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# Sisplatin ve Dosetaksel Kullanan Küçük Hücreli Dışı Akciğer Kanserli Hastalarda İnme Sıklığının Değerlendirilmesi

## Evaluation of Stroke Frequency in Non-Small Cell Lung Cancer Patients Receiving Cisplatin and Docetaxel

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***ÖZ***

***GİRİŞ ve AMAÇ:*** *İnme, beyin damar hastalığını takip ederek ortaya çıkan klinik bir durumu, ani bir nörolojik yetersizliği ifade eder ve hasarın patolojisine göre iskemik ve kanayıcı olarak iki alt gruba ayrılır. Sisplatin ve dosetaksel çeşitli kanserlerin tedavisinde kullanılan bir ilaçtır. Bizim bu çalışmadaki amacımız, sisplatin ile birlikte dosetaksel alan küçük hücre dışı akciğer kanseri hastalarında tedavi esnasında veya sonrasında inme sıklığını araştırmaktı.*

***YÖNTEM ve GEREÇLER:*** *Tıbbi Onkoloji Kliniği'nde küçük hücre dışı akciğer kanseri tanısı olan ve 21 günde bir en az 6 kür sisplatin 75mg/m2 ile birlikte dosetaksel 75mg/m2 tedavisi alan ve 18 yaşından büyük hastalar ileriye dönük olarak 6 ay süre ile takip edildi. Çalışmaya alınan hastaların ne zaman tanı aldığı, metastazı olup olmadığı sorgulandı ve nörolojik muayenesi yapıldı. İlaç tedavisi tamamlandığında hastaların tedavi esnasında ve sonrasında inme geçirip geçirmediği, inme geçirdi ise türü (hemorajik/iskemik) sorgulandı.*

***BULGULAR:*** *İzlem süresinde hastaların 6 (%3) tanesinde iskemik inme gelişti. Bu hastaların 4'ü (%2,3) erkek, 2'si (%7,7) kadındı. 61 (%31) hastada lenf nodu, 25 (%12,7) hastada beyin, 24 (%12,2) hastada kemik, 7 (%3,6) hastada sürrenal, 4 (%2) hastada karaciğer metastazı saptandı. Beyin ve kemik metastazı olması ile iskemik inme arasında ilişki saptanmadı (sırasıyla p=0,075, p=0,169, p=0,112).*

***TARTIŞMA ve SONUÇ:*** *Sisplatin ve dosetaksel alan küçük hücre dışı akciğer kanserli hastalarda kanserin kendisi ya da tedavilerin yan etkisi ile beyin damar hastalıkları neredeyse 10 kata kadar artmaktadır.*

***Anahtar Kelimeler:*** *inme, küçük hücreli akciğer kanseri, sisplatin, dosetaksel*

***ABSTRACT***

***INTRODUCTION:*** *Stroke refers to a clinical condition following cerebrovascular disease and a sudden neurological failure. It's divided into two subgroups according to damage pathology. Cisplatin and docetaxel are drugs used in various cancer treatments. In this study, we aimed to investigate the frequency of stroke in non-small cell lung cancer patients receiving docetaxel with cisplatin during and after the therapy*

***METHODS:*** *Patients, over 18 diagnosed with non-small cell lung cancer and receiving at least six therapies of docetaxel(75mg/m2) and cisplatin(75mg/m2) in every 21 days, were monitored prospectively in Medical Oncology Clinique for 6 months. Patients were questioned when they were diagnosed with cancer and if they have metastases, then the neurological examination was performed. When the drug treatment was completed, the patients were questioned as to whether they experienced stroke during or after the therapy. If they experienced stroke, its type (hemorrhagic / ischemic) was examined.*

***RESULTS:*** *During the follow-up period, ischemic stroke developed in six (3%) of the patients. Four of these patients(2.3%) were male, two (7.7%) were female. Lymph node metastasis in 61 (31 %) patients, brain metastasis in 25 (12.7%), bone metastasis in 24 (12.2%), surrenal metastasis in 7 (3.6 %) and liver metastasis in 4 patients (2 %) were determined. There wasn't correlation between brain and bone metastasis and ischemic stroke (p = 0,075, p = 0,169, p = 0,112, respectively).*

***DISCUSSION and CONCLUSION:*** *Cisplatin and docetaxel use in patients with non-small cell lung cancer increase cerebrovascular diseases up to ten folds due to the cancer itself or side effects of treatments.*

***Keywords:*** *stroke, non-small cell lung cancer, cisplatin, docetaxel*

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## INTRODUCTION

Brain vascular diseases are the third most common cause of death after cardiovascular diseases and cancer in the world. The stroke, which has an important place in the admission to the hospital, can be fatal and it can also cause various bodily dysfunctions often requiring rehabilitation and care, which cause individual, social and economic problems (1). Stroke refers to a clinical condition resulting from cerebrovascular disease, a sudden neurological failure, and it is divided into two subgroups as ischemic and hemorrhagic according to the pathology of the damage. Of all strokes, 60-80% are ischemic stroke, 10-15% are intracerebral hemorrhages and 3-10% are subarachnoid hemorrhages (2).

Cisplatin and docetaxel are drugs used in the treatment of various cancers. They form the basis of treatment, especially in germ cell tumours, ovarian, lung, colon, pancreas and breast cancers (3). Vascular events are common in cancer patients. They may be caused by cancer treatment (chemotherapy/radiotherapy), possibly causes the hypercoagulable state (4). Additionally incidence of stroke is 1,5 times higher in lung cancer patients than general population (5). In cancer patients treated with cisplatin, iliac artery thrombosis, myocardial infarction, deep vein thrombosis, pulmonary embolism and stroke could occur (3). However, there is not much information about stroke frequency in cancer patients. In this study, we aimed to investigate stroke in non-small cell lung cancer patients receiving docetaxel with cisplatin.

## METHODS

Between June 2011 and July 2012, 197 patients were monitored prospectively during treatment and for 6 months after treatment in İstanbul Dr Lütfi Kırdar Kartal Training and Research Hospital, Medical Oncology Clinic. Inclusion criterias were beeing over 18 year-old, diagnosed as non-small cell lung cancer, receiving at least six therapies of docetaxel (75mg/m2) and cisplatin (75mg/m2) in every 21 days, and not having history of stroke or other vascular events such as coronary artery diseases, pulmonary embolism, deep vein thrombosis.

All patients' age, gender, disease duration, metastases, radiotherapy history, and history of stroke and other vascular events were questioned. Patients having history of stroke or other vascular events were excluded from study. Patients were examined at the begining of the study. Besides, neurological examination was performed in every chemotherapy cure. All stroke patients were examined at onset of symptoms and modified Rankin Scores (mRS) were noted. Its type (hemorrhagic / ischemic) was examined with brain computerized tomography (CT) or magnetic resonance (MR). All stroke patients' risk factors such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), cardiac failure, atrial fibrillation (AF), smoking, duration of treatment and vascular terriotory were analyzed. Transthoracic echocardiography and carotid-vertebral artery doppler ultrasonography were performed to all stroke patients. Neurological examination was performed to all stroke patients at 6th month.

The data obtained from the study were transferred to the electronic medium and were analysed by SPSS (Statistical Package for Social Sciences) 11.5 statistical package program. For the analysis and evaluation, frequency tables, centre, frequency measures and for ratio comparisons $\chi 2$ (chi-square) test was used.

This study was approved by Dr Lütfi Kırdar Kartal Training and Research Hospital Ethics Committee.

## RESULTS

197 patients with non-small cell lung cancer were included in the study. 171 (86.8%) of the patients were male, 26 (13.2%) were female. The mean age of the patients was 57.68 ± 9.48 years (male: 57.95 ± 9.47; female: 55.88 ± 9.57). There was not significant difference between the mean age of men and women (p = 0.613). The mean duration of illness was 5.42 ± 12.90 months (Male: 5.49 ± 13.55, Female: 4.92 ± 8.05). There was not significant difference between the mean duration of illness in males and females (p = 0.808). Table 1 shows the demographic datas of patients.

**Table 1: Demographic data and metastatic distributions of patients.**

| | Total | Male | Female | p |
|---|---|---|---|---|
| n(%) | 197 | 171(%86.8) | 26(%13.2) | |
| Age | 57.68±9.48 | 57.95±9.47 | 55.88±9.57 | 0.613 |
| Duration of disease (months) | 5.42±12.90 | 5.49±13.55 | 4.92±8.05 | 0.808 |
| Lymph node metastasis | 61(%31) | 52(%30.4) | 9(%34.6) | 0.655 |
| Brain Metastasis | 25(%12.7) | 22(%12.9) | 3(%11.5) | 1.000 |
| Bone Metastasis | 24(12.2) | 23(%13.5) | 1(%3.8) | 0.212 |
| Adrenal Gland Metastasis | 7(%3.6) | 7(%4.1) | 0 | |
| Liver Metastasis | 4(%2) | 4(%2.3) | 0 | |
| Ischemic Stroke | 6(%3) | 4(%2.3) | 2(%7.7) | 0.180 |
| Duration of Stroke (days) | 56.67±29.44 | 45±17.32 | 80±42.43 | 0.071 |

Six (3%) of the patients developed ischemic stroke during 6 months follow-up. Four of these (2.3%) were male and 2 (7.7%) were female. There was no difference in the ischemic stroke rates among male and female patients (p = 0.180). Hemorrhagic stroke was not observed in patients. Five patients (83.3%) developed carotid artery disease, one patient had an ischemic stroke due to vertebrobasilar system involvement. Four pateints (66,6%) had HT, 1 patient (16,7%) had DM, 1 patient (16,7%) had HL, 1 patient (16,7%) had smoking. All patients' transthorasic echocardiograhy findings were normal. Carotid artery stenosis >50% at sympthomatic side was found in 1 (16,7%) patient. Distribution of stroke types according to TOAST classification is shown in Table 2.

**Table 2: Stroke Types**

| Stroke Type | n(%) |
|---|---|
| Atherosclerotic | 1(%16,7) |
| Cardioembolic | 1(%16,7) |
| Lacunar | 1(%16,7) |
| Other causes | 1(%16,7) |
| Undetermined causes | 2(%33,3) |

The mean time from the onset of ischemic stroke until the beginning of treatment was 56.67 ± 29.44 days. This was 80 ± 42.43 days for women and 45 ± 17.32 days for men (p = 0,071).Mean mRS of stroke patients were 4±0,89 at onset and 3,17±1,6 at 6thmonth of stroke (p=0,046). Four of 6 patients' mRSwere>2 at 6thmonth of stroke. It was observed that ischemic stroke occurred in five patients after the third dose and in one after the first dose.The findings are summarized in Table 1. Findings of stroke patients are shown Table 3.

**Table 3: Clinical findings of stroke patients**

| Case | Gender | Age | HT | DM | HL | Cardiac Failure | AF | Smoking | Chemotherapy times at stroke onset | Stroke territory | mRS at onset | mRS at 6th month |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Male | 65 | + | - | - | - | - | - | 4 | Anterior | 4 | 3 |
| 2 | Male | 51 | - | - | - | - | - | - | 3 | Anterior | 4 | 3 |
| 3 | Female | 54 | + | - | + | - | - | - | 3 | Anterior | 3 | 1 |
| 4 | Female | 70 | + | + | - | - | - | - | 5 | Anterior | 5 | 5 |
| 5 | Male | 56 | - | - | - | - | + | - | 2 | Anterior | 5 | 5 |
| 6 | Male | 66 | + | - | - | - | - | + | 3 | Posterior | 3 | 2 |

We spotted lymph node metastasis in 61 (31 %) patients, brain metastasis in 25 (12.7%), bone metastasis in 24 (12.2%), surrenal metastasis in 7 (3.6 %) and liver metastasis in 4 patients (2 %) were determined (Table1). Four of the patients with stroke had metastasis. All of the patients with metastasis had lymph nodes, bone and brain metastases were observed in three and two patients respectively. Other organs of patients were not metastatic. Stroke frequency was 6.6% in patients with lymph node metastases, 12.3% in patients with bone metastases, and 8% in patients with brain metastases. Patients with other metastases had no stroke. There was no correlation between lymph node metastasis, brain and bone metastasis and ischemic stroke (p = 0.075, p = 0.169, p = 0.112, respectively).

## DISCUSSION

Stroke in cancer patients has been investigated in many studies. Numico et al. observed stroke in one (0.9%) of 108 patients with non-small cell lung cancer who received cisplatin and gemcitabine (6).In a study, Li et al found stroke rate 0,13% in 10963 cancer

patients (7). Also, De Bruin et al. found that 2.5% of 2201 patients with Hodgkin lymphoma developed stroke (8). In our study, it was found as 3%, which is compatible with the literature. Prevalence studies in healthy populations vary across the world. While the prevalence of stroke varies with age, it is between 0,17% and 0,3%(9). These findings showed that stroke frequency may increase ten times in cancer patients.It was reported that it may be caused by the tumour itself, coagulation disorders, infections, treatment and paraneoplastic reasons (10).

In cancer patients, stroke can also occur as a complication of the treatment. Li et al. reported that cisplatin use may be related to stroke (7).However, no data on docetaxel and ischemic stroke have been found in the literature. According to a study by Periard et al., It is thought that microparticles originating from endothelium and thrombosis, especially after the 3rd and 4th infusions, may cause stroke (11).In our study, in five of patients with stroke, the case occurred after the 3rd dose. This indicates that stroke may develop due to endothelial and platelet-derived microparticles. In addition, treatment-induced endothelial damage can also cause vasculitis-like changes, causing stroke (12).

Tumour-related stroke is very rare (10). Stroke in cancer patients may develop due to direct tumour embolization (atrial mycosis and lung cancers), great vessel stress (head and neck tumours), vascular infiltration (leptomeningeal metastases) and hyperviscosity (hematological cancers) (10, 13). Cancer is an important cause of acquired prothrombotic state. Elevated D-dimer level is a sensitive but unspecific measure of activation of the coagulation cascade and thrombus formation (14). In recent studies, serum D-dimer levels found increased in stroke patients with cancer than stroke patients without cancer (15,16). Disseminated intravascular coagulation (DIC) has been reported to be more frequent in hematologic and metastatic cancers (10). DIC and nonbacterial thrombotic endocarditis are more common in cancer patients than in normal population .

De Bruin et al. found that 76% of the strokes were in the carotid system and 18% were in the vertebrobasilar system. In the study performed by Li et al., it was revealed that 81.2% of them were in the carotid system and 18.2% were in the vertebrobasilar system (7,8).In our patients, carotid system-related stroke rate is %83,3, and it's similar to literature.

In a recent study, the most frequent stroke type according to TOAST classification was cryptogenic stroke (31,6%). In this study, other stroke type rates were found as cardioembolic 26,5%, atherosclerotic 14,2%, lacunar 14,2%, other etiology 14,2% (17). They found cryptogenic stroke rate significantly high in cancer group. Our patients' stroke type rates are similar to this study. But we didn't compare our stroke type rates with non-cancer group due to absence of control group. In same study, frequencies of risk factors were found as HT 67,6%, DM 14,7%, AF 18,6% and HL 15,3% (17). In an other study, Schwarzbach et al found HT, HL, DM and smoking rates in order as 77%, 27%, 33% and 16% (15). Our findings are similar to these studies.

In a study conducted by Kim et al. in 241 cancer patients who hadstrokes, there was no relationship between metastasis and cancer-related stroke (18). Contrary to this finding, the study, in advanced lung and prostate cancer patients conducted by Behrendt et al., obtained a correlation between metastasis and cancer-related stroke. We didn't found relationship between metastasis and stroke.

Zhang et al found that follow up mRS of stroke patients in cancer and non-cancer group was similar. They reported that death rate in hospital was significantly higher in cancer group (19). Scwarzbach et al didn't found difference between mRS of cancer and non-cancer group stroke patients(15). We couldn't compared our patients' mRS due to not having control group, but most of our patients' mRS were>2 at 6th month of stroke.

Our study has small number of patients. Studies with larger patient groups may provide different results. Additionally we don'thave a control group for stroke patients. These are the limitations of our study.

In conclusion, this study shows that cisplatin and docetaxel, in patients with non-small cell lung cancer, increase cerebrovascular diseases almost ten times through the cancer or side effects of treatments. Further studies with more patient groups are needed to increase the information in this area.

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