ORIGINAL ARTICLE

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Efficacy Comparison Between Weekly and Triweekly Regimens of Carboplatin-paclitaxel in Non-small Cell Lung Cancer

Küçük Hücreli Dışı Akciğer Kanserinde Haftalık ve Üç Haftalık Karboplatin Paklitaksel Tedavi Etkinliğinin Karşılaştırılması

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ABSTRACT

Aim: Around 40% of non-small cell lung cancers have stage 3b or 4 disease at the time of diagnosis. In the treatment, platinum-based therapy can still be used in patients who do not carry a driver mutation or who are not suitable for immunotherapy with advanced non-small cell lung cancers (NSCLC). The objective of this study was to compare the effectiveness of weekly carboplatin-paclitaxel regimen with triweekly carboplatin-paclitaxel regimen.

Materials and Methods: This is a retrospectively structured study. Patients who were followed-up and treated for lung cancer in Adana City Training and Research Hospital's Oncology Department between January 1, 2017 and July 1, 2021 were included.

Results: Out of the 104 patients, 52 (50%) patients received weekly carboplatin-paclitaxel (C-P), and 52 (50%) received C-P every 3 weeks. The mean overall survival was 19.64±2.53 months in the weekly C-P group and 17.47±1.64 months in the triweekly C-P group (p=0.675). The mean progression-free survival (PFS) was 8.5±1.01 months in the weekly C-P group and 5.76±0.61 months in the triweekly C-P group (p=0.017).

Conclusion: We demonstrated that weekly C-P treatment, which is known to have fewer toxicity in NSCLC, provided better PFS compared to triweekly treatment.

Keywords: Non-small cell lung cancer, carboplatin-paclitaxel, triweekly, progression free survival, overall survival

ÖZ

Amaç: Küçük hücreli dışı akciğer kanser tanılı hastaların yaklaşık %40'ı tanı anında evre 3b veya 4 hastalığa sahiptir. Platin bazlı sistemik kemoterapi, şu anda ilerlemiş küçük hücreli dışı akciğer kanserlerli hastalar için yerleşik konvansiyonel tedavidir. Bu çalışmanın amacı, daha düşük toksisite beklenen haftalık karboplatin-paklitaksel (K-P) rejiminin etkinliğininin üç haftalık K-P rejimi ile karşılaştırmaktır.

Gereç ve Yöntem: Bu retrospektif yapılandırılmış bir çalışmadır; Adana Şehir Eğitim ve Araştırma Hastanesi Onkoloji Kliniği'nde 1 Ocak 2017-1 Temmuz 2021 tarihleri arasında akciğer kanseri nedeniyle takip ve tedavi edilen hastalar dahil edildi.

Bulgular: Yüz dört kişiden 52'si (%50) haftalık K-P ve 52'si (%50) 3 haftada bir K-P aldı. Ortalama genel sağkalım haftalık K-P grupda 19,64±2,53 ay ve üç haftada bir K-P alan grubunda 17,47±1,64 aydı (p=0,675). Ortalama progresyonsuz sağkalım (PFS) haftalık K-P grubunda 8,57±1,01 ay ve üç haftada bir K-P alan grupda 5,76±0,61 ay olup, anlamlı olarak daha yüksek bir değerdi (p=0,017).

Sonuç: Daha az toksisiteye sahip olduğu bilinen haftalık K-P tedavisinin benzer hasta grubunda üç haftalık tedaviye göre daha iyi PFS sağladığını gösterdik.

Anahtar Kelimeler: Küçük hücreli dışı akciğer kanseri, karboplatin-paklitaksel, haftada bir, progresyonsuz sağkalım, genel sağkalım

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INTRODUCTION

Among all cancers, lung cancer is the one that most frequently leads to death, according to World Health Organization data[1]. Approximately 80% of lung cancers are non-small cell lung cancers (NSCLC)[2]. Around 40% of the patients in this group have stage 3b or 4 disease at the time of diagnosis[3]. Platinum-based systemic chemotherapy is currently the established conventional treatment for patients with advanced NSCLC[4,5]. Immunotherapies are included in current treatment guidelines as important therapeutic agents for lung cancer. Because immunotherapies are expensive and therefore, difficult to access, they have not yet become a standard for care outside developed countries. However, these agents are not routinely used in the first line due to reimbursement issues in our country, pemetrexed is also not reimbursed in the first line treatment of NSCLC in Turkey. As a result, platinum-based treatments are predominantly used in our country. One of these regimens is carboplatin-paclitaxel (C-P) treatment. Studies have compared C-P protocol with other treatment protocols and found no superiority of any of these against others[4]. In studies investigating the side effect profile, the most frequently seen toxicities in patients receiving treatment with C-P may include myelosuppression, neuropathy, nausea, weakness, and arthralgia. While no difference is seen in terms of effectiveness compared to triweekly C-P treatment, toxicity rates have been shown to decline when paclitaxel is given weekly and carboplatin is administered every 3 weeks[6]. The objective of this study was to compare the effectiveness of weekly C-P regimen with triweekly C-P regimen in NSCLC.

MATERIALS AND METHODS

This study assessed patients followed-up and treated for lung cancer in Adana City Training and Research Hospital's Oncology Clinic between January 1, 2017 and July 1, 2021. Ethical approval was obtained from Adana City Training and Research Hospital (decision no: 1913, date: 21.04.2022). Patients evaluated were those diagnosed with lung cancer in the hospital automation system. The files of 104 patients with pathologically diagnosed lung cancer were screened for suitability for the study. A total of 181 patients with neuroendocrine carcinoma or small cell lung cancer were excluded from the study. In the second step treatments given to 623 patients with NSCLC were evaluated. Four hundred forty patients who received first line therapy other than C-P were excluded. Among the remaining 176 patients, 49 who first received chemo-radiotherapy for primary lung cancer were also excluded from the study. Out of remaining 127 patients, 23 patients who received weekly C-P treatment 3 times or less, or 1 cycle of triweekly C-P treatment were also excluded. Patients with driver mutations (EGFR, ALK, ROS etc.) were not included in the study.

Patients receiving paclitaxel at a dose of 80 mg/m^2 weekly and carboplatin 2 AUC (area under the curve) for the weekly treatment protocol, or paclitaxel at a dose of 175 mg/m^2 every 3 weeks and 5 AUC doses of carboplatin every 3 weeks for the triweekly treatment protocol were included.

Data from 104 eligible patients were evaluated statistically. Response to treatment and progression were adjudicated based on the assessment of conventional imaging reports registered in the hospital automation system according to RECIST 1.1. For patients who were followed up with positron emission tomography/computed tomography, adjudication was made by the assessment of final reports.

Statistical Analysis

Statistical Package for the Social Sciences 23.0 package software was used for the statistical analysis of the data. Categorical measurements were summarized in terms of number and percentage, continuous measurements were summarized as mean, deviation and minimum-maximum. Suitability for normal distribution was examined using the Shapiro-Wilk test. The chi-square test and Fisher's exact test were used for comparison of categorical variables. The Independent Student's t-test was used in groups conforming normal distribution and the Mann-Whitney U test in those not conforming normal distribution. The Spearman correlation test was used to investigate the relationship between overall survival (OS) and progression-free survival (PFS) values and continuous measurement values. The Kaplan-Meier and log-rank tests were used in survival analyses. Statistical significance level was set to 0.05 for all tests.

RESULTS

Out of the 104 patients included in the study, 90 (86.5%) were male and 14 (13.5%) were female. Fifty-two (50%) patients received weekly C-P and 52 (50%) received C-P every 3 weeks. Fifty-seven (54.8%) patients were followed-up for the diagnosis of adenocarcinoma, 21 (20.2%) for squamous cell carcinoma, and 26 (25%) for not otherwise specified (NOS). During the course of the treatment, 48 (46.2%) patients experienced radiological progression and 66 (63.5%) patients died. Clinical and demographic findings of the patients are presented in Table 1. Patients in the weekly C-P group received treatment for a median of 7 weeks and those in triweekly C-P group received a median of 3 cycles. Size of the primary mass was the same in both groups while SUV value of the primary mass was higher in the weekly C-P group (p=0.029). No difference was noted between the groups in terms of laboratory parameters (Table 1).

The mean OS was 19.64±2.53 months in the weekly C-P group and 17.47±1.64 months in the triweekly C-P group (p=0.675) (Figure 1).

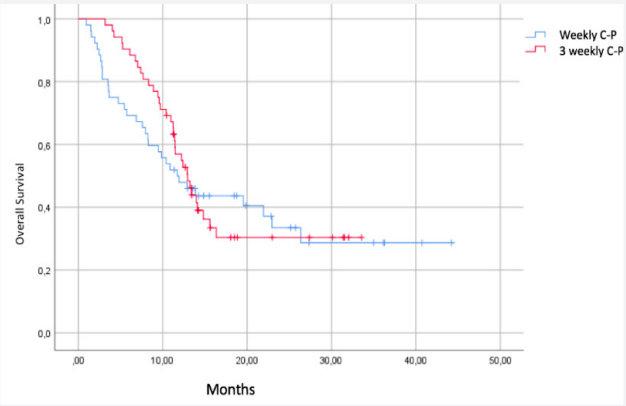

Figure 1. Overall survival according to chemotherapy regimen

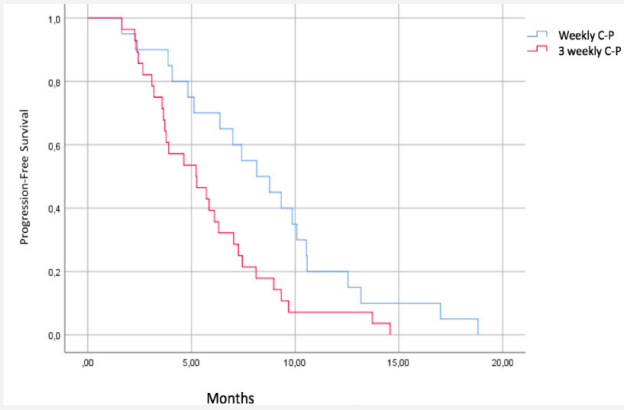

Figure 2. Progression-free survival according to chemotherapy regimen

Table 1. Demographic, clinical and laboratory characteristics of patients

	Weekly C-P[a]	Triweekly C-P[a]	Total	p
Age of diagnosis (mean, SD)	65.7 (8.9)	60.1 (8.9)	62.9 (9.3)	0.002[b,c]
Gender	**n (%)**	**n (%)**	**n (%)**	
Male	45 (86.5)	45 (86.5)	90 (86.5)	NA[d]
Female	7 (13.5)	7 (13.5)	14 (13.5)	
Diagnosis				
Adenocancer	29 (55.8)	28 (53.8)	57 (54.8)	0.896[d]
Squamous cell carcinoma	11 (21.2)	10 (19.2)	21 (20.2)	
Not otherwise specified	12 (23.1)	14 (26.9)	26 (25.0)	
Location of metastasis				
None	2 (23.1)	11 (21.2)	23 (22.1)	
Brain	7 (13.5)	9 (17.3)	16 (15.4)	0.603[d]
Other[g]	31 (59.6)	27 (51.9)	58 (55.8)	
Brain + other	2 (3.8)	5 (9.6)	7 (6.7)	
Number of metastases	2 (1-5)	2 (1-5)	2 (1-5)	0.275[e]
Number of treatments	7 (3-29)	3 (2-11)	5 (2-29)	**<0.001[e,c]**
Lactate dehydrogenase	267 (135-1736)	253 (159-10848)	260 (135-10848)	0.413[e]
Progression status				
None	32 (61,5)	24 (46.2)	56 (53.8)	0.116[f]
Yes	20 (38,5)	28 (53.8)	48 (46.2)	
Death status				
None	19 (36.5)	19 (36.5)	38 (36.5)	NA[d]
Yes	33 (63.5)	33 (63.5)	66 (63.5)	
Location of metastasis				
None	12 (23.1)	11 (21,2)	23 (22,1)	0.603[d]
Brain	7 (13.5)	9 (17,3)	16 (15.4)	
Other[g]	31 (59,6)	27 (51,9)	58 (55.8)	
Brain + other[g]	2 (3.8)	5 (9.6)	7 (6.7)	
Primary mass size in mm	48.5 (10-157)	52 (10-110)	51.5 (10-157)	0.352[b]
PET SUV value of the primary mass	13.3 (2.2-43)	11,1 (4.8-29.3)	11.8 (2.2-43)	**0.029[b,h]**
PET SUV value of the metastasis	6.8 (1.8-23)	5.6 (1.86-18.5)	6.1 (1.8-23)	0.374[b]

[a]C-P: Carboplatin-paclitaxel, [b]Independent Student's t-test (mean, SD), [c]p<0.001, [d]Chi-square test, [e]Mann-Whitney U test (median minimum-maximum), [f]Fisher's exact test, [g]Liver, bone, surrenal glands, [h]p<0.05.

PET: Positron emission tomography, LDH: Lactate dehydrogenase, SD: Standard deviation

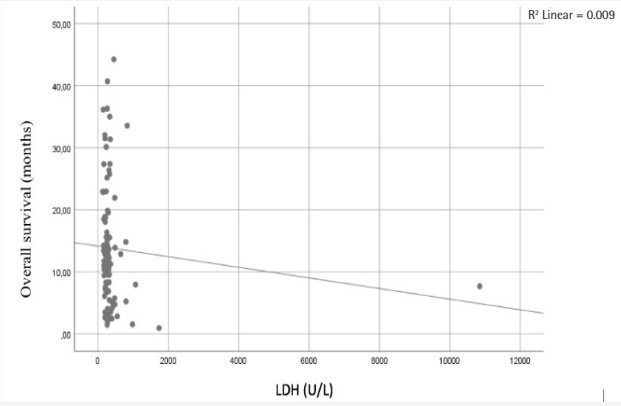

Figure 3. Overall survival according to LDH level

LDH: Lactate dehydrogenase

The mean PFS was 8.57±1.01 months in the weekly C-P group and 5.76±0.61 months in the triweekly C-P group with a significantly higher value (p=0.017) (Figure 2). There was no difference regarding lactate dehydrogenase (LDH) level between the groups (p=0.413). Considering all the patients included in the study, a correlation was found between LDH value and OS (r=-0.227; p=0.021) (Figure 3).

DISCUSSION

Many studies are available about the first-line therapy of patients with advanced NSCLC. In our study, we found that the PFS value was statistically longer with weekly C-P treatment, which is preferred because it is less toxic in advanced NSCLC patients[6]. Although it did not reach statistical significance, we found a 2.2-months prolongation in the OS value. Our study is the first to compare the effectiveness of weekly and triweekly C-P treatments. Comparative studies demonstrated that treatment with cisplatin-gemcitabine, cisplatin-vinorelbine, C-P and cisplatin-irinotecan had no superiority to each other[4,5,7,8].

OS value for triweekly C-P treatment varies between 7.3 and 11.4 months in different studies[9-12]. In the phase 2 study performed by Kallab et al.[13] in stage 3B and 4 NSCLC, paclitaxel was given at a weekly dose of 100 mg/m^2 and carboplatin was given weekly as 2 AUC. These two treatments were given during the first 3 weeks of 4-week cycle. The last week was left empty and effectiveness of the treatments was compared. In our study, paclitaxel was given at a dose of 80 mg/m^2, which is lower than they administered, and carboplatin was continuously administered weekly at 2 AUC with no breaks. Kallab et al.[13] found a PFS value of 5.4 months and OS of 10.8 months, which were longer with 8.57 and 19.64 months, respectively, in our study. Although the patients were of similar age, we attribute the difference between the spans to the fact that 97% of the patients in their study had stage 4 disease.

In the study by Sakakibara et al.[14], in which they investigated the effectiveness and toxicity in patients over the age of 70 years with stage 3B, stage 4 NSCLC and postoperative recurrence, paclitaxel was given at a weekly dose of 70 mg/m^2 and carboplatin as 3-week cycles at 6 AUC. PFS was found to be 6 months and OS 14.7 months. Despite advanced patient age, statistically fewer neutropenia and febrile neutropenia were found in weekly C-P compared to C-P every 3 weeks (p<0.0001 and p=0.018, respectively). The lower frequency of side effects makes weekly treatment favorable. Although ECOG score was not evaluated in our study, weekly treatment is preferred for patients with poorer health in our clinic owing to lower toxicity. While PFS was still longer compared to weekly treatment, our opinion is that weekly C-P treatment may be preferred to triweekly C-P in patients with advanced stage NSCLC without driver mutation.

Although the reason for not preferring weekly treatment is more frequent hospital visits and the additional financial burden on healthcare system[15], we think that lower toxicity compared to triweekly treatment may reduce hospitalizations due to side effects.

Despite the fact that the age, sex and histological subtypes of the two groups were the same, PFS was found to be statistically different between the groups. Because the groups were homogeneous, this difference was thought to be treatment-related. It may be related to the stable course of active drug blood concentration in weekly treatment.

We found a correlation between LDH value and OS (r=-0.227; p=0.021), which demonstrated that patients with higher tumor burden lived shorter as expected. Similarly, previous studies have also shown that high LDH levels are associated both with the presence of metastasis and with lower OS[16-18].

Study Limitations

The retrospective nature of the study and the inclusion of single center patients were our limitations. ECOG performance status could not be evaluated since patient data were accessed through hospital automation system. However, we consider the presence of a bias between the two groups while weekly treatment was preferred for patients with clinically poorer health and triweekly treatments were preferred in those with better health condition. Besides, drug toxicities could not be assessed in detail.

CONCLUSION

In conclusion, a considerable portion of patients with lung cancer have shorter survival because of not being suitable for local therapies at the time of diagnosis. Some of the patients who received systemic treatment die from tumor progression, and some due to drug toxicity. We demonstrated that weekly

C-P treatment, which is known to have fewer toxicity, provided better PFS in the similar patient group compared to triweekly treatment. Therefore, we assert that weekly C-P treatment may be used as the first option in patients with advanced stage NSCLC. Studies with prospective study design are needed to compare these two treatment protocols in terms of toxicity and effectiveness.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Adana City Training and Research Hospital (decision no: 1913, date: 21.04.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.A., T.K., T.Ç., Design: S.A., A.Z.B., T.K., B.B.D., Data Collection or Processing: S.A., O.K., B.A.B., H.D., Analysis or Interpretation: S.A., B.A.B., B.B.D., Literature Search: S.A., A.Z.B., Writing: S.A., T.Ç., B.B.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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