DOI:10.24938/kutfd.465529 Kırıkkale Üniversitesi Tıp Fakültesi Dergisi 2019;21(1):28-36
Original Article *Özgün Araştırma*

CORRELATION OF HISTOPATHOLOGIC RESPONSE AND PROGNOSTIC MARKERS WITH THE SURVIVAL IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY

Neoadjuvan Kemoterapi ile Tedavi Edilen Lokal İleri Evre Küçük Hücreli Dışı Akciğer Kanseri Hastalarının Sağkalımında Histopatolojik Yanıt ve Prognostik Belirteçlerin Korelasyonu

Samed RAHATLI[1] Nadire KÜÇÜKÖZTAŞ[2], Selim YALÇIN[3], Merih TEPEOĞLU[4], Dalokay KILIÇ[5], Özden ALTUNDAĞ[6]

[1,6] Başkent Üniversitesi Tıp Fakültesi Ankara Hastanesi, Tıbbi Onkoloji Bölümü, ANKARA, TÜRKİYE
[2] Başkent Üniversitesi Tıp Fakültesi İstanbul Hastanesi, Tıbbi Onkoloji Bölümü, ANKARA, TÜRKİYE
[3] Kırıkkale Üniversitesi Tıp Fakültesi, Tıbbi Onkoloji Bölümü, ANKARA, TÜRKİYE
[4] Başkent Üniversitesi Tıp Fakültesi Ankara Hastanesi, Patoloji Bölümü, ANKARA, TÜRKİYE
[5] Başkent Üniversitesi Tıp Fakültesi Ankara Hastanesi, Göğüs Cerrahisi Bölümü, ANKARA, TÜRKİYE

ABSTRACT

Objective: We aimed to determine the response and prognosis to neoadjuvant chemotherapy in patients with stage III non-small-cell lung cancer (NSCLC) who had received neoadjuvant therapy and to determine the relationship with prognosis and treatment response of the expression of excision repair cross-complementation group 1 protein (ERCC1) and Ribonucleotide reductase regulatory subunit M1 (RRM1) protein.

Material and Methods: Twenty-seven patients with stage III NSCLC who received neoadjuvant chemotherapy and had been operated between 2003 and 2013 were included in this study. Lung tissue biopsies were evaluated by immunohistochemical methods for ERCC1 protein expression in patients who received cisplatin and RRM1 protein expression who received gemcitabine.

Results: Median age was 59 (45-75). Nineteen patients (70.4%) were at stage IIIA and eight patients (29.6 %) were at stage IIIB. All patients received neoadjuvant cisplatin-based chemotherapy. Fifteen patients (55.6%) relapsed during follow-up. The median follow-up time was 36 months. The median disease-free survival (DFS) was 26.6 months, overall survival (OS) was 48 months. From the perspective of stage IIIA and IIIB DFS (p=0.379) and OS (p=0.69) did not differ significantly. Sixteen patients' (59.3%) viable tumor ratio was ≤10%, 11 patients' (40%) viable tumor ratio was >10%. When considered from this point of view DFS (p=0.16) and OS (p=0.097) showed no difference. More patients survived in the low ERCC1 expression group. Patients with low ERCC1 expression and patients with high ERCC1 expression showed no difference in terms of survival.

Conclusion: Patients with high RRM1 expression showing resistance to gemcitabine and with low RRM1 expression had similar survival rates. In patients with stage III NSCLC who received neoadjuvant chemotherapy, OS and DFS durations longer than literature were found.

***Keywords**: ERCC1, RRM1, Lung Cancer, Stage III, Neoadjuvant Chemotherapy*

ÖZ

Amaç: Neoadjuvan kemoterapi almış olan evre III küçük hücreli dışı akciğer kanserli (KHDAK) hastalarda neoadjuvan tedavi yanıtlarının belirlenmesi ile, prognoza katkısı ile eksizyon onarım çapraz-tamamlayıcı grup 1 (ERCC1) ve Ribonükleotid Redüktaz alt ünitesi Ml (RRM1) ekspresyonunun tedavi yanıtı ve prognozla ilişkisinin belirlenmesini hedeflendi.

Gereç ve Yöntemler: Bu çalışmaya 2003-2013 yılları arasında Evre III KHDAK tanısıyla neoadjuvan kemoterapi alıp 27 hasta dahil edildi. Neoadjuvan cisplatin alan hastaların akciğer biyopsi dokularında ERCC1 ve gemsitabin alan hastaların biyopsi materyallerinde RRM1 protein ekpresyonu immünohistokimyasal yöntemle değerlendirildi.

Bulgular: Medyan yaş 59 (45-75)'du. Hastaların 19 (%70.4)'u evre IIIA, 8 (%29.6)'i evre IIIB idi. Hastaların hepsi cisplatin bazlı neoadjuvan kemoterapi aldı. Hastaların 15 (%55.6)'inin takiplerinde nüks tespit edildi. Ortanca takip süresi 36 aydı. Tüm olgulara ilişkin ortalama hastalıksız sağ kalım (HSK) 26.6 aydı. Genel sağkalım (GSK) ise 48 ay olarak bulundu. Evre IIIA ve IIIB açısından bakıldığında HSK (p=0.379) ve GSK (p=0.69) açısından anlamlı fark bulunmadı. Hastaların 16 (%59.3)'sında neoadjuvan KT sonrası cerrahi patoloji materyallerinde viabl tümör oranı %10 ve altında, 11 (%40) hastada ise viabl tümör oranı %10'nun üstünde bulundu. Bu açıdan da değerlendirildiğinde HSK (p=0.16) ve GSK (p=0.097) farkı saptanmadı. Düşük ERCC1 ekspresyonu olan hastalarla yüksek ERCC1 ekspresyonu olan hastalar arasında sağkalım farkı saptanmadı. Gemsitabin direncini gösteren RRM1 yüksek ekpresyonu olan hastalar da düşük ekspresyon olan hastalar ile benzer sağ kalım oranlarına sahipti.

Sonuç: Çalışmamızda neoadjuvan kemoterapi alan evre III KHDAK'li hastalarda HSK ve GSK süreleri genel verilere göre daha uzun bulundu. Sisplatin ve gemsitabin tedavisi açısından prediktif markerlar olan ERCC1 ve RRM1 ile tedavi yanıtı ve sağkalım arasında anlamlı ilişki bulunmadı.

***Anahtar Kelimeler**: ERCC1, RRM1, akciğer Kanseri, Evre III, Neoadjuvan Kemoterapi*

Correspondence / Yazışma Adresi: **Dr. Samed RAHATLI**
Başkent Üniversitesi Tıp Fak. Mareşal Fevzi Çakmak Cad. 53. Sok. No:48 Bahçelievler, ANKARA, TÜRKİYE
Phone / Telefon: +9005321654350 **E-mail** / E-posta: samedrahatli@hotmail.com
Received / Geliş Tarihi: 09.10.2018 **Accepted** / Kabul Tarihi: 25.02.2019
ORCID NO: [1]0000-0003-3163-7429, [2]0000-0001-5588-0306 [3]000-0003-1970-2849, [4]0000-0002-9894-8005
[5]0000-0001-7813-5317, [6]0000-0003-0197-6622

KÜ Tıp Fak Derg 2019;21(1):28-36
Doi: 10.24938/kutfd.465529

INTRODUCTION

Currently, lung cancer is the leading cause of cancer-related deaths in men and women. As opposed to breast, colon and prostate cancer, about 85 % of patients diagnosed with lung cancer died of this disease (1). Non-small cell lung cancer (NSCLC) constitutes 80-85% of all lung cancers (2). Approximately 35% of patients with NSCLC are diagnosed at locally advanced (stage III) (3). Stage III involves heterogeneous group of patients. Therefore, it is the group of patients with most controversy for treatment (4). Primary treatment for localized disease of NSCLC is surgery (5). However, randomized controlled trials showed that treatment with surgery alone has limited contribution on survival in stage III patients (6). In the last 20 years, numerous studies have been made for the different treatment strategies (7-9). It is difficult to make appropriate clinical treatment plan for these patients.

There are studies showing the efficacy of neoadjuvant therapy with platinum-based combination in patients with stage III NSCLC (10,11). However, a standard chemotherapy protocol could not be determined. In recent studies, "excision repair cross-complementation group 1 protein" (ERCC1) stands out as an effective predictive and prognostic marker. ERCC1 is a key enzyme to eliminate platinum-DNA adducts in nucleotide excision repair pathway. Therefore, platinum resistance occurs in tumors that express ERCC1. ERCC1-negative tumors have been shown to have longer survival than those with ERCC1-positive (12).

Ribonucleotide reductase (RR) plays a catalytic role in the formation of the deoxyribonucleotide diphosphate which is a raw material for RNA synthesis and repair. M1 subunit of RR is nucleotide binding region and determines the specificity of enzyme activity. It is also a cellular target for gemcitabine. In studies, RRM1 has been shown to cause gemcitabine resistance (13).

In this study, the determination of response and contribution for prognosis of neoadjuvant therapy in patients with stage III NSCLC who received neoadjuvant chemotherapy was aimed. We also aimed to determine the relationship between treatment response and prognosis in terms of RRM1 and ERCC1 expression.

MATERIALS AND METHODS

Twenty-seven patients with stage III NSCLC were enrolled in this study. Patients who took neoadjuvant chemotherapy at Başkent University Faculty of Medicine (BUFM) Department of Medical Oncology and were operated at Başkent University Faculty of Medicine Department of Thoracic Surgery between the years 2003 and 2013 were included. Patient files were analyzed retrospectively. Sex, age at diagnosis, smoking status, treatment modalities, operation dates, recurrence dates, death dates were recorded. Time between the initial diagnosis and appearance of local or distant metastasis was considered as disease free survival (DFS). Time elapsed from initial diagnosis to death was considered as overall survival (OS). After neoadjuvant chemotherapy, patients with viable tumor negative in postoperative pathology material and undetectable metastatic lymph node were evaluated as pathological complete response. Others were considered as partial response.

Neoadjuvant cisplatin-based chemotherapy was administered by Department of Medical Oncology to patients with stage III NSCLC whose performance status were evaluated as appropriate.

Biopsy of lung tissues taken from patients, who received neoadjuvant platinum and gemcitabine were assessed by immunohistochemical method for ERCC1 and RRM1 protein expression, respectively. Pathology slides were prepared from sections of paraffin blocks (4mm). Tissue sections were marked with specific antibodies for ERCC1 and RRM1. Counterstain was

KÜ Tıp Fak Derg 2019;21(1):28-36
Doi: 10.24938/kutfd.465529

performed with hematoxylin. Human tonsil tissue samples were used as positive control for nuclear staining positive control of ERCC1. Human placental tissue samples were used as positive control for cytoplasmic staining positive control of RRM1. Staining rate was scored as follows: Score 0: none to low expression; score 1: 1-10% expression; Score 2: 11-50% of expression, score 3: >50% expression. In the statistical evaluation, score 0 and 1 were taken as the lowest expression but score 2 and 3 were taken as high expression.

Descriptive statistics were performed for demographic and clinical characteristics of the patients. Chi-square test was used to compare rates between groups. Kaplan-Meier analysis was performed to investigate the effect of predefined factors on the survival. Survivals of different groups were compared using the log-rank test. Cox regression analysis was used to make the multivariate analysis of factors associated with disease free survival or overall survival. Statistical analysis was performed with SPSS software version 17.0 (SPSS Inc, Chicago, IL), and the statistical significance value p was determined as being lower than 0.05. Our study is retrospective study for which we have received the approval of local ethics committee (Date: 09/04/2013, number: 2012-KA-13/73) prior to commencing.

RESULTS

Between the ages of 43 and 76, 1 (3.7%) female and 26 (96.3%) male patients were included in the study. The median age was 59 (45-75), respectively. Fifteen (55.6%) patients had squamous cell carcinoma, 10 (37%) had adenocarcinoma, 1 (3.7%) had adenosquamous and 1 (3.7%) had non-typeable NSCLC. Number of smokers was 26 (96%) and the average duration of smoking was 42 packs / year. Fourteen patients (51.9%) had undergone lobectomy and 13 patients (48.1%) had undergone pneumonectomy. According to the TNM staging system, 19 (70.4%) were stage IIIA and 8 (29.6%) were stage IIIB. The demographic characteristics of the patients are summarized in Table 1.

Table 1. Demographic features of patients

Variables	n (%)
Age: 59 (45-75)	
Gender	
Female	1 (3,7)
Male	27 (96,3)
Smoking (package/year)	42
Pathology	
Squamous cell carcinoma	15 (55,6)
Adenocarcinoma	10 (37)
Adenosquamous carcinoma	1 (3,7)
Not otherwise specified NSCLC	1 (3,7)
Neoadjuvant Chemotherapy	
Cisplatin+Gemcitabine	12 (44,4)
Cisplatin+Vinorelbine	8 (29,6)
Cisplatin+Docetaxel	6 (22,2)
Carboplatin+Gemcitabine	1 (3,7)
Surgery	
Lobectomy	14 (53,8)
Pneumonectomy	13 (42,3)
Stage	
Stage IIIA	19 (70,4)
Stage IIIB	8 (29,6)

All patients received neoadjuvant platinum-based chemotherapy. During follow-up 15 patients (55.6%) developed recurrence. Median follow-up was 36 months. Fourteen patients died during follow-up.

With neoadjuvant chemotherapy, pathological complete response was achieved in 4 patients (14.8%). After neoadjuvant chemotherapy, at surgical pathologic examination of the material rate of viable tumor was

KÜ Tıp Fak Derg 2019;21(1):28-36
Doi: 10.24938/kutfd.465529

≤10% in 16 (59.3%) patients of and >10% in 11 (40%) patients.

Looking for ERCC1 protein expression was the intention in lung tissue biopsy samples of patients who underwent neoadjuvant platinum-based chemotherapy. Lung biopsy paraffin blocks of 24 patients were obtained while 3 patients' paraffin blocks could not be retrieved. Tumor tissue sections were not found in 2 patients' paraffin blocks, thus pathologic examination failed. Likewise, of the 12 patients that underwent neoadjuvant gemcitabine, 9 patients' paraffin blocks could be provided. Immunohistochemical evaluation of the patients is given in Table 2. ERCC1 expression ratios are shown in the images 2A and 2B, RRRM1 expression ratios are shown in the images 1A and 1B.

The median overall survival for all of the patients was 26.6 months (Figure 1). The median overall survival was 48 months (Figure 2). In Stage IIIA and IIIB patients, PFS (p=0.379) and OS (p=0.69) were not significantly different. When considered in terms of percentage of viable tumor in patients, for those who had viable tumor ≤10%, median DFS and OS was 36 months and 62 months, respectively. In patients who had viable tumor >10%, median DFS was 15.5 months and OS was 27 months, but the results were not statistically significant (p=0.16 for DFS, p=0.097 for OS).

Table 2. Immunohistochemical evaluation of the patients

	Low expression	High expression
ERCC1	11 patients	10 patients
RRM1	4 patients	5 patients

Although the number of patients who survived was more in the group with low ERCC1 expression, no significant survival difference was found between low and high ERCC1 expression patients (p=0.99 for PFS and p=0.18 for OS). Survival rates were similar in patients with high RRM1 expression and low RRM1 expression (p=0.18 for DFS, p=0.9 for OS).

More than half of patients with a good response for neoadjuvant chemotherapy had high ERCC1 expression. But there was no significant correlation between best histopathological response to neoadjuvant therapy and ERCC1 expression (p=0.5). There was also no correlation between levels of RRM1 and response to the neoadjuvant treatment.

After neoadjuvant therapy, viable tumor rate was ≤10% in 52.6% of patients with stage IIIA and 75% of patients with stage IIIB, but the difference was not statistically significant (p=0.28).

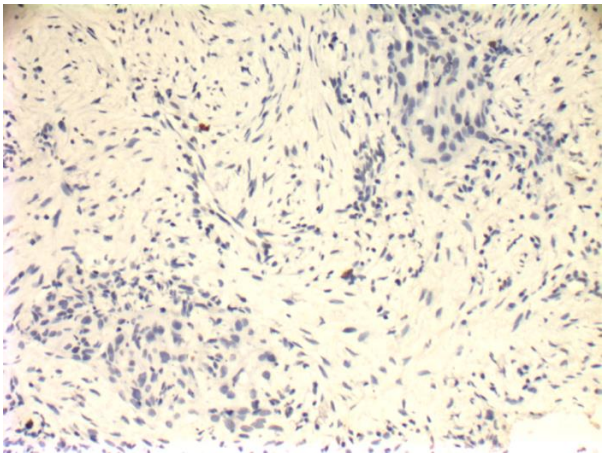

Image 1A: RRM-1, high expression (ERCC, x200), tumor specimen

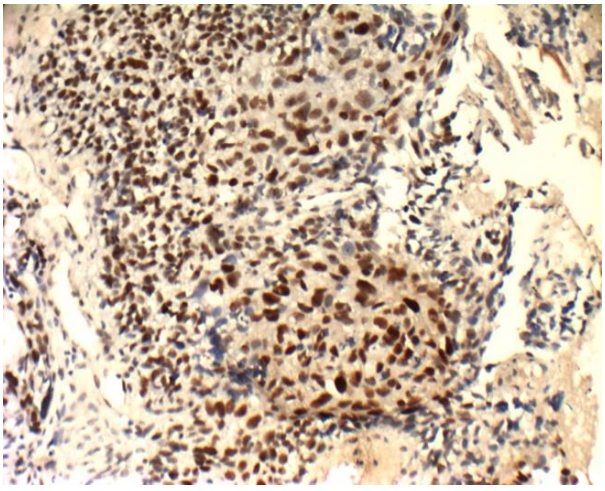

Image 1B: RRM-1, low expression (ERCC, x200), tumor specimen

KÜ Tıp Fak Derg 2019;21(1):28-36
Doi: 10.24938/kutfd.465529

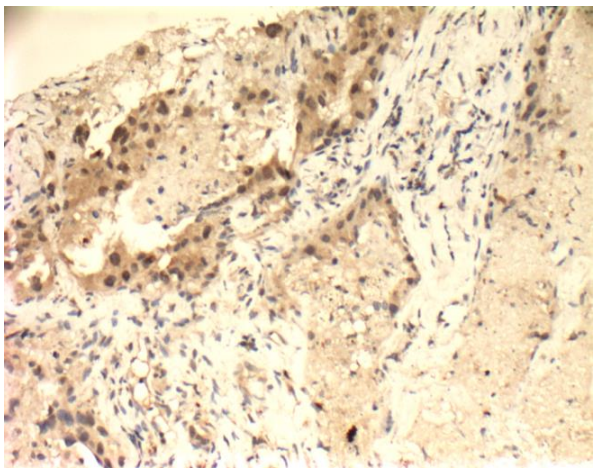

Image 2A: ERCC-1, high expression (RRM-1, x200), tumor specimen

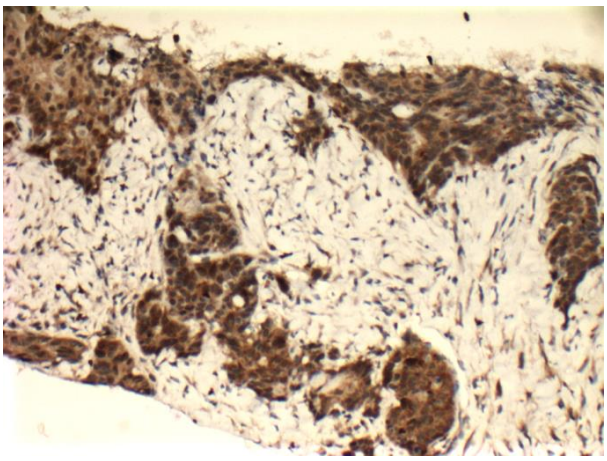

Image 2B: ERCC-1, high expression (RRM-1, x200), tumor specimen

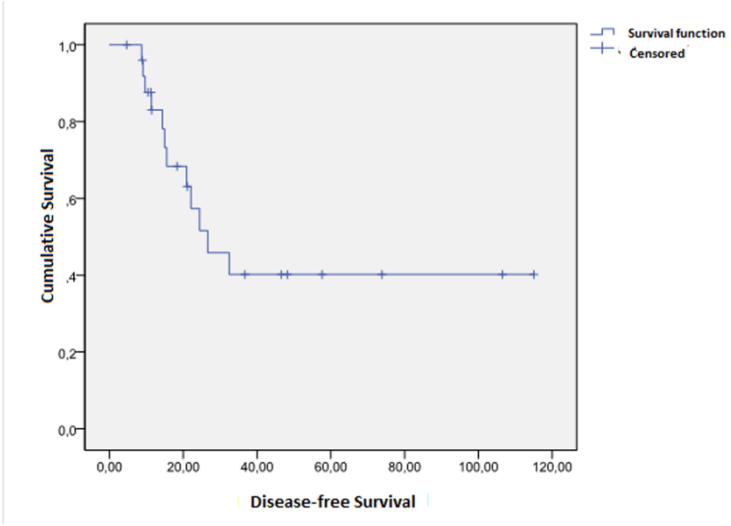

Figure 1: Disease-free survival curve for all patients

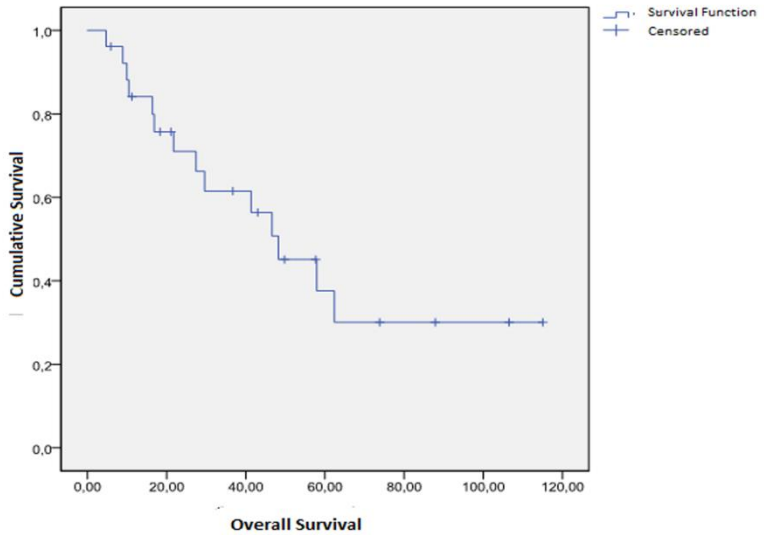

Figure 2: Overall survival curve on all cases

KÜ Tıp Fak Derg 2019;21(1):28-36
Doi: 10.24938/kutfd.465529

DISCUSSION

Stage III NSCLC comprises the heterogeneous patient population with locally advanced disease. Survival is poor because of the early local and distant recurrence rates. Different treatment modalities to improve survival are still discussed. Neoadjuvant chemotherapy is one of these modalities. In a meta-analysis published by Burdett et al., compared with surgery alone preoperative chemotherapy has been shown to provide 6% survival advantage at 5 years (14). However, it was indicated that this meta-analysis was not powerful enough to change standard treatment due to coverage small scale studies. In a randomized, multicenter MRC LU22 study by Gilligan et al., there was no survival benefit of neoadjuvant chemotherapy (HR:1.22, p=0.86) (15). But later, the published studies and meta-analysis showed that survival was better in patients who underwent surgery after neoadjuvant chemotherapy than surgery alone. Survival advantage is especially pronounced in patients with Stage III. In the meta-analysis published by Song et al., subgroup analysis performed for stage III patients and survival was significantly higher in the neoadjuvant chemotherapy arm (HR:0.84, p=0.005) (16). Horita et al. concluded that preoperative chemotherapy was especially effective in patients with stage III (HR:0.77, p<0.001) (17). A recently published meta-analysis in the Lancet has also concluded that neoadjuvant chemotherapy is effective (18). According to our study, disease-free survival was 26.6 months and overall survival was 48 months for the patients undergoing surgery after neoadjuvant chemotherapy. In another neoadjuvant chemotherapy study including stage III patients, average event-free survival was 27.5 months, and median overall survival was 66.7 months (19). In the study by DePierre et al., involving patients undergoing surgery after neoadjuvant chemotherapy, event free survival was 26.7 months and overall survival was 37 months (20).

Pataer et al. compared the survival of patients who had ≤10% viable tumor and who had >10% viable tumor after neoadjuvant chemotherapy. In patients who had less than ≤10% viable tumor, disease-free and overall survival were significantly longer (5-year OS 85% to 40%, p<0.0001, 5-year DFS 78%, 35%, p<0,0001) (5). In our study, PFS and OS were longer in patients with viable tumor ≤10% than in patients with >10% viable tumor (median DFS of 36 months to 15.5 months, p=0.16, median OS of 62 months to 27 months p=.097). In NSCLC cornerstone treatment is adjuvant or neoadjuvant platinum-based chemotherapy. Despite 33-64% response rates after neoadjuvant therapy, absolute increase in overall survival with adjuvant therapy is 5-15% (21,22). Predictive markers can determine the appropriate treatment increasing response rates for the patient while reducing unnecessary drug usage (23). In recent years, one of the most commonly used predictive markers is ERCC1 which is associated with platinum resistance and the other predictive marker is RRM1 which predicts the response to gemcitabine treatment. In our study, ERCC1 and RRM1 were studied by immunohistochemistry in the lung biopsy specimens of patients. In previous studies it has been shown that high ERCC1 expression leads to platinum resistance (24). Olaussen et al. have concluded that patients with completely resected non–small-cell lung cancer and ERCC1-negative tumors appear to benefit from adjuvant cisplatin-based chemotherapy, whereas patients with ERCC1-positive tumors do not (HR=0.65, p=0.0002) (25). In a phase III prospective randomized trial, patients in the control arm received docetaxel plus cisplatin. In the genotypic arm, patients with low ERCC1 levels received docetaxel plus cisplatin, and those with high levels received docetaxel plus gemcitabine. The primary end point was the overall objective response rate. Genotype study group had significantly higher response rates than the control group (p=0.02). This study was the first prospective

KÜ Tıp Fak Derg 2019;21(1):28-36
Doi: 10.24938/kutfd.465529

randomized clinical trial testing the concept of customized chemotherapy in NSCLC (26). But in our study, there was no significant relationship between the ERCC1 expression and pathological response. We thought that this may be associated with our small number of patients and with absence of unresponsive patient population. However, results of several studies in the literature were similar to ours. Li and colleagues have investigated the relationship between the expression of several genes and response to neoadjuvant therapy in patients with locally advanced NSCLC. But they have not determined the correlation between ERCC1 expression and histopathologic response (27). In studies conducted by Cappi et al. and Lord et al., ERCC1 expression does not correlate with histopathologic response (28,29).

High RRM1 expression is known to be directly related to the gemcitabine resistance (30). A recently published meta-analysis showed that gemcitabine treatment response is significantly higher in patients with low expression of RRM1 (response rate of 22.2% to 44.9%, $p<0.00001$) (31). However, in our results correlation of RRM1 expression with treatment response was not significant. Also, there was no relationship between RRM1 expression and treatment response in the study by Lee et al. ($p=0.149$) (32). Similar results were also demonstrated in studies conducted by Rosell et al. (33).

In our study, in stage III NSCLC patients who underwent neoadjuvant chemotherapy, disease-free survival and overall survival were significantly longer compared to the literature. Limitation of the randomized controlled studies comparing adjuvant chemotherapy with neoadjuvant chemotherapy, as well as the lack of phase III studies comparing neoadjuvant chemoradiotherapy with neoadjuvant chemotherapy complicates the formation of standards in definitive treatment of Stage III NSCLC. However, results of recently published meta-analysis and the results of our study albeit small-scale suggests that especially in stage IIIA and in appropriate stage IIIB NSCLC patient's neoadjuvant chemotherapy can be applied as a standard approach.

We did not find a relationship between ERCC1 and RRM1 expression which are predictive markers for cisplatin and gemcitabine with treatment response and survival. Confusing results of published studies shows that randomized prospective studies are needed for routine use of ERCC1 and RRM1 as a predictive marker.

All authors declare no conflict of interest.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29.
2. Jiang J, Liang X, Zhou X, Huang R, Chu Z, Zhan Q. ERCC1 expression as a prognostic and predictive factor in patients with non-small cell lung cancer: a meta-analysis. Mol Biol Rep. 2012;39(6):6933-42.
3. Gadgeel SM, Ramalingam SS, Kalemkerian GP. Treatment of lung cancer. Radiol Clin North Am Sep. 2012;50(5):961-74.
4. Fakhrejahani F, Sadraei NH, Mekhail T. The Role of consolidation treatment in locally advanced unresectable NSCLC. Curr Oncol Rep. 2013;15(4):424-32.
5. Pataer A, Kalhor N, Correa AM, Raso MG, Erasmus JJ, Kim ES et al. University of Texas M. D. Anderson Lung Cancer Collaborative Research Group. Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. J Thorac Oncol. 2012;7(5):825-32.
6. Kelsey CR, Marks LB, Hollis D, Hubbs JL, Ready NE, D'Amico TA et al. Local recurrence after surgery for early stage lung cancer: An 11-year

experience with 975 patients. Cancer. 2009;115(22):5218-27.

7. Park BB, Park JO, Kim H, Ahn YC, Choi YS, Kim K et al. Is trimodality approach better then bimodality in stage IIIA, N2 positive non-small cell lung cancer? Lung Cancer. 2006;53(3):323-30.
8. Saynak M, Higginson DS, Morris DE, Marks LB. Current status of postoperative radiation for non-small-cell lung cancer. Semin Radiat Oncol. 2010;20(3):192-200.
9. Anderson CS, Curran WJ. Combined modality therapy for stage III non-small-cell lung cancer. Semin Radiat Oncol. 2010;20(3):186-91.
10. Carretta A, Ciriaco P, Melloni G, Sayed I, Bandiera A, Ferla L et al. Results of surgical treatment after neoadjuvant chemotherapy for stage III non-small cell lung cancer. World J Surg. 2008;32(12):2636-42.
11. Lv C, Ma Y, Wu N, Shi Yan, Qingfeng Zheng, Yu Sun et al. A retrospective study: platinum-based induction chemotherapy combined with gemcitabine or paclitaxel for stage IIB-IIIA central non-small-cell lung cancer. World J Surg Oncol. 2013;11(76):1-11.
12. Besse B, Olaussen KA, Soria JC. ERCC1 and RRM1: ready for prime time? J Clin Oncol. 2013;31(8):1050-60.
13. Bepler G, Williams C, Schell MJ, Chen W, Zheng Z, Simon G et al. Randomized international phase III trial of ERCC1 and RRM1 expression-based chemotherapy versusgemcitabine/carboplatin in advanced non-small-cell lung cancer. J Clin Oncol. 2013;31(19):2404-12.
14. Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. J Thorac Oncol. 2006;1(7):611-21.
15. Gilligan D, Nicolson M, Smith I, Dalesio O, Goldstraw P, Hatton M et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRCLU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. Lancet. 2007;369(9577):1929-37.
16. Song WA, Zhou NK, Wang W, Chu XY, Liang CY, Tian XD et al. Survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer: an updated meta-analysis of 13 randomized control trials. J Thorac Oncol. 2010;5(4):510-6.
17. Horita N, Miyazawa N, Morita S, Kojima R, Kimura N, Kaneko T et al. Preoperative chemotherapy is effective for stage III resectable non-small cell lung cancer: metaanalysis of 16 trials. Clin Lung Cancer. 2013;14(5):488-94.
18. Burdett S, Rydzewska LH, Tierney JF, Auperin A, Le Pechoux C, Le Chevalier T et al. Preoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis of individual participant data. NSCLC Meta-analysis Collaborative Group. Lancet. 2014;383(9928):1561-71.
19. Liao WY, Chen JH, Wu M, Shih JY, Chen KY, Ho CC et al. Neoadjuvant chemotherapy with docetaxel-cisplatin in patients with stage III N2 non-small-cell lung cancer. Clin Lung Cancer. 2013;14(4):418-24.
20. Depierre A, Milleron B, Moro-Sibilot D, Chevret S, Quoix E, Lebeau B et al. French Thoracic Cooperative Group. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. J Clin Oncol. 2002;20(1):247-53.
21. Scagliotti G. Preliminary results of Ch.E.S.T.: A phase III study of surgery alone or surgery plus preoperative gemcitabine-cisplatin in clinical early

stages non-small cell lung cancer. Journal of Clinical Oncology. 2005; abst23, no.16_suppl. DOI: 10.1200/jco.2005.23.16_suppl.lba7023. PubMed PMID: 27943944. (Epub 2011 Nov 28).

22. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004;350(4):351-60.
23. Bepler G, Sommers KE, Cantor A, Li X, Sharma A, Williams C et al. Clinical efficacy and predictive molecular markers of neoadjuvant gemcitabine and pemetrexed in resectable non-small cell lung cancer. J Thorac Oncol. 2008;3(10):1112-8.
24. Britten RA, Liu D, Tessier A, Hutchison MJ, Murray D. ERCC1 expression as a molecular marker of cisplatin resistance in human cervical tumor cells. Int J Cancer. 2000;89(5):453-7.
25. Olaussen KA, Dunant A, Fouret P, Brambilla E, André F, Haddad V et al. DNA repair by ERCC1 in non-small cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med. 2006; 355(10):983-91.
26. Cobo M, Isla D, Massuti B, Montes A, Sanchez JM, Provencio M et al. Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: a phase III trial in non-small-cell lung cancer. J Clin Oncol. 2007;25(19):2747-54.
27. Li J, Li ZN, Yu LC, Bao QL, Wu JR, Shi SB et al. Association of expression of MRP1, BCRP, LRP and ERCC1 with outcome of patients with locally advanced non-small cell lung cancer who received neoadjuvant chemotherapy. Lung Cancer. 2010;69(1):116-22.
28. Cappi P, Volante M, Novello S, Rapa I, Danenberg KD, Danenberg PV et al. ERCC1 and RRM1 gene expressions but not EGFR are predictive of shorter survival in advanced non-small-cell lung cancer treated with cisplatin and gemcitabine. Ann Oncol. 2006;17(12):1818-25.
29. Lord RVN, Brabender J, Gandara D, Alberola V, Camps C, Domine M et al. Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res. 2002;8(7):2286-91.
30. Simon GR, Begum M, Bepler G. Setting the stage for tailored chemotherapy in the management of non-small cell lung cancer. Future Oncol. 2008;4(1):51-9.
31. Gong W, Zhang X, Wu J, Chen L, Li L, Sun J et al. RRM1 expression and clinical outcome of gemcitabine-containing chemotherapy for advanced non-small-cell lung cancer: a meta-analysis. Lung Cancer. 2012;75(3):374-80.
32. Lee JJ, Maeng CH, Baek SK, Kim GY, Yoo JH, Choi CW et al. The immunohistochemical overexpression of ribonucleotide reductase regulatory subunit M1 (RRM1) protein is a predictor of shorter survival to gemcitabine-based chemotherapy in advanced non-small cell lung cancer (NSCLC). Lung Cancer. 2010;70(2):205-10.
33. Rosell R, Felip E, Taron M, Majo J, Mendez P, Sanchez-Ronco M et al. Gene expression as a predictive marker of outcome in stage IIB-IIIA-IIIB non-small cell lung cancer after induction gemcitabine-based chemotherapy followed by resectional surgery. Clin Cancer Res. 2004;10(12):4215-9.