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Research Article

Effects of genetic polymorphisms of ERCC1, XRCC1, GSTP1, ABCB1, and CYP on prognosis of patients with non-small cell lung cancer receiving platinum-based chemotherapy

ERCC1, XRCC1, GSTP1, ABCB1 ve CYP genetik polimorfizmlerinin platin tabanlı kemoterapi alan küçük hücreli dışı akciğer kanseri hastalarının prognozu üzerine etkileri

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Abstract

Aim: Lung cancer has the greatest mortality rates among both men and women and is the primary cause of cancer-related fatalities globally. The effectiveness of chemotherapy as a treatment for lung cancer varies greatly from patient to patient. Genetic factors affect the effectiveness of chemotherapy.

Material and Methods: age of patients, types of lung cancer, smoking status, genetic profiles (ERCC-C8062A, ERCC G28152A, GSTP1-A313G, ABCB1-C1236T, ABCB1-C3435T CYP3A5*2B, CYP3A4*1B), clinical stages of cancer, and treatment were evaluated by Kaplan-Meier estimates, and a cox regression model was conducted to assess survival probability and hazard of death of different groups.

Results: Cox regression analysis revealed that ABCB1-C1236T and ABCBC-C3435T wild and heterozygous alleles, smoking, adenocarcinoma, and other types of cancer were used for predicting progression time in advanced-stage lung cancer patients. However, no variables were found to be significant predictors of progression time in early-stage lung cancer patients.

Conclusions: Overall, our results imply that genetic variables may play a substantial influence in the rate of lung cancer progression and emphasize the need for tailored medication in the treatment of this disease. Discovering genetic markers that can predict the advancement time of lung cancer could assist clinicians in customizing treatment approaches for individual patients and improving the prognosis for people afflicted with this dreadful disease.

Keywords: lung cancer, NSCLC, chemotherapy, polymorphism, platinum

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Öz

Amaç: Akciğer kanseri, hem erkekler hem de kadınlar arasında en yüksek ölüm oranlarına sahip ve küresel olarak kanserle ilişkili ölümlerde birinci sırada yer almaktadır. Kemoterapinin akciğer kanseri tedavisindeki verimliliği, genetik faktörlerin kemoterapinin etkinliğini etkilemesinden dolayı hastadan hastaya büyük ölçüde değişiklik göstermektedir.

Gereç ve Yöntemler: Hastaların yaşı, akciğer kanseri tipleri, sigara içme durumu, genetik profili (ERCC-C8062A, ERCC G28152A, GSTP1-A313G, ABCB1-C1236T, ABCB1-C3435T CYP3A5*2B, CYP3A4*1B), kanserin klinik evreleri ve tedavi yöntemleri Kaplan-Meier tahminleri ve farklı grupların sağ kalma olasılıkları ve ölüm tehlikesini değerlendirmek amacıyla yapılan Cox regresyon modeli ile değerlendirildi.

Bulgular: Progresyon süresinin tahmin etmek için akciğer kanseri hastalarının, ABCB1-C1236T ve ABCBC-C3435T yabanıl ve heterozigot alelleri, sigara içme, adenokarsinomun ve diğer kanser türlerini kullanarak Cox regresyon analizi ile ileri evre akciğer kanseri hastalarında progresyon süresini tahmin edilebileceği ortaya koyulmuştur. Ancak, erken evre akciğer kanseri hastalarında progresyon süresinin tahmin etmek için hiçbir değişken bulunamamıştır.

Sonuçlar: Genel olarak, sonuçlarımız genetik değişkenlerin akciğer kanseri ilerleme oranında önemli bir etkiye sahip olabileceğini ve bu hastalığın tedavisinde kişiye özel ilaç tedavisine olan ihtiyacı vurgulamaktadır. Akciğer kanserinin progresyon süresini tahmin edebilecek genetik belirteçlerin keşfedilmesi, klinisyenlerin bireysel hastalar için tedavi yaklaşımlarını özelleştirmelerine ve bu korkunç hastalıktan muzdarip kişilerin prognozunu iyileştirmelerine yardımcı olabilir.

Anahtar Kelimeler: akciğer kanseri, KHDAK, kemoterapi, polimorfizm, platin

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Lung cancer was the most diagnosed cancer in 2022, accounting for nearly 2.5 million new cases, which represents approximately 12.4% of all cancer cases worldwide. Therefore, new therapy and diagnosis strategies are quite essential [2].

Platinum-based chemotherapy is the first-line treatment for lung cancer patients. Chemotherapy medications containing platinum, such as cisplatin, carboplatin, and oxaliplatin, function by binding to DNA and interfering with cell division, causing the death of rapidly dividing cancer cells. These medications have been widely utilized for over four decades and have greatly contributed to the improving cancer survival rates. The success of platinum-based chemotherapy varies depending on the type and stage of cancer, the patient's age, overall health, and genetics. Some patients may develop resistance to platinum-based chemotherapy, while others may experience severe side effects [3]. Thus, biomarkers that can predict the response to platinum-based chemotherapy and enhance patient outcomes must be identified [4].

Genetic variations in genes related to drug metabolism, drug transport, and DNA repair are some of the variables that could affect the response to platinum-based chemotherapy. Polymorphisms are changes in DNA sequences that can affect how proteins encoded by those sequences function. Certain polymorphisms may result in increased or decreased enzyme activity, impacting chemotherapeutic drug metabolism. Others may affect DNA repair ability, leading to increased chemotherapy sensitivity or resistance. The discovery of genetic variables that may affect the rate at which lung cancer progresses is one field of study that has attracted a lot of interest lately.

Several studies have investigated the association between polymorphisms in genes involved in drug metabolism, DNA repair, and transport and the lung cancer progression. ERCC1 and XRCC1 are genes involved in DNA repair, while GSTP1, CYP3A4, CYP3A5, and ABCB1 are genes involved in drug metabolism and transport [5-8]. Polymorphisms in these genes might affect their function and, in turn, impact the response to chemotherapy and the overall prognosis of patients with lung cancer. The ERCC1 gene plays a critical role in the nucleotide excision repair pathway, which is responsible for removing DNA damage induced by chemotherapeutic agents such as cisplatin. Polymorphisms in ERCC1 have been associated with reduced DNA repair efficiency and increased cellular sensitivity to cisplatin-based chemotherapy [9]. Base excision repair is a process that corrects oxidative stress-induced DNA damage. This process is facilitated by the XRCC1 gene. Polymorphisms in the XRCC1 gene have been associated with a reduced capacity to repair DNA and an increased sensitivity to chemotherapy drugs such as cisplatin and etoposide [10]. GSTP1 is a gene involved in the metabolism of chemotherapy

drugs, including taxanes and platinum-based drugs. CYP3A5 is a gene involved in the metabolism of chemotherapeutic agents like docetaxel and paclitaxel. Polymorphisms in the GSTP1 and CYP3A5 genes have been linked to diminished drug metabolism, resulting in increased toxicity and diminished efficacy [6,7]. ABCB1 is a gene involved in the transport of chemotherapy drugs such as paclitaxel and vinblastine out of cells, resulting in diminished drug accumulation and efficacy. Polymorphisms in the ABCB1 gene have been linked to an increase in drug efflux and a reduction in drug accumulation, leading to a decrease in the efficacy of chemotherapy [8].

In this article, we aim to investigate the association between polymorphisms in the ERCC1, XRCC1, GSTP1, CYP3A4, CYP3A5, and ABCB1 genes and progression of lung cancer.

Material and Methods

Patient recruitment

This study was conducted at the Pamukkale University, Department of Medical Genetics and included 74 patients diagnosed with lung cancer. Patients were recruited from January 2013 to December 2016. The inclusion criteria were as follows: patients with histologically confirmed lung cancer, aged 18 years or older, and scheduled for platinum-based chemotherapy. Patients with a history of other cancers, autoimmune diseases, or concurrent infections were excluded. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Pamukkale University Non-Interventional Clinical Research Ethics Committee (Decision No: E-60116787-020-443429, dated October 31, 2023).

Genotyping

The Qiagen EZI DNA Blood Kit (Qiagen, Hilden, Germany) has been used to isolate gDNA from peripheral blood samples. Genotyping of the ERCC1-C8092A, ERCC1-T19007C, XRCC1-G28152A, GSTP1-A313G, ABCB1-C1236T, ABCB1-C3435T, CYP3A5*2B, and CYP3A4*1B polymorphisms was performed using the pyrosequencing method (PyroMark Q24) (Qiagen Hilden, Germany). After polymerase chain reaction (PCR) was conducted according to the manufacturer's protocol, GE Healthcare's streptavidin Sepharose HP (Waukesha, WI, USA) was bound to PCR products., followed by purification, washing, and denaturation steps for pyrosequencing. Genotyping was performed by two independent researchers who were blinded to the clinical data, using the PyroMark Q24 Advanced Software.

Chemotherapy regimen

All patients received platinum-based chemotherapy as the first-line treatment, consisting of either cisplatin or carboplatin, combined with a taxane or gemcitabine. The chemotherapy regimens were selected by the attending oncologists based on the patient's clinical characteristics and the tumor histology.

Follow-up and survival analysis

Patients were followed up every three months after the completion of chemotherapy. Follow-up evaluations included a physical examination, chest computed tomography (CT) scan, and laboratory tests. The primary endpoint of this study was progression time, defined as the duration between the initial diagnosis of cancer and the point at which the disease progresses or worsens. All progression data were obtained from medical records.

Variables

The evaluated variables included patient age, gender, lung cancer subtypes, number of affected individuals in the family, treatment and smoking status, ERCC1-C8092A, ERCC1-T19007C, XRCC1-G28152A, GSTP1-A313G, ABCB1-C1236T, ABCB1-C3435T, CYP3A5*2B, CYP3A4*1B, polymorphisms, and clinical cancer stages.

Statistical Analysis

The log-rank test and the Kaplan-Meier method were used to examine the relationship between polymorphisms and progression time. Utilizing the Cox proportional hazards model, 95% CIs and hazard ratios (HRs) were computed. Potential confounding factors, including smoking status, cancer subtypes (adenocarcinoma, squamous cell carcinoma, and others), and cancer stage, were adjusted in the multivariate analysis. Statistical analyses were conducted using SPSS software (version 25.0, IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was deemed statistically significant.

To ensure the accuracy of genotyping, 10% of the samples were randomly selected for repeat genotyping.

Results

Descriptive statistics

Descriptive statistics are shown in table 1. Of the 74 patients included in the study, 64 (86.5%) were male (38 in the advanced-stage group, 26 in the early-stage group), while 10 (13.5%) were female (2 in the advanced-stage group, 8 in the early-stage group). The median and average age at diagnosis of lung cancer were 61 (range: 40–78) and 60.43 ± 8.91 years, respectively. Fifty-six (75.7%) patients were active smokers, whereas 18 (24.3%) had never smoked. Seventeen out of 74 patients had a family history of cancer. Among them, 9 (52.9%) had first-degree relatives, 4 (23.5%) had second-degree relatives, and 3 (17.6%) had third-degree relatives affected by cancer (Table 1).

Table 1. Clinical and demographic characteristics of the patients.	
Variables	Frequency (n, %)
Age (n=74)	
<65	16 (21.6)
65-74	30 (40.5)
>75	28 (37.8)
Gender (n=74)	
Male	64 (86.5)
Female	10 (13.5)
Family history(n=17)	
First degree relatives	9 (52.9)
Second degree relatives	8 (47.1)
Number of affected relatives(n=17)	
1	10 (58.8)
2	4 (23.5)
3	3 (17.6)
Smoking (package/years) (n=53)	56 (71.6)
<40	21 (39.6)
41-59	26 (49.1)
>60	6 (11.3)
Subtypes of cancer	
Adenocarcinoma	16 (21.6)
Squamous cell carcinoma	37 (50.0)
Others	21(28.4)
Stages	
I-II	13 (17.6)
III	31 (42.9)
IV	30 (40.5)
Platin based chemotherapy	68 (91.9)
Events progressed secondary time	27 (36.5)

Survival tests

The median progression time of each polymorphism at each stage of lung cancer is shown in figure 1. Before implementing the Kaplan-Meier test, extreme values and outliers were excluded from the analysis. After excluding one extreme value (Patient 72) from the study, a statistically significant difference was found in the progression times of ERCC1-T19007C polymorphisms in the advanced-stage lung cancer group (log-rank test p-value: 0.04).

Figure 1. Median progression time of each polymorphism per stage of lung cancers.

Cox proportional hazard models

In this study, a Cox regression model was implemented to predict the progression time of advanced (stage IV) and early stage (stage I, stage II, and stage III) lung cancer patients. The variables were divided into two categories based on the stage of lung cancer. First, a univariate analysis was conducted to identify the variables that were significant in predicting progression time. A threshold of 0.1 was set for including variables in the analysis. Based on the results of the univariate analysis, six variables GSTP1-A313G, XRCC1-G28152A, ABCB1-C3435T, ABCB1-C1236T, cancer subtype, and smoking were selected for the multivariate Cox regression model.

Our Cox regression analysis revealed that the ABCB1-C1236T and ABCB1-C3435T wild-type and heterozygous alleles, smoking, adenocarcinoma, and other cancer types were significant predictors of progression time in advanced-stage lung cancer patients (Table 2). However, no variables were found to be significant predictors of progression time in early-stage lung cancer patients (Table 3).

Table 2. Prognostic factors affect progressing time in multivariate analysis in high stage lung cancer patients.		
Variables	Sig.	OR (95 CI %)
GSTP1-313		
A/A	0.278	
A/G	0.654	0.815(0.334-1.992)
3G/G	0.110	0.227(0.037-1.397)
XRCC1-28152		
G/G	0.127	
G/A	0.100	0.409(0.141-1.186)
A/A	0.087	0.324(0.089-1.179)
ABCB1-3435		
C/C	0.085	
C/T	0.049	0.311(0.098-0.993)
T/T	0.112	0.403(0.131-1.238)
ABCB1-1236		
C/C	0.060	
C/T	0.026	0.278(0.090-0.860)
T/T	0.972	1.020(0.330-3.159)
Subtype of cancer		
Adenocarcinoma	0.008	
Squamous cell carcinoma	0.677	1.255(0.431-3.649)
Others	0.006	0.262(0.101-0.681)
Smoking	0.041	3.480(1.055-11.477)

Table 3. Prognostic factors affect progressing time in multivariate analysis in early-stage lung cancer patients.

Variables	Sig.	OR (95 CI %)
GSTP1- 313		
A/A	0.481	
A/G	0.421	1.359 (0.644-2.869)
G/G	0.449	0.606 (0.166-2.215)
XRCC1- 28152		
G/G	0.382	
G/A	0.190	1.659 (0.778-3.539)
A/A	0.458	1.509 (0.510-4.469)
ABCB1- 3435		
C/C	0.838	
C/T	0.605	0.796 (0.334-1.894)
T/T	0.676	0.803 (0.287-2.248)
ABCB1-1236		
C/C	0.476	
C/T	0.562	1.336 (0.502-3.557)
T/T	0.224	1.994 (0.656-6.062)
Subtype of cancer		
Adenocarcinoma	0.208	
Squamous cell carcinoma	0.204	1.890 (0.708-5.047)
Others	0.091	2.080 (0.889-4.864)
Smoking status	0.296	0.641 (0.278-1.476)

Discussion

The treatment of lung cancer is a very difficult and long process because there are a lot of factor such as late diagnosis, inadequate treatment strategies, regular follow-up after treatment, tumor mutation burden, drug response and toxicity [11]. The first-line treatment for NSCLC is platinum-based chemotherapy, and a recent study showed that platinum-based chemotherapy is affected by inherent factors such as DNA repair, signaling, and metabolism [12]. In this study, we have aimed to examine the relationship between the GSTP-A313G (rs1695), CYP3A4*1B (rs2740574), CY3A5-2B (rs776746), ABCB1-C1236T (rs1128503), ABCB1-C3435T (rs1045642), ERCC1-C8092A (rs3212986), ERCC1-T19007C (rs11615) and XRCC1-G28152A (rs25487) genes polymorphisms and progression free survival in 72 patients who are receiving platinum-based chemotherapy. Our results particularly emphasize the importance of ERCC1 and ABCB1 polymorphisms in predicting progression time in advanced-stage NSCLC patients, while no significant predictors were observed for early-stage patients.

ERCC1 and DNA repair mechanisms

The statistically significant difference in progression times for the ERCC1-T19007C polymorphism (log-rank test $p = 0.04$) highlights the key role of ERCC1 in treatment outcomes. ERCC1 is a vital component of the nucleotide excision repair (NER) pathway, which is responsible for repairing platinum-induced DNA damage. Polymorphisms in ERCC1 may alter protein function, leading to differences in chemotherapy response.

Our findings align with earlier studies that reported associations between ERCC1 expression and chemotherapy resistance. For example, Olaussen et al. demonstrated that high ERCC1 expression correlates with poor responses to platinum-based therapies in NSCLC patients, supporting its role as a potential biomarker for chemotherapy sensitivity [13]. Similarly, a meta-analysis by Wei et al. (2011) revealed that ERCC1 polymorphisms, particularly T19007C, influence both overall survival and progression-free survival in NSCLC patients undergoing platinum-based regimens [14].

ABCB1 polymorphisms and drug resistance

Our multivariate Cox regression analysis identified ABCB1-C1236T and ABCB1-C3435T polymorphisms as significant predictors of progression time in advanced-stage NSCLC. ABCB1 (also known as P-glycoprotein) encodes a membrane-bound transporter that mediates drug efflux, reducing intracellular concentrations of chemotherapeutic agents like cisplatin.

Several studies support our observations regarding ABCB1 polymorphisms. For instance, a study by Kim et al. (2006) demonstrated that the C3435T polymorphism is associated with reduced drug efflux and improved chemotherapy efficacy [15]. Moreover, Jia et al. showed that genetic variations in ABCB1 could predict progression time and survival in patients receiving platinum-based chemotherapy, underscoring its clinical relevance as a predictive biomarker [16].

Smoking remains a critical determinant of lung cancer progression and treatment outcomes. Our findings confirm its association with shorter progression times in advanced-stage patients, reinforcing smoking cessation's importance in improving clinical outcomes. Active smokers exhibit increased DNA damage and resistance to platinum-based therapies, possibly due to smoking-induced alterations in DNA repair pathways [17].

Additionally, adenocarcinoma, identified as a significant predictor, is the most common histological subtype of NSCLC. Adenocarcinoma patients often present with distinct genetic and molecular characteristics, including EGFR and ALK

mutations, which influence treatment responses (18). Our results suggest that the cancer subtype should be carefully considered when predicting prognosis and tailoring therapies for advanced-stage NSCLC patients.

Early-stage NSCLC: challenges in prediction

Unlike advanced-stage patients, no significant predictors of progression time were identified in the early-stage group. This finding may reflect biological differences between early- and late-stage tumors or the limited power to detect associations due to the small sample size. Early-stage NSCLC patients often undergo surgical resection, which complicates comparisons with chemotherapy-treated advanced-stage patients.

Future research examining the clinical and genetic factors influencing disease development in early-stage non-small cell lung cancer (NSCLC) requires longer follow-up periods in a larger cohort.

Limitations and future directions

Limitations of the study: The results of this study suggest that ABCB1-C1236T and ABCB1-C3435T polymorphisms, smoking, and subtype of lung cancer are significant predictors of progression time in high-stage lung cancer patients. Individualized management and therapy of patients with lung cancer may benefit from these findings. However, note that there was a limited sample size (n = 72), and larger sample sizes are required for more research to validate these results and look into the underlying mechanisms of these correlations. In addition, the lack of significant predictors for early-stage lung cancer patients suggests that other factors may play a more important role in the progression of the disease at this stage.

The results of this analysis suggest that there is a significant difference in progression times between early-stage lung cancers and high-stage lung cancers. However, it is important to note that the log-rank test only tests for a difference in survival times and does not provide information on the direction of the difference. Further analysis is needed to determine which group has a longer or shorter survival time.

Future studies should concentrate on examining the functional implications of ERCC1 and ABCB1 polymorphisms as well as verifying these results in larger, multicenter cohorts. Integrating genetic markers with emerging biomarkers, such as PD-L1 expression and tumor mutation burden, may further enhance prognostic accuracy and guide personalized treatment strategies.

In conclusion, our study highlights the significant role of ERCC1 and ABCB1 polymorphisms, smoking status, and adenocarcinoma subtype in predicting progression time for advanced-stage NSCLC patients receiving platinum-based chemotherapy. These findings underscore the value of genetic and clinical predictors in optimizing treatment strategies for advanced NSCLC. However, to overcome the difficulties in validating these markers and predicting the prognosis of early-stage lung cancer, high-throughput data obtained from larger study groups and algorithms created using these data are needed.

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Declaration of conflicting interests

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Ethics approval

Ethical approval was obtained from the Pamukkale University Non-Interventional Clinical Research Ethics Committee (Decision No: E-60116787-020-443429, dated October 31, 2023).

Authors contributions

ERK, AD: designed all experimental procedures of the study, ER, MTA: wrote the manuscript and analyzed data. GGD, FB: searched literature, collected data, HA: developed the theoretical framework. The final manuscript was read and approved by all authors.

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