



Cytochrome P-450 Polymorphisms and Clinical Outcome in Patients with Non-Small Cell Lung Cancer

Küçük Hücreli Dışı Akciğer Kanseri Hastalarında Sitokrom P-450 Polimorfizmleri ve Klinik Sonuçları

Mümtaz İŞCAN*, Ahmet Oğuz ADA

Ankara University, Faculty of Pharmacy, Department of Toxicology, Ankara, Turkey

ABSTRACT

Lung cancer is an increasing worldwide public health problem. Most patients with lung cancer have non-small cell lung cancer (NSCLC). These patients are mainly treated with standard platinum-based chemotherapy. Poor response and great inter-individual variety in treatment response occurs among these patients. There is accumulating evidence to support the hypothesis that genetic polymorphisms alter the drug response and survival. Cytochrome P450 (CYP) enzymes metabolize antineoplastic drugs and are involved in drug resistance. Polymorphic CYPs have altered enzyme activities and thus they may influence the response to chemotherapy and survival in patients with lung cancer. In the current review, recent findings with respect to the role of mainly *CYP1A1*, *CYP1B1*, *CYP2D6*, *CYP2E1* and *CYP3A4* gene polymorphisms in response to chemotherapy and survival in patients with NSCLC have been provided, which could be useful for clinicians in the prognosis of these patients who are mainly treated with platinum-based chemotherapy.

Key words: CYP, polymorphisms, response to chemotherapy, survival, lung cancer

ÖZ

Akciğer kanseri dünyada artan bir sağlık sorunudur. Akciğer kanseri hastalarının çoğu küçük hücreli dışı akciğer kanseridir (KHDAK). Bu hastalar genelde ilk basamakta standart platin bazlı kemoterapi ile tedavi olmaktadır. Bu hastalarda kemoterapiye yanıt ise düşük düzeyde olmakta ve tedaviye yanıtta bireyler arasında büyük farklılıklar görülmektedir. Genetik polimorfizmlerin ilaca karşı alınan yanıt ile sağkalım üzerinde etkili olduğu hipotezini destekleyen kanıtlar giderek artmaktadır. Sitokrom P450 (CYP) enzimleri antineoplastik ilaçları metabolize etmekte ve ilaç direncine neden olabilmektedir. Polimorfik CYP'lerin enzim aktiviteleri değişiklik göstermekte ve dolayısıyla akciğer kanseri hastalarının kemoterapiye yanıtlarında ve sağkalım süreleri üzerinde etkileri olabilmektedirler. Bu derlemede, özellikle platin bazlı kemoterapi alan KHDAK hastalarının prognozunda klinisyenlere yararlı olabilecek, *CYP1A1*, *CYP1B1*, *CYP2D6*, *CYP2E1* ve *CYP3A4* gen polimorfizmlerinin bu tedaviyi alan KHDAK hastalarının kemoterapiye yanıt ve sağkalım süreleri üzerindeki etkileri ile ilgili olarak son yıllarda elde edilen bulgular ortaya konmaktadır.

Anahtar kelimeler: CYP, polimorfizm, kemoterapiye yanıt, sağkalım, akciğer kanseri

INTRODUCTION

Lung cancer is an increasing worldwide public health problem, particularly in men.¹ It is responsible for the majority of the deaths arising from cancer.² However, non-small cell lung cancer (NSCLC) is the most common type among patients with lung cancer and standard platinum chemotherapy has poor efficiency in these patients.^{3,4} Thus, the investigation of the reasons behind this failure of chemotherapy and thus possibly poorer survival in these patients is very important. There are various mechanisms involved in the resistance of tumors against antineoplastic agents.⁵ There is accumulating evidence to support the hypothesis that genetic polymorphisms alter drug response and survival.⁶⁻¹¹

Cytochrome P450 (CYP) is a superfamily of phase I oxidation enzymes, the first 3 families of which metabolize xenobiotics such as environmental carcinogens and various drugs (Table 1) including antineoplastic drugs (Table 2).¹²⁻¹⁶ They are also involved in drug resistance.^{14,15} These *CYP* genes are polymorphic, and the most common alleles of these CYP polymorphisms have been shown to alter enzyme activities (Table 3).¹⁷

The therapeutic efficiency and survival period may vary among patients with lung cancer because CYPs metabolize several chemotherapeutic agents depending on CYP activity.^{16,18,19} Therefore, the relationship between *CYP* gene polymorphisms and response to chemotherapy and survival in patients with cancer is currently a major area of research. All these kinds of

*Correspondence: E-mail: iscan@pharmacy.ankara.edu.tr, Phone: +90 533 343 48 24 ORCID-ID: orcid.org/

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Table 1. Examples of xenobiotics/drugs metabolized by CYP enzymes^{12,13,15}

Enzyme	Xenobiotics/Drugs
CYP1A1	PAHs, chemical epoxides, aromatic and halogenic amines, heterocyclic hydrocarbons
CYP1B1	PAHs, chemical epoxides, and diol epoxide, halogenic and heterocyclic hydrocarbons
CYP2D6	Carvedilol, paroxetine, haloperidol, propranolol, nitrosamines (e.g. NNK)
CYP2E1	N-nitroso dimethylamine, halothane, acetaminophene, benzene, ethanol, chloroform, vinylchloride
CYP3A4	Cyclosporine, tacrolimus, clarithromycin, diazepam, Aflatoxin B ₁ &G ₁ , 1-nitropyrene, benzo(a)pyrene 7,8-dihydrodiol

PAHs: Polycyclic aromatic hydrocarbons, NNK: Nitroamine 4-(methylnitrosamino)-1-(3-pridyl)-1-butanone

Table 2. Role of CYP enzymes in antineoplastic drug metabolism^{14,16}

Enzyme	Antineoplastic drugs
CYP1A1*	Flutamide ¹ , Ifosfamide ¹ , Imatinib, Tamoxifen ¹ , Toremifene ¹ ,
CYP1B1*	Docetaxel ¹ , Flutamide ¹ , Tegafur ¹
CYP2D6	Gefinitib ¹ , Tamoxifen ² , Vincristine ¹ , Vinorelbine ¹ , Imatinib ¹
CYP2E1	Etoposide ¹ , Vinorelbine ¹
CYP3A4	Cyclophosphamide ² , Docetaxel ² , Etoposide ² , Gefinitib ² , Ifosfamide ² , Imatinib ² , Tamoxifen ² , Teniposide ² , Vincristine ²

¹Minor metabolism by corresponding CYP, ²Major metabolism by corresponding CYP, *Mainly extrahepatic (Lung, Gastrointestinal tract, Kidney)

Table 3. Polymorphisms of CYPs and changes in corresponding enzyme activities¹⁷

Subfamily	Chromosome	Allele	Nucleotide change	Enzyme activity
CYP1A	15q22	CYP1A1*2A	3798T>C	Increase
		CYP1A1*2C	2454A>G	Increase
CYP1B	2	CYP1B1*2	142C>G; 355G>T	No change
		CYP1B1*3	4326 C>G	Increase
		CYP1B1*4	4390A>G	Decrease
CYP2D	22	CYP2D6*10A	100 C>T	Decrease
CYP2E	10	CYP2E1*5B	-1293G>C; -1053C>T	Decrease
		CYP2E1*6	7632 T>A	Decrease
		CYP2E1*7B	-71G>T; -333T>A	Not known
CYP3A	7	CYP3A4*1B	-392A>G	Increase
		CYP3A4*3	23171T>C	Not known
		CYP3A4*18	20070T>C	Decrease

information obtained from studies are necessary and important to lead physicians toward the new era of precision medicine in lung cancer therapy.

Several previous reviews described the potential of CYP polymorphisms in cancer therapy.^{16,20,21} The research area is rapidly developing, with many studies and insights being published, bringing the possibility of individualized cancer therapy closer. However, this review provides a different aspect of CYP polymorphisms compared with previous ones, particularly focusing on recent findings with respect to the role of CYP1A1, CYP1B1, CYP2E1, CYP2D6, and CYP3A4 gene polymorphisms in response to chemotherapy and survival in patients with NSCLC.

The associations between CYP polymorphisms and response to chemotherapy and survival in patients with lung cancer

Studies investigating the relationship between CYP gene polymorphisms and response to platinum-based chemotherapy and survival in patients with lung cancer have mainly focused on CYP1A1, CYP1B1, CYP2E1, CYP2D6, and CYP3A4 (Table 4).

As seen in Table 4, a couple of studies exist with respect to the CYP1A1 polymorphism and survival in lung cancer, and their results are contradictory.^{7,18,22,23} Goto et al.²² found that the CYP1A1*2A mutant allele significantly shortened survival compared with those of wild-type genotypes in patients with NSCLC. However, Li et al.¹⁸ found no such association in

Table 4. CYP polymorphisms, response to platinum-based chemotherapy and survival in patients with lung cancer

Allele	Survival	Response to chemotherapy	Reference
<i>CYP1A1*2A</i>	Mutant allele (Shorter)	ND	(22)
	No effect	wild type allele (better response) ^b	(18)
<i>CYP1A1*2C</i>	No effect	ND	(23)
	No effect	No effect	(7)
<i>CYP1B1*3</i>	Mutant allele (Shorter)	mutant allele (worse response) ^c	(19)
<i>CYP1B1*4</i>	No effect	No effect	(7)
	No effect	No effect ^c	(19)
<i>CYP2D6*10A</i>	No effect	No effect	(18)
<i>CYP2E1*5B</i>	Mutant allele (Longer)	ND	(24)
	Mutant allele (Shorter)	ND	(25)
	No effect	No effect	(18)
	No effect	No effect	(9)
<i>CYP2E1*6</i>	No effect	ND	(18)
	No effect	No effect	(9)
<i>CYP2E1*7B</i>	No effect	No effect	(9)
<i>CYP3A4*1B</i>	ND	No effect ^c	(26) ^d
<i>CYP3A4*3</i>	ND	No effect	(26)
<i>CYP3A4*18</i>	ND	No effect	(26)

ND: Not determined, ^aCisplatin+Etoposide, Cisplatin+Gemcitabine, Cisplatin+Docetaxel, Cisplatin+Vinorelbine, Cisplatin+Paclitaxel, Carboplatin+Paclitaxel, ^bNon-platinum-based chemotherapy, ^cMainly docetaxel-based chemotherapy, ^dHistologic type was not provided

this regard for the *CYP1A1*2A* polymorphism. Pryzgodzki et al.²³ observed no association between the *CYP1A1*2C* polymorphism and survival in patients with NSCLC. Likewise, a recent study also demonstrated the lack of association between the *CYP1A1*2C* polymorphism and survival in patients with NSCLC.⁷

There are only two studies in regard to the influences of *CYP1B1* polymorphisms on survival in lung cancer (Table 4). Recently, Vasile et al.¹⁹ demonstrated that *CYP1B1*3* mutant allele carriers had shorter survival compared with wild-type allele carriers. These investigators, however, observed no association between *CYP1B1*4* polymorphisms and survival in patients with NSCLC. In line with Vasile et al.¹⁹, Ada et al.⁷ previously showed that the *CYP1B1*4* polymorphism was not associated with survival in patients with NSCLC, although a notable trend towards worsening of survival in *CYP1B1*4* mutant allele carriers was determined (Table 4).

On the other hand, in recent years, data about the associations between the *CYP1A1*2A*, *CYP1A1*2C*, *CYP1B1*3*, and *CYP1B1*4* polymorphisms and responses to mainly platinum-based chemotherapy have been provided by researchers (Table 4).^{7,18,19} Li et al.¹⁸ found that wild-type allele carriers of the *CYP1A1* gene had a better response to non-platinum drug therapy only, but not to platinum-based chemotherapy, than those of variant allele carriers of the gene. There was no influence of

the *CYP1A1*2C* polymorphism on the response to platinum-based chemotherapy in patients with NSCLC.⁷ The response to chemotherapy of *CYP1B1*3* variant allele carriers was worse than wild-type allele carriers of the *CYP1B1* gene in patients with NSCLC who were treated with docetaxel after platinum-based chemotherapy.¹⁹ However, no association was found between the *CYP1B1*4* polymorphism and response to chemotherapy.^{7,19}

A study investigating the association between the *CYP2D6*10A* polymorphism and therapeutic response or survival in patients with NSCLC has recently been reported (Table 4).¹⁸ These investigators observed no influence of this polymorphism on response to either platinum-based chemotherapy or non-platinum-based chemotherapy and survival in patients with advanced NSCLC.

Studies concerning the relationship between the *CYP2E1* polymorphism and survival in patients with lung cancer are also rather limited and the results are not conclusive (Table 4). For example, studies on the *CYP2E1*5B* polymorphism are rather conflicting. Oyama et al.²⁴ found an increase in survival in mutant allele carriers, whereas Haque et al.²⁵ observed shorter survival in mutant carriers, and Li et al.¹⁸ found no association between this *CYP* gene polymorphism and survival in patients with NSCLC. Pryzgodzki et al.²³ reported no significant association between the *CYP2E1*6* polymorphism and survival in patients with NSCLC. Moreover, almost no information is available with

respect to the relationship between these polymorphisms and response to chemotherapy in patients with NSCLC. The first data in this regard were provided by Li et al.¹⁸ who observed no significant association between the *CYP2E1*5B* polymorphism and response to chemotherapy in NSCLC. Likewise, the recent results of Karacaoğlan et al.⁹ on the *CYP2E1*5B* polymorphism are also in line with the findings of Li et al.¹⁸, both in regard to response to chemotherapy and survival. However, their findings are in contrast to those of Oyama et al.²⁴ and Haque et al.²⁵ in respect to survival. The findings of Karacaoğlan et al.⁹ in regard to the effect of *CYP2E1*6* polymorphism on survival also coincided with the results of Przygodzki et al.²³ The only study for the *CYP2E1*7B* polymorphism on this issue was reported by Karacaoğlan et al.⁹ who observed no association between the *CYP2E1*7B* polymorphism and response to chemotherapy and survival in patients with NSCLC.

Choi et al.²⁶ investigated the influences of *CYP3A4* polymorphisms on response to chemotherapy in patients who had various type of cancer, including lung cancer (Table 4). The authors genotyped *CYP3A4* polymorphisms, namely *CYP3A4*1B*, *CYP3A4*3*, and *CYP3A4*18*, but could find no association between these polymorphisms and response to chemotherapy in patients with lung cancer treated with docetaxel concomitantly with cisplatin, doxorubicin, capecitabine, cisplatin-cetuximab, and ifosfamide.

Multigene polymorphisms in response to chemotherapy and survival in lung cancer

Recent studies have demonstrated that the simultaneous analysis of gene polymorphisms may correlate well with the clinical outcome better than the single polymorphism studies. This seems to be valid for CYPs as well. For example, the combined *CYP1A1*2A* mutant allele and *GSTM1* null genotype were associated with better response to chemotherapy in NSCLC patients.¹⁸ The study of Ada et al.⁷ in NSCLC patients also revealed that the combined *CYP1A1*2C* and *GSTP1* (Ile105Val) mutant alleles or *CYP1B1*4* and *GSTP1* (Ile105Val) mutant alleles had notable trends toward worsening of survival. Recently, Karacaoğlan et al.⁹ demonstrated that combined *CYP1A1*2C* and *TP53* (Arg72Pro) mutant genotypes were associated with the worsening of the survival in NSCLC patients. In addition, they observed that the combined *CYP2E1*7B* and *TP53* (Arg72Pro) mutant alleles had notable trends toward worsening survival. Hence, the analysis of more than one gene polymorphisms of CYPs with other gene polymorphisms as shown with other xenobiotic/drug metabolizing enzymes and *TP53* gene polymorphisms could provide more important information of their involvement in the clinical outcome in NSCLC.

CONCLUSION

Based on current data, the role of polymorphisms of genes that encode CYP enzymes in response to chemotherapy and survival in patients with NSCLC seems to depend on the individual *CYP* gene and to a certain extent, the treatment regimen.

The altered enzyme activities due to gene mutations appear to have no significant impact in patients with NSCLC treated with distinct chemotherapy regimens, namely platinum-based chemotherapy, non-platinum-based chemotherapy or docetaxel-based chemotherapy because there is a lack of associations between *CYP1A1*2C*, *CYP1B1*4*, *CYP2D6*10A*, *CYP2E1*6*, *CYP2E1*7B*, *CYP3A4*1B*, *CYP3A4*3*, and *CYP3A4*18* polymorphisms and response to chemotherapy. These findings are also likely to show that these CYP polymorphisms are not functioning as a predictor of response to the distinct chemotherapy regimens mentioned above. However, wild-type allele carriers of *CYP1A1* gene seems to benefit more from non-platinum-based treatment than platinum-based chemotherapy. On the other hand, *CYP1B1*3* mutant allele carriers had a poor response, mainly to docetaxel-based chemotherapy. However, further studies are required to confirm these findings.

Conflicting results are also noted with respect to the influence of *CYP1A1*2A* and *CYP2E1*5B* polymorphisms in particular on the survival of patients with NSCLC. These inconsistencies need to be clarified through further studies. On the other hand, the lack of association between the *CYP1A1*2C*, *CYP1B1*4*, and *CYP2E1*6* polymorphisms and survival in patients with NSCLC appears to be conclusive. The *CYP2D6*10A* and *CYP2E1*7B* polymorphisms are also likely to have no influence on survival in patients with NSCLC. However, these findings need to be verified in further studies.

It is noteworthy that other important factors should also be considered when evaluating the role of these genes in the clinical outcome of cancer therapy. For example, besides single gene polymorphisms, multiple function *CYP* gene polymorphisms with other gene polymorphism analyses have also shown to provide important information about their involvement in clinical outcomes in NSCLC.

Overall, current studies have shown that the effects of each individual *CYP* gene polymorphism on clinical outcomes in patients with NSCLC are likely to be modest, which suggests that more comprehensive information is necessary to predict more accurately the role of CYP polymorphisms in selecting the most appropriate chemotherapy regimen. Recent efforts in this regard are promising.²⁷

Thus, future studies that incorporate multigene polymorphisms, and phenotypic, epigenetic, and clinical variables will hopefully provide a better understanding of the role of CYP polymorphisms in precision medicine for patients with NSCLC.

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