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ARAŞTIRMA / RESEARCH

Concurrent chemoradiotherapy with weekly carboplatin and paclitaxel may be a feasible option in inoperable stage III non-small cell lung cancer: a single center experience

Haftalık karboplatin/paklitaksel ile kemoradyoterapi inoperabl evre III küçük hücreli dışı akciğer kanserinde uygun bir seçenek olabilir: tek merkez deneyimi

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Abstract

Purpose: Concurrent chemoradiotherapy (CCRT) is a standard treatment for patients with unresectable stage III non-small cell lung cancer (NSCLC). An optimal chemotherapy regimen with concurrent thoracic radiotherapy is not known. In this study, we investigated the efficacy and toxicity of CCRT with carboplatin [area under curve (AUC) 2] and paclitaxel (80 mg/m^2) during CCRT.

Materials and Methods: We performed a retrospective survival analysis using medical records of 40 patients with inoperable stage III NSCLC that were treated with concurrent chemoradiotherapy with carboplatin-paclitaxel (AUC 2, 60 mg/m^2).

Results: The most common histopathology was adenocarcinoma, which was diagnosed in 18 patients (45%). There were 12 stage IIIA patients (30%) and 28 stage IIIB patients (70%). The median follow-up time was 22.5 months [95% confidence interval (CI), 2.9–72.2]. Median disease-free survival (DFS) and overall survival (OS) were 22.5 months (95% CI, 18.1–27.0) and 53.5 months (95% CI, 23.5–82.8). Grade 3-4 hematological and non-hematological toxicities were seen in 8 (20%) and 5 (12.5%) patients, respectively.

Conclusion: This study showed that CCRT with weekly carboplatin-paclitaxel provides similar outcomes to cases in the literature and the regimen seems to be feasible with a low rate of grade 3-4 toxicity during CCRT of non-operable stage III NSCLC.

Keywords: Carboplatin, non-small cell lung cancer, chemoradiotherapy, paclitaxel

Öz

Amaç: Eşzamanlı kemoradyoterapi (KRT) cerrahi tedaviye uygun olmayan lokal ileri evre küçük hücreli dışı akciğer kanseri (KHDAK) tanılı hastalar için standart bir tedavi yöntemidir. KRT için optimal bir kemoterapi rejimi tanımlanmamıştır. Bu çalışmada, karboplatin (AUC 2) ve paklitaksel (80 mg / m2) ile kombine KRT tedavisinin etkinliği ve toksisitesini araştırdık.

Gereç ve Yöntem: Bu çalışma hastane bazlı retrospektif gözlemsel vaka seri çalışması olarak tasarlanmıştır. İnoperabl evre III KHDAK'li toplam 40 hasta haftalık karboplatin-paklitaksel ile eş zamanlı kemoradyoterapi ile tedavi edildi.

Bulgular: En sık görülen histopatoloji, 18 hastada (%45) teşhis edilen adenokarsinomdu. 12 hasta (%30) evre IIIA ve 28 hasta (%70) evre IIIB idi. Ortanca takip süresi 22.5 ay idi [%95 (CI), 2.9-72.2]. Medyan hastalıksız sağkalım (DFS) ve genel sağkalım (OS) 22.5 ay (%95 CI, 18.1–27.0) ve 53.5 ay (%95 CI, 23.5-82.8) idi. Hastaların 8'inde (%20) ve 5'inde (%12.5) sırasıyla grade 3-4 hematolojik ve non-hematolojik toksisite izlendi.

Sonuç: Bu çalışma, haftalık karboplatin-paklitaksel ile KRT'nin literatürdeki vakalara benzer sonuçlar verdiğini ve inoperable evre III KHDAK'de KRT sırasında düşük dereceli 3-4 derece toksisite ile uygulanabilir olduğunu gösterdi.

Anahtar kelimeler: Karboplatin, küçük hücreli dışı akciğer kanseri, kemoradyoterapi, paklitaksel

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INTRODUCTION

Lung cancer is the most common cause of cancer-related deaths in both sexes, even though the incidence of breast cancer is higher than lung cancer in women. Non-small cell lung cancer (NSCLC) includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Development of a treatment plan for a patient with lung cancer depends upon the cell type, tumor stage and an assessment of the patient's overall medical condition. Certain tumors are characterized by local invasiveness (or size). The stage classification for non–small-cell lung cancer (NSCLC) follows the tumor, node, metastasis (TNM) paradigm used for most solid tumors. Although they are classified as stage IIb, IIIa or IIIb, they may be biologically different than tumors distinguished primarily by nodal involvement.

Locally advanced NSCLCs are highly heterogeneous tumors with their extent, localization and lymph node involvement sites. Only curative treatment is the complete surgical resection for early stage (stage 1 and 2) patients. The management of patients with stage III NSCLC, which usually requires a combined modality approach. There have been major improvements in surgical techniques for patients with stage 3 cancer. But concurrent chemoradiotherapy (CCRT) is the standard treatment for non-operable patients[1,2,3]. CCRT provides better overall survival (OS) compared to sequential chemotherapy followed by radiotherapy or thoracic radiotherapy only. The most commonly used regimens are mitomycin-vindesine and cisplatin, etoposide and cisplatin, paclitaxel and carboplatin, and vinorelbine and cisplatin. Despite the high response rate with CCRT, median overall survival time for these patients is 15–25 months and the optimal chemotherapy regimen in CCRT is not well-defined. In this study we investigated the effectiveness and toxicity of weekly carboplatin (AUC 2) and paclitaxel (60 mg/m^2) during CCRT. Therefore, we aimed to show that a less toxic treatment option could be used among treatment modalities with similar response rates.

MATERIALS AND METHODS

The Acibadem Mehmet Ali Aydinlar Unıversity Department of Medical Oncology database was searched for the International Classification of Diseases (ICD) codes for lung cancer between the years of 2011 and 2017. Patients with stage 3 who were not eligible for surgical treatment were included in the study and other patients excluded. Of 350 lung cancer patients, 40 patients (11.4%) were unresectable stage III NSCLC (determined by consultation with thoracic surgeon). All patients had histological confirmation and patients determined by whole body positron emission tomography-computed tomography (PET-CT) 18F-fluorodeoxyglucose (18F-FDG) scans and cranial magnetic resonance imaging (MRI) for staging. The patients with primary lung mass and lymph node involvement were included as locally advanced patients and patients with distant metastases were excluded from the study. *Unresectable stage 3* was used for patients not eligible for surgery. The endpoint of the study was PFS and OS and treatment toxicities also evaluated.

Table-1. Patient characteristics.

Variable	n(%)
Gender	
Men	36 (90)
Women	4 (10)
ECOG	
0	23 (57.5)
1	17 (42.5)
Median age (years)	62 (40-77)
Smoking	36 (90)
Histology	
Adenocarcinoma	18 (45)
Squamous cell carcinoma	15 (37.5)
Adenosquamous type	1 (2.5)
Non-classified NSCLC	6 (15)
Stage	
IIIA	12 (30)
IIIB	28 (70)
Comorbidities	10 (25)

All patients underwent three-dimensional conformal radiotherapy (3DCRT), field-in-field intensity modulated radiotherapy (FinF IMRT), or hybrid volumetric modulated arc therapy. Treatment planning CT was obtained in a supine, arms-raised position using a 2-mm slice thickness. The gross tumor volume included the primary disease, as well as any involved regional lymph nodes, which were defined as those with a short-axis diameter of at least 1 cm on the CT scan or with high fluorodeoxyglucose (FDG) uptake on the PET-CT scan. The clinical tumor volume included the primary tumor, plus a 0.8 cm margin radially and 1.5 cm cranio-caudally. A planning target volume (PTV)

margin of 0.5 cm was added with involvement of ipsilateral hilum and mediastinal nodal stations. A total dose of 60-66 Gy (2 Gy per fraction, five times/week) was prescribed. Treatment verification was performed by daily on-board kV imaging.

Table-2. Major toxicities during CCRT

Hematological Toxicities	
Neutropenia	7 (17.5)
Anemia	1 (2.5)
Non-hematological toxicities	
Pneumonia	2 (4.5)
Neuropathy	3 (7.5)
Rate of Mortality	16 (40)

Treatment protocols for patients included carboplatin (AUC 2 for 1 week)-paclitaxel (60 mg/m² for 1 week) during radiotherapy (5-6 doses in total) plus two cycles of consolidation chemotherapy with carboplatin (AUC 5 for 3 weeks)-paclitaxel (175 mg/m² for 3 weeks) after CCRT. Clinical examination at every 3 months and radiological examination at every 6 months imaging were used for patient surveillance. Types of first relapses (distant and local) were recorded.

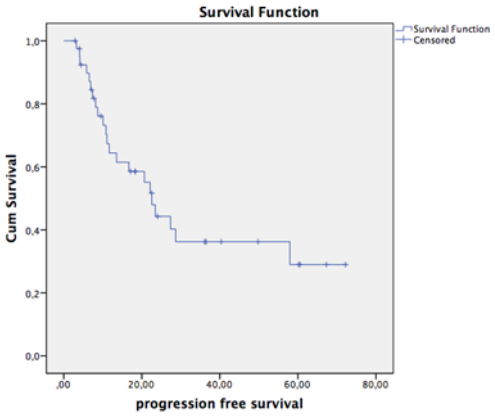

Figure-1. Kaplan-Meier Disease-free survival of patients treated with concurrent chemoradiotherapy with carboplatin-paclitaxel, 22.5 months ([(95% CIs), 18.1–27.0).

Ethical approval was sought and granted by the institutional ethics committee in Acibadem University Hospital, Adana, Turkey. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Results for categorical values are presented as a rate and results for continuous variables as mean and median. OS was defined as the time between diagnosis and death; DFS was defined as the time between the last visit and disease recurrence or the day of the last visit. Survival curves were estimated by Kaplan-Meier analysis and log-rank tests were used for univariate statistical comparisons. The Cox-regression model was used for the multi-variate analysis. Adjusted Hazard Ratio (HR) and 95% CIs were used for estimation. All statistical data were analyzed using SPSS version 17.0 and a p-value of <0.05 was considered statistically significant.

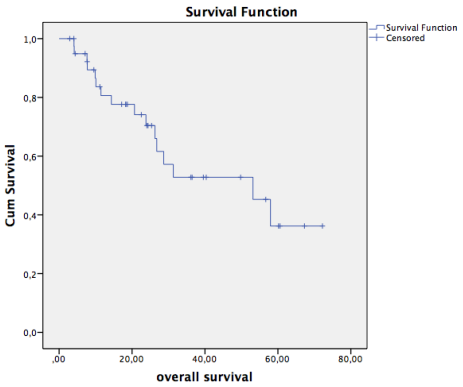

Figure-2. Kaplan-Meier Overall survival of patients treated with concurrent chemoradiotherapy with carboplatin-paclitaxel, 53.5 months ([(95% CIs), 23.5–82.8)

RESULTS

Patient baseline characteristics are shown in Table 1. The median age was 62 years (range 40–77) and 36 patients (90%) were men. The majority of patients (n = 23, 57.5%) had an ECOG performance score of 0. There were 18 patients (45%) with an adenocarcinoma subtype. There were 12 stage IIIA patients (30%) and 28 stage IIIB patients (70%).

Treatment and outcomes

The median follow-up time to the study was 22.5 months (95% CI, 2.9 – 72.2). During the study period, 16 patients (40%) died. Median DFS and OS were 22.5 months (95% CI, 18.1–27.0) and 53.5 months (95% CI, 23.5–82.8), respectively (Figures 1 and 2). Disease relapse occurred in 23 patients (57.5 %). Distant and local relapse rates were 45% (n = 18) and 12.5% (n = 5), respectively. In all patients who received the planned CCRT therapy, no death

was seen during active CCRT or consolidation chemotherapy. Furthermore, hematological and non-hematological grade 3–4 toxicities were seen in 8 (20%) and 5 (12.5%) patients, respectively (Table 2).Discussion

Despite advances in monitoring and radiologic imaging techniques, most patients were diagnosis at advanced stage. Data in the literature strongly suggest that CCRT significantly improves survival rates when compared to thoracic radiotherapy and sequential chemoradiotherapy Treatment of stage III non-operable NSCLC is controversial in an era of genome directed treatment. However, bulky stage IIIA and stage IIIB tumors are treated with CCRT in most cases[4-6]. But the best chemotherapy regimen in CCRT is not well defined. Results from two randomized studies showed a survival advantage with a CCRT approach, compared to a sequential approach[7, 8]. In this study, we reported the clinical outcomes and toxicity associated with a regimen of weekly carboplatin and paclitaxel during CCRT with two cycles of consolidation chemotherapy with carboplatin (AUC 5 for 3 weeks)-paclitaxel (175 mg/m^2 for 3 weeks). Our results showed that CCRT with the current protocol resulted in a DFS of 22.5 months (95% CI, 18.1–27.0) and an OS of 53.5 months (95% CI, 23.5–82.8). Hematological and non-hematological grade 3-4 toxicities were found in 8 (20%) and 5 (12.5%) patients, respectively. These results suggest that this regimen can produce a fairly good survival rate with acceptable toxicity. However, our results showed a high distance failure rate of 45%, which was consistent with studies of CCRT therapy in other research.

Cisplatin-etoposide and carboplatin-paclitaxel regimens in CCRT are most commonly used in the United States [9]. These two regimens were compared in a randomized trial of 191 patients with stage III NSCLC receiving CCRT. At a median follow-up of 73 months, those receiving cisplatin plus etoposide had an improved 3-year survival rate (41% versus 26%, absolute difference 15%) and a trend towards improved OS (23.3 versus 20.7 months), with a greater rate of esophagitis in patients treated with cisplatin-etoposide[9]. In a phase III trial of approximately 600 patients, pemetrexed-cisplatin with RT and pemetrexed consolidation was associated with a similar survival rate as cisplatin-etoposide treatment (median OS: 27 versus 25 months) and a lower incidence of drug-related grade 3 to 4 adverse events (64% versus 77%) [10]. Although, our results with a regimen of carboplatin and paclitaxel during CCRT provide compelling evidence for a high DFS and OS with low toxicity.

We acknowledge that the current study has crucial limitations that must be considered. First, as a retrospective study with a limited number of patients, the study design is subject to inherited biases. Second, we present data from weekly carboplatin-paclitaxel treatment that was also studied in a large phase III study. Nonetheless, the current study has several strengths. The data were obtained from the single reference center over a specific period. All patients staged with PET-CT and cranial MRI presented with detailed clinicopathological characteristics. There was a considerable follow-up period with a mean of 22.5 months and the death rate in the study was 39%.

In the literature, there are more trials in patients with squamous cell carcinoma for stage III. But in this study, we evaluated both squamous and adenocarcinoma patients.

This study showed that CCRT with a carboplatin-paclitaxel regimen promoted patient survival with acceptable toxicity rates. This research provides evidence that CCRT with weekly carboplatin-paclitaxel is a feasible option for non-operable stage III NSCLC patients.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ZÇ; Veri toplama: ZÇ; Veri analizi ve yorumlama: AMS; Yazı taslağı: ZÇ, AMS; İçeriğin eleştirel incelenmesi: PS; Son onay ve sorumluluk: ZÇ, AMS, PS; Teknik ve malzeme desteği: ZÇ, AMS, PS; Süpervizyon: AMS, PS; Fon sağlama (mevcut ise): yok.
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