cycles of chemotherapy were documented in patients. CBC values of control subjects were also recorded.

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| Table 1. The effects of chemotherapy on platelet parameters |
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| | Baseline | Before 2. CT | p* | After 6. CT | p** |
| Platelet Count | 312±92 | 373±191 | 0,13 | 295±169 | 0,35 |
| Plateletcrite | 0,23±0,06 | 0,26±0,13 | 0,26 | 0,21±0,11 | 0,22 |
| Platelet Distribution Width | 16,02±0,89 | 16,06±1,08 | 0,59 | 16,59±1,01 | 0,02 |
| Mean Platelet Volume | 7,55±0,88 | 7,28±0,96 | 0,10 | 7,41±1,00 | 0,49 |

* : Between baseline and before second chemotherapy cycle
** : Between baseline and after sixth chemotherapy cycle
platelet, associates with thromboembolic disease. Butterworth et al. (20) found that high MPV occurs in ischemic stroke patients particularly with poor prognosis. In other study, Muscari et al. (11) found association high MPV value with ischemic lesion size and stroke severity.

MPV has been also studied in patients with myocardial infarction. Martin et al. (10) showed that MPV is high in patients with further ischemic event. Endler et al. (21) compared MPV in patients with myocardial infarction and healthy subjects and reported that patients with high MPV had a significantly higher risk of myocardial infarction when compared with patients having low MPV.

Thus, platelet parameters can be easily identified during routine hematological analysis and might be a predictive marker for thromboembolic events during cancer treatment (chemotherapy, endocrine treatment). We have previously investigated platelet parameters after endocrine treatment in breast cancer patients (22). We found that MPV increased after tamoxifen treatment (with higher thromboembolic risk), but not after anastrazole treatment (with lower thromboembolic risk). In present study, we did not find alteration of MPV value after chemotherapy. We found increased PDW after cisplatin-etoposide chemotherapy. It might be related to increased platelet turnover during chemotherapy.

In conclusion, this study showed that MPV, platelet count or Pct didn’t change after cisplatin-etoposide chemotherapy in lung cancer patients. The future case-control and cohort studies about chemotherapy induced thromboembolism and platelet parameters should be established.

Conflict of interest statement
The authors do not declare any conflict of interest or financial support in this study.

References
1. Li SH, Chen WH, Tang Y, Rau KM, Chen YY, Huang TL et al. Incidence of ischemic stroke post-chemotherapy: a retrospective review of 10,963 patients. Clin Neurol Neurosurg. 2006;108:150-6.
2. Karagoz B, Bilgî O, Akyol I, Oızgün A, Turken O, Kandemir EG. Cerebrovascular accident after chemotherapy for testicular cancer. Mil Med. 2009;174:320-1
3. Doll DC, List AF, Greco FA, Hainsworth JD, Hande KR, Johnson DH. Acute vascular ischemic events after cisplatin-based combination chemotherapy for germ-cell tu-
mors of the testis. Ann Intern Med. 1986;105:48-51.
4. Nichols CR, Roth BJ, Williams SD, Gill I, Muggia FM, Stablein DM et al. No evidence of acute cardiovascular complications of chemotherapy for testicular cancer: an analysis of the Testicular Cancer Intergroup Study. J Clin Oncol. 1992;10:760-5.
5. Czaykowski PM, Moore MJ, Tannick IF. High risk of vascular events in patients with uterine transitional cell carcinoma treated with cisplatin based chemotherapy. J Urol. 1998;160:2021-4.
6. Licciardello JT, Moake JL, Rudy CK, Karp DD, Hong WK. Elevated plasma von Willebrand factor levels and arterial occlusive complications associated with cisplatin-based chemotherapy. Oncology. 1985;42:296-300.
7. Yen T, Walsh JD, Pejler G, Berndt MC, Gezcy CL. Cisplatin-induced platelet activation requires mononuclear cells: role of GMP-140 and modulation of procoagulant activity. Br J Haematol. 1993;85:259-69.
8. Jakubowski JA, Thompson CB, Vaillancourt R, Valeri CR, Deykin D. Arachidonic acid metabolism by platelets of differing size. Br J Haematol. 1983;53:503-11.
9. Martin JF, Trowbridge EA, Salmon G, Plumb J. The biological significance of platelete volume: its relationship to bleeding time, platelet thromboxane B2 production and megakaryocyte nuclear DNA concentration. Thromb Res. 1983;32:443-60.
10. Martin JF, Bath PM, Burr ML. Influence of platelet size on outcome after myocardial infarction. Lancet. 1991;338:1409-11.
11. Muscari A, Puddu GM, Cenni A, Silvestri MG, Giulio R, Rosati M, Santoro N, Bianchi G, Magalotti D, Zoli M. Mean platelet volume (MPV) increase during acute non-lacunar ischemic strokes. Thromb Res. 2009;123:587-91.
12. Icli F, Karaoguz H, Dincol D, Demirkazik A, Gunel N, Karaoguz R, Uner A. Severe vascular toxicity associated with cisplatin-based chemotherapy. Cancer. 1993;72:587-93.
13. Karagoz B, Ayata A, Bilgî O, Uzun G, Unal M, Kandemir EG et al. Hemicentral retinal artery occlusion in a breast cancer patient using anastrozole. Onkologie. 2009;32:421-3.
14. Jackson AM, Rose BD, Graff LG, Jacobs JB, Schwartz JH, Strauss CM et al. Thrombotic microangiopathy and renal failure associated with antineoplastic chemotherapy. Ann Intern Med. 1986;105:48-51.
15. Fields SM, Lindley CM. Thrombotic microangiopathy associated with chemotherapy: case report and review of the literature. DICP. 1989;23:582-8.
16. Vogelzang NJ, Torkelson JL, Kennedy BJ. Hypomagnesemia, renal dysfunction, and Raynaud’s phenomenon in patients treated with cisplatin, vinblastine, and bleomycin. Cancer. 1985;55:2675-70.
17. Togna GI, Togna AR, Franconi M, Caprino L. Cisplatin trig-
gers platelet activation. Thromb Res. 2000;99:503-9.

18. Aitokallio-Tallberg A, Viinikka L, Ylikorkala O. Urinary excretion of prostacyclin and thromboxane degradation products in patients with ovarian malignancy: effect of cytostatic treatment. Br J Cancer. 1989;60:785-8.

19. Blochl-Daum B, Pehamberger H, Kurz C, Kyrle PA, Kyrle PA, Wagner O, Muller M et al. Effects of cisplatin on urinary thromboxane B2 excretion. Clin Pharmacol Ther. 1995;58:418-24.

20. Butterworth RJ, Bath PM. The relationship between mean platelet volume, stroke subtype and clinical outcome. Platelets. 1998;9:359-64.

21. Endler G, Klimesch A, Sunder-Plassmann H, Schillinger M, Exner M, Mannhalter C et al. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. Br J Haematol. 2002;117:399-404.

22. Karagoz B, Bilgi O, Alacacioglu A, Ozgun A, Sayan O, Erikci AA et al. Mean platelet volume increase after tamoxifen, but not after anastrazole in adjuvant therapy of breast cancer. Med Oncol. 2010;27:199-202.