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CLINICAL OUTCOMES OF PATIENTS WITH STAGE III LUNG CANCER OPERATED AFTER NEOADJUVANT CHEMOTHERAPY: EFFECT OF CHEMOTHERAPY REGIMEN

NEOADJUVAN KEMOTERAPİ SONRASI OPERE OLAN EVRE III AKCİĞER KANSERLİ HASTALARIN KLİNİK SONUÇLARI: KEMOTERAPİ REJİMİNİN ETKİSİ

Özlem YERSAL

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Anahtar Sözcükler: Küçük hücreli dışı akciğer kanseri, indüksiyon tedavisi, neoadjuvan kemoterapi

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SUMMARY

Introduction: *The neoadjuvant therapeutic approach remains one of the most debated topics in NSCLC treatment. In this study, we aimed to evaluate patients with stage III NSCLC retrospectively, who were operated after neoadjuvant chemotherapy in a single instution and compare the long term clinical outcomes according to the chemotherapy protocols.*

Material and Method: *Between 2014 and 2017; 30 patients who had surgery for NSCLC after neoadjuvant chemotherapy at our institution were included. Patients received 3 cycles of one of the induction chemotherapy schedules. Following completion of induction therapy, all patients underwent resection of the primary tumor, in terms of pneumonectomy, lobectomy, or bilobectomy and lymph node dissection. Kaplan-Meier curves were used to calculate the overall survival (OS) and progression free survival (PFS). Univariate analyses and multivariate analyses were performed by the Cox proportional hazards model to assess the influence of variables on progression free and overall survival. All analyses were performed with SPSS version 23 (IBM SPSS, Armonk, NY, USA).*

Results*: Neoadjuvant chemotherapy protocols were chosen according to histological subtype. The most preferred regimen was cisplatin plus docetaxel (66.7%) for adenocancer subtype and cisplatin and gemcitabine combination(47.1%) for squamous cancer subtype. Progression free survival was 31 months and the median overall survival for the whole study population was 42 months. Neither PFS (p: 0.363) nor OS (p:0.604) did not correlate with chemotherapy regimens.*

Conclusion*: Our results suggest that chemotherapy regimens do not have prognostic value in NSCLC patients who but large scale trials are needed to confirm this findings.*

ÖZ

Giriş: *Neoadjuvan tedavi, küçük hücreli dışı akciğer kanseri (KHDAK) tedavisinde en tartışmalı konulardan birisidir. Bu çalışmada, neoadjuvan kemoterapiden sonra opere edilen evre III KHDAK'li hastaların, kemoterapi protokollerine göre uzun dönem klinik sonlanımlarının karşılaştırılmasını amaçladık.*

Gereç ve Yöntem: *2014-2017 arasında; kurumumuzda neoadjuvan kemoterapi sonrası opere olan 30 hasta çalışmaya alındı. Hastalara, 3 siklus indüksiyon kemoterapi verildi. İndüksiyon tedavisinin tamamlanmasının*

ardından tüm hastalara pnömonektomi, lobektomi veya bilobektomi ve lenf nodülü diseksiyonu uygulandı. Genel sağkalım (OS) ve progresyonsuz sağkalımı (PFS) hesaplamak için Kaplan-Meier yöntemi kullanıldı. Tek değişkenli ve çok değişkenli analizlerin, progresyonsuz ve genel sağkalım üzerindeki etkisini değerlendirmek için Cox regresyon analizi yapıldı. Tüm analizler SPSS 23 (IBM SPSS, Armonk, NY, ABD) ile gerçekleştirilmiştir.

Bulgular: *Neoadjuvan kemoterapi protokolleri histolojik alt tiplere göre seçilmiştir. En çok tercih edilen rejim, skuamöz kanser alt tipi için cisplatin ve gemsitabin kombinasyonu (% 47.1) ve adenokanser için cisplatin ve dosetaksel (% 66.7) idi. Tüm çalışma popülasyonu için progresyonsuz sağkalım 31 ay ve median genel sağkalım 42 aydı. PFS (p: 0.363) ve OS (p: 0.604) kemoterapi rejimleri ile korelasyon göstermedi.*

Sonuç: *Bulgularımız, KHDAK hastalarında kemoterapi rejimlerinin prognostik değere sahip olmadığını göstermektedir, ancak bu bulguları doğrulamak için büyük ölçekli çalışmalara ihtiyaç vardır.*

INTRODUCTION

Stage III non-small cell lung cancer (NSCLC) is a heterogeneous group of disease which includes tumors with local structure invasion, and/or microscopic or bulky mediastinal lymph node metastasis. The extent of mediastinal lymph node involvement is one of the most significant prognostic factors (1). Definitive chemoradiation or induction chemotherapy followed by surgical resection in particular patients are the treatment options for stage III disease. Today, the neoadjuvant therapeutic strategy remains one of the most controversial topics in NSCLC treatment (2).

Multiple randomized-controlled trials showed a significant survival benefit, supporting the use of induction chemotherapy for patients with stage III NSCLC before surgical resection (3-6). A meta-analysis of 12 randomized studies from 1995 to 2005, also demonstrated a survival benefit for neoadjuvant chemotherapy in NSCLC (7).

Preoperative chemotherapy provides opportunity for evaluation of response to therapy, which may detect patients that would benefit from adjuvant treatment; theoretically may prevent distant metastasis via early treatment of micrometastasis, and may reduce drug resistance due to early treatment exposure. It is also associated with increased rate of resectability and conservation of pulmonary function (8).

Neoadjuvant treatment regimens with novel chemotherapeutic drugs including gemcitabine, paclitaxel, vinorelbine, docetaxel, and pemetrexed have demonstrated response rates between 44–80%, and complete resection rates of 67–79% (9-11). Platinum-based neoadjuvant regimens have shown the highest overall response rates ranging from 50 to 70% depending on the combination protocol (12-14).

In this study, we aimed to evaluate patients with stage III NSCLC who were operated after neoadjuvant regimens and compare the long term clinical outcomes according to chemotherapy protocols.

MATERIAL AND METHOD

Patients

This retrospective study evaluated a total of 30 stage III lung cancer patients who were treated with neoadjuvant chemotherapy followed by surgical resection at a single institution between 2014 and 2017.

All patients had FDG-PET or chest and abdomen tomography evaluation before and after induction chemotherapy. Patients who progressed after chemotherapy or those who did not operated for any reason were excluded from the study. Mediastinal staging was performed by contrast enhanced CT of the chest and FDG-PET/CT. All patients were evaluated by a multidisciplinary team consisting of radiation oncologist, medical oncologist, thoracic surgeon, and pulmonary medicine specialist. Response evaluation was performed either with PET BT and pathologic evaluation of operation specimen. Pulmonary function tests were done for all patients.

Demographic data, clinicopathological data and treatment parameters (i.e. extent of surgical resection, radiotherapy and chemotherapy protocols) were obtained from medical records. Staging was determined according to the 8th edition of TNM classification of malignant tumors. Data on patient death was obtained from the

Electronical National Registry of Death System, Turkey

Treatment

All patients were treated with preoperative chemotherapy and after surgical resection. Patients received 3 cycles of one of the induction chemotherapy schedules. Chemotherapy regimens were as follows; cisplatin 75 mg/m2 and gemcitabine 1250 mg/m2 day 1 and 8 every 21 days; or cisplatin 75 mg/m2 and docetaxel 75 mg/m2 day 1 every 21 days; or cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 day 1 every 21 days; or cisplatin 100 mg/m2 and etoposide 100 mg/m2 day 1-3 every 21 days; or carboplatin AUC 5 day 1 and paclitaxel 175 mg/m2 every 21 days.

Following completion of induction therapy, all patients underwent resection of the primary tumor, in terms of pneumonectomy, lobectomy, or bilobectomy and lymph node dissection.

Statistical evaluation

Qualitative variables were expressed as absolute frequency and percentage. Progression-free survival (PFS) was calculated as the duration from the diagnosis to detection of tumor progression on radiologic evaluation or to death. The time between the date of diagnosis and death, or to the last follow-up for surviving patients was defined as overall survival time. Kaplan-Meier curves were used to calculate the overall survival (OS) and progression free survival (PFS). Patients, who alive at last visit were censored in the analysis. Univariate analyses and multivariate analyses were performed by the Cox proportional hazards model to evaluate the influence of variables on progression free and overall survival. $P<0.05$ was considered statistically significant. All analyses were performed with SPSS version 23 (IBM SPSS, Armonk, NY, USA).

RESULTS

Patient characteristics

The patient characteristics are shown in Table 1. All patients exhibited an ECOG PS of 0 or 1, the median age of patients was 66 years (range, 47-84 years). All patients had stage III NSCLC at diagnosis, and 11(36.7%) patients had N2 mediastinal node involvement.

Table 1. Patient clinical and demographic characteristics

Age		66 (47-84)
Gender	Female	1 (3.3%)
	Male	29 (96.7%)
Histology	Squamous	17 (56.7%)
	Adeno	12 (40%)
	Adenosquamous	1 (3.3%)
Side	Right	15 (50%)
	Left	15 (50%)
N2 involvement	Yes	11 (36.7%)
	No	19 (63.3%)
Postchemo N2	Yes	5 (16.7%)
	No	25 (83.3%)
Operation type	Lobectomy	22 (73.3%)
	Pneumonectomy	7 (23.3%)
	Bilobectomy	1 (3.3%)
PET response	Complete	4 (13.3%)
	Partial	21 (70%)
	Stable	1 (3.3%)
	Progression	1 (3.3%)
Ypstage	Complete	2 (6.7%)
	Stage IA	4 (13.3%)
	Stage IIA	6 (20%)
	Stage IIB	12 (39%)
	Stage IIIA	

Neoadjuvant chemotherapy protocols and response to treatment

Neoadjuvant chemotherapy protocols were chosen according to histological subtype. The most preferred regimen was cisplatin plus docetaxel (66.7%) for adenocancer subtype and cisplatin and gemcitabine combination (47.1%) for squamous cancer subtype.

According to PET BT evaluation; a total of 25 patients (83.3%) responded to induction treatment; a total of 4 patients (13.3%) showed a complete response and 21 patients (70%) showed a partial response according to the Response Evaluation Criteria In Solid Tumors criteria Four patients (13.3%) experienced a stable response, and 1 patient (3.3%) progressed after induction chemotherapy. The chemotherapy regimens and response rates were shown in Table 2. There was no statistically significant difference between response rates according to protocols ($p>0.05$).

Table 2. Response rates according to chemotherapy protocols

	Protocol	N(%)	Response rate
Squamous (n:17)	Cisplatin+docetaxel	4 (23.5%)	4 (100%)
	Cisplatin+gemcitabine	8 (47.1%)	6 (75%)
	Other	5 (29.4%)	4 (75%)
Adenocarcinoma (n:12)	Cisplatin+docetaxel	8 (66.7%)	6(75%)
	Cisplatin+pemetrexed	2 (16.7%)	2(100%)
	Other	2 (16.7%)	2(100%)
Adenosquamous (n:1)	Cisplatin+gemcitabine	1	1 (100%)

Progression free survival

Progression free survival was 31 months in the whole study population. PFS was not different according to chemotherapy protocols in both adenocancer and squamous cell cancer subtypes (p:0.363). Patients who had bilobectomy had lower PFS than patients with lobectomy (HR: 28.517; 95% CI: 1.73-470.12; p:0.019). The other clinicopathologic features such as prechemotherapy N2 (p:0.872), residual N2 disease (p:0.320), histologic subtype (p:0.977), PET response(complete or not) (p:0.167), tumor diameter(p:0.416), metastatic lymph node count(p:0.161) were not associated with progression free survival.

Overall survival

Median follow up time was 29 months. 10 patients had died at the end of the follow up period. The median overall survival for the whole study population was 42 months. There was no significant difference according to histologic subtype. 2-year overall survival rate was 55% for adenocarcinoma patients and 49% for squamous lung cancer patients(p:0.604).

The overall 1 year, 2 year and 3 year survival rates for patients with adenocarcinoma; were 80%, 48% and 48% for cisplatin+docetaxel arm; 100%, 100%, 100% for cisplatin and pemetrexed and 100%, 100% and 0% for other protocol arm respectively. There was no statistically significant difference between chemotherapy regimens (Figure 1).

The overall 1 year, 2 year and 3 year survival rates for patients with squamous cell carcinoma; were 58%, 43% and 22% for cisplatin+ gemcitabine arm; 71%, 71%, 71% for other arm and 1 year survival was 100%, for cisplatin+ docetaxel arm. There was no statistically significant difference between chemotherapy regimens (Figure 2).

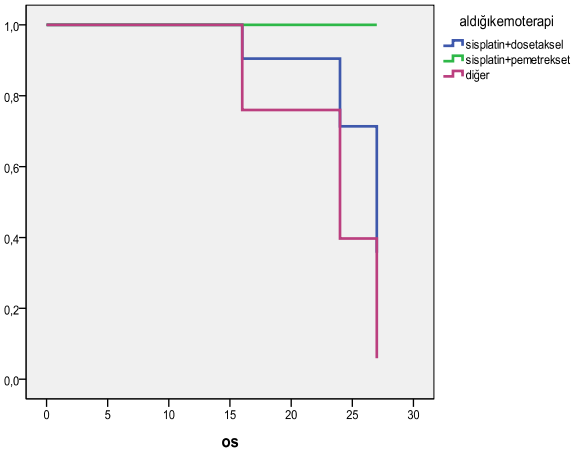


Figure 1. Overall survival according to chemotherapy regimens in adenocarcinoma

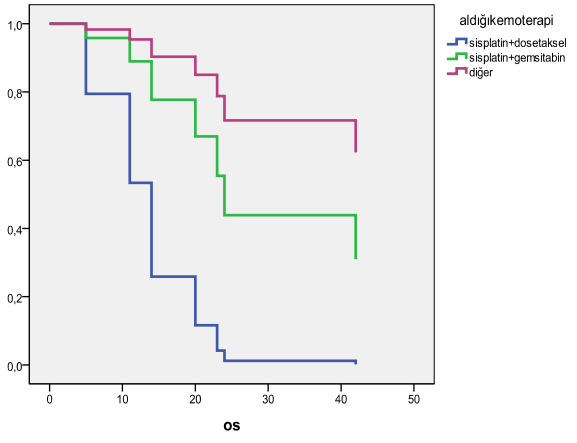


Figure 2. Overall survival according to chemotherapy regimens in squamous cell carcinoma

In univariate analysis, there was not any significant differences between any of the clinicopathological patient characteristics in terms of prechemotherapy N2(p:0.151), residual N2 disease(p:0.373), histologic subtype(p:0.936), PET response(complete or not) (p:0.735), tumor diameter (0.594), metastatic lymph node count (p:0.126) and overall survival were identified.

DISCUSSION

NSCLC patients receiving neoadjuvant chemotherapy demonstrate approximately a median survival time of 20 months and a 3-year survival rate of 34% (15). In resected patients survival time is longer as compared to than those who had not operated. (16). Krzakowski et al, found that; the median survival time was 48.5 months in 62 completely resected patients, 12.9 months in 13 incompletely resected patients, and 16.8 months in 15 non-resected patients after induction chemotherapy (17). In the present study, clinical outcomes were compatible with literature with a median OS of 42 months and a 3 year survival rate of 42%. We evaluated the effect of chemotherapy regimens on overall survival and we could not find any difference on clinical outcomes according to chemotherapy regimens.

Despite, two studies reported higher rates, generally complete response rates for neoadjuvant chemotherapy varies from 0 to 9.5% (18-19) In this study, the complete response rate was 13.3%. Although, it is a striking result, it was not associated significantly with the overall survival due to the small sample size.

The efficacy of various chemotherapy regimens in the neoadjuvant setting has been evaluated in many phase II trials. Current standard of induction therapy is a platinum doublet; as platinum-based neoadjuvant regimens have shown the highest overall response rates ranging between 50 and 70%. One of the most studied regimen in the neoadjuvant setting is cisplatin and etoposide with or without radiation therapy (20). However, more modern agents, such as cisplatin–vinorelbine, cisplatin–gemcitabine, cisplatin–docetaxel, and cisplatin–pemetrexed have also evaluated in clinical trials (21). Also, carboplatin and paclitaxel is another chemotherapy combination option with more favorable toxicity profile. This combination regimen studied in patients with stage IIIA (N2) NSCLC in a phase II trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) which demonstrated a response rate of 64% and a median survival time of 20.5 months(3). There is no randomised controlled trials comparing the efficacy of different platin based regimens. Spanish group trial which used a platin-based regimen with three drugs, resulted with increased toxicity and postoperative deaths. (7.8%) (16) In our study; the most preferred chemotherapy protocol was cisplatin plus docetaxel for adenocarcinoma subtype, and cisplatin and gemcitabine for squamous cell carcinoma subtype with a response rate of 75%.

Neoadjuvant platinum-based chemotherapy for NSCLC produce 12% relative survival gain or 5% OS improvement in 5 years (21). Patients had improved compliance with neoadjuvant chemotherapy. One of the most important aspect is that, neoadjuvant chemotherapy is not associated with higher post-operative complications or death (22). In our study there was no postoperative deaths.

In conclusion; neoadjuvant chemotherapy is a reliable option for stage III NSCLC patients. Our results suggest that chemotherapy regimens do not have prognostic value in NSCLC patients who but large scale trials are needed to confirm this findings.

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