Gene Polymorphisms and Chemotherapy in Non-small Cell Lung Cancer

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Abstract

The phamacogenetics is being used to predict whether the selected chemotherapy will be really effective and tolerable to the patient. Irinotecan, oxidized by CYP3A4 to produce inactive compounds, is used for treatment of various cancers including advanced non small cell lung cancer (NSCLC) patients. CYP3A4*16B polymorphism was associated with decreased metabolism of irinotecan. Irinotecan is also metabolized by carboxylesterase to its principal active metabolite, SN-38, which is subsequently glucuronidated by UGT1As to form the inactive compound SN-38G. UGT1A1*28 and UGT1A1*6 polymorphisms were useful for predicting severe toxicity with NSCLC patients treated with irinotecan-based chemotherapy. Platinum-based compounds (cisplatin, carboplatin) are being used in combination with new cytotoxic drugs such as gemcitabine, paclitaxel, docetaxel, or vinorelbine in the treatment of advanced NSCLC. Cisplatin activity is mediated through the formation of cisplatin-DNA adducts. Gene polymorphisms of DNA repair factors are therefore obvious candidates for determinants of repair capacity and chemotherapy efficacy. ERCC1, XRCC1 and XRCC3 gene polymorphisms were a useful marker for predicting better survival in advanced NSCLC patients treated with platinum-based chemotherapy. XPA and XPD polymorphisms significantly increased response to platinum-based chemotherapy. These DNA repair gene polymorphisms were useful as a predictor of clinical outcome to the platinum-based chemotherapy. EGFR kinase inhibitors induce dramatic clinical responses in NSCLC patients with advanced disease. EGFR gene polymorphism in intron 1 contains a polymorphic single sequence dinucleotide repeat (CA-SSR) showed a statistically significant correlation with the gefitinib response and was appeared to be a useful predictive marker of the development of clinical outcome containing skin rashes with gefitinib treatment. The other polymorphisms of EGFR were also associated with increased EGFR promoter activity. EGFR gene mutations and polymorphisms were also associated with EGFR kinase inhibitors response and toxicity.

Key words  Lung neoplasms; Genetic polymorphism; Drug therapy

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Introduction

Lung cancer is one of the most prevalent cancers worldwide, and it is classified into small cell lung cancer (SCLC, comprising 20% of lung cancers), and non small cell lung cancer (NSCLC, comprising 80% of lung cancers). NSCLC is the leading cause of cancer related deaths in the world. The occurrence of several cancers, including lung cancer, is caused by many genetic and environmental factors (e.g. tobacco smoke, dietary factors, infectious agents and radiation). Many chemical carcinogens and anticancer drugs require metabolic activation by Phase I enzymes, such as cytochrome P-450s (CYP), and activated metabolites are subjected to detoxification by conjugation with various Phase II enzymes such as uridine diphosphate-glucuronosyl transferase (UGT), glutathione S-transferase, N-acetyltransferase (NAT), and sulfotransferase. Functional variants of these metabolizing enzymes are created by single nucleotide polymorphisms (SNPs) in genes encoding these enzymes. We have previously reported that the joint association of NAT2 and CYP1A2 polymorphisms for a never-smokers group was a significantly lung cancer risk compared with its association for an ever smokers group.[1] Moreover, if carcinogens are not deactivated by metabolism, the reactive molecules would bind to cellular DNA forming adducts. The diversity of DNA damage induced by a complex carcinogen mix requires the combined activity of multiple DNA repair pathways to prevent deleterious mutations. The main repair pathways include nucleotide excision repair (NER) for the removal of UV damage and bulky DNA adducts, and base excision repair (BER) for restoring chemical alterations of a single methylated, oxidized, or reduced base. There is an increased interest in DNA repair genes for can-
cer risk because of their critical role in maintaining genome integrity\(^1\). We focused on genes encoding two key proteins in the BER pathway: OGG1 (8-oxoguanine DNA glycosylase), and MUTYH/MYH (Mut Y homolog), and found that lung cancer risk was 3-fold in individuals with the homozygous His/His genotype of MUTYH Gln324His [95% confidence interval (CI) 1.31−7.00, \(P=0.010\)]\(^1\).

SNPs are useful markers of genetic susceptibility to lung cancer, but require verification before their use as predictive biomarkers. Moreover, the functional variants caused by SNPs in genes encoding drug-metabolizing enzymes, transporters, ion channels, and drug receptors are known to be associated with individual variation in survival, drug responses, and toxicity\(^4\). The pharmacogenetics is being used to predict whether the selected chemotherapy will be really effective and tolerable to the patient. This mini review focuses on the impact of SNPs, highlighting their effects on the survival, response, and toxicity to commonly used chemotherapy of drugs, especially with respect to drug-metabolising enzymes and DNA repair genes.

**Irinotecan**

Irinotecan, an anticancer prodrug, inhibits the activity of topoisomerase I, and is used for treatment of various cancers including advanced NSCLC patients\(^5\). Irinotecan is oxidized by CYP3A4 to produce inactive compounds, and CYP3A4*16B [554 C>G (Thr185Ser) and IVS10+12G>A] polymorphism is associated with decreased metabolism of irinotecan\(^6\). Irinotecan is also metabolized by carboxylesterase to its principal active metabolite, SN-38, which is subsequently glucuronidated by UGT1As to form the inactive compound SN-38G\(^7\). Diarrhea and neutropenia are two well-characterized toxicities associated with irinotecan treatment and this severe toxicity is partly attributed to increased exposure to SN-38 caused by decreased UGT1A1 activity due to genetic polymorphisms\(^8\). The distribution of UGT1A1*28, a variant sequence in the promoter region [(TA)\(\overline{7}\)TAA], greatly differs between Caucasians and Asians; the frequency of UGT1A1*28 is high in Caucasians, whereas it is low in Asians\(^8\). The genotype, either heterozygous or homozygous, for UGT1A1*28 is a significant risk factor for severe toxicity by irinotecan (Odds ratio 7.23, 95%CI 2.52−22.3, \(P<0.001\)), whereas no statistical association if UGT1A1*6 (211 G>A) with irinotecan induced toxicity has been observed\(^11\). Additionally, Font et al\(^12\) concluded that heterozygous or homozygous genotypes of UGT1A1*28 could influence the activity of irinotecan/docetaxel in previously treated NSCLC patients. The Asian cancer patients study of irinotecan reported that the UGT1A1*6 allele is more predictive of neutropenia\(^13,14\). It has also been reported that the genetic variants of UGT1A1*6 in addition to UGT1A1*28 are associated with the occurrence of adverse events in irinotecan chemotherapy in Asian cancer patients\(^9\). Genetic linkage of UGT1A7 and UGT1A9 polymorphisms to UGT1A1*6, related to reduced catalytic and transcriptional activities of UGTs, is associated with the decreased glucuronosyltransferase activity for SN-38 in Japanese patients with cancer\(^15\).

Furthermore, polymorphic organic anion-transporting polypeptide 1B1 (OATP1B1, SLCO1B1) is reported to be involved in the hepatocellular uptake of SN-38. The OATP1B1 polymorphisms affect irinotecan-pharmacokinetics, subsequent toxicity, and tumor response of patients with advanced NSCLC\(^16\). SLCO1B1*15 is suggested to be useful in irinotecan chemotherapy to avoid unpredicted severe toxicity, although the homozygous genotype is rare among the Japanese\(^17\). Specific polymorphisms of ABCB1 and ABCC2, the multidrug transporter genes, can also influence the disposition and tumor response to irinotecan by regulating transporter activity\(^18\).

**Platinum-based chemotherapy**

In more recent trials, platinum compounds (cisplatin, carboplatin) are being used in combination with new cytotoxic drugs such as gemcitabine, paclitaxel, docetaxel, or vinorelbine in the treatment of advanced NSCLC. Cisplatin activity is mediated through the formation of cisplatin-DNA adducts. DNA repair pathways are the critical mechanism of resistance for platinum-based chemotherapy to lead to the removal of cisplatin-DNA adducts\(^19\). Gene polymorphisms of DNA repair factors are therefore obvious candidates for determinants of repair capacity and chemotherapy efficacy.

The excision repair cross-complementation group 1 (ERCC1), xeroderma pigmentosum group A (XPA), and xeroderma pigmentosum group D (XPD) are the lead enzymes in the NER pathway. The C/C genotype in codon 118 of ERCC1 is a useful marker for predicting better survival in advanced NSCLC patients treated with platinum-based chemotherapy\(^20,21\), but contrary evidence exists that shows no significant association between clinical outcome and the C/C genotype in codon 118 of ERCC1\(^22-24\). The other polymorphism, ERCC1 C8092A may be a useful predictor of overall survival in advanced NSCLC patients\(^25\), but no significant association has been reported\(^26\). The XPA A23G polymorphism significantly increased response to platinum-based chemotherapy\(^28\). The XPD Asp312Asn polymorphism, associated with a reduction in DNA repair capacity, resulted in a significant increase in the hazard-ratio\(^27\), whereas other studies showed inconsistent results\(^20,21\).

X-ray cross-complementing group 1 (XRCC1) is a key enzyme in the gap-filling step of short patch BER pathway. The XRCC1 Arg399Gln polymorphism was associated with a better survival in NSCLC patients following platinum-based...
chemotherapy\cite{24,29}. The XRCC3 Thr241Met polymorphism was also an independent determinant of favorable survival in patients treated with cisplatin/gemcitabine\cite{23}. Cytidine deaminase (CDA), which catalyzes the metabolic inactivation of gemcitabine, showed Lys27Gln or Ala70Thr polymorphisms and were associated with pharmacogenetics of this drug\cite{24,30}.

**EGFR-tyrosine kinase inhibitor (EGFR-TKI)**

Epidermal growth factor receptor (EGFR) is expressed in 50% of NSCLCs, and EGFR kinase inhibitors induce dramatic clinical responses in NSCLC patients with advanced disease. Those responses are well correlated with the presence of somatic activating **EGFR** mutations\cite{31}. The **EGFR** gene polymorphism in intron 1 contains a polymorphic single sequence dinucleotide repeat (CA-SSR), inversely correlating EGFR mRNA and protein level, showed a statistically significant correlation with the gefitinib response and appeared to be a useful predictive marker of the development of clinical outcome containing skin rashes with gefitinib treatment\cite{32,33}. Two polymorphisms of **EGFR**, -216 G/T and -191 C/A, are associated with increased **EGFR** promoter activity\cite{34}. -216 G/T was reported to be associated with gefitinib response and toxicity in lung cancer\cite{35}. These **EGFR** gene polymorphisms were also rare in East Asians as compared to other ethnicities in NSCLC patients\cite{36}.

In summary, there are many recent genetic studies of SNPs in NSCLC patients treated with variant chemotherapy. The **UGT1A1** gene polymorphisms might be useful for predicting severe toxicity with NSCLC patients treated with irinotecan-based chemotherapy. The DNA repair gene polymorphisms were useful as a predictor of clinical outcome to the platinum-based chemotherapy. EGFR gene mutations and polymorphisms were also associated with **EGFR-TKI** response and toxicity. Further clinical research will be necessary to clarify the usefulness of these biomarkers.

**Reference**


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