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SNPs in *ERCC1* and drug response to cisplatin in non-small-cell lung cancer patients

"SNPs ... have been known to be predictive markers of treatment response, toxicity, time to disease progression and survival in cancer patients."

KEYWORDS: cisplatin ■ *ERCC1* ■ SNP

Pharmacogenomics can be a useful tool to predict drug responsiveness (e.g., toxicity) as well as outcome, including survival. It can therefore also be used to engineer individual treatment according to the genetic characteristics of cancer patients. The target for pharmacogenomics is genetic information on polymorphisms and gene expression. The major approach involves the SNPs (a point mutation) which have been known to be predictive markers of treatment response, toxicity, time to disease progression and survival in cancer patients.

There are several general methods for the genotyping of SNPs [1]. One such method is PCR-RFLP. This lacks powerful high throughput, which means that it cannot be used for the identification of all genotypes. Quantitative reverse transcription (RT)-PCR is limited by its cost, whereas the 5'-nuclease assay for allelic discrimination is relatively new. Another recent method, 3D polyacrylamide gel-based DNA microarray, has been shown to be inexpensive and extremely powerful for the genotyping of many samples.

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Lung cancer is one of the leading common causes of cancer-related deaths worldwide. Non-small-cell lung cancer (NSCLC) constitutes >85% of cases of primary lung cancer and approximately two thirds of patients with NSCLC are diagnosed at an advanced stage [2]. Moreover, NSCLC is a chemoresistant tumor. The prognosis for patients with NSCLC is dismal regardless of the chemotherapy regimen used [3].

The standard care for patients with advanced NSCLC is platinum-based chemotherapy. Platinum is one of the most extensively used chemotherapeutic agents and remains the first-line treatment in various types of cancer [4].

Three commonly used platinum compounds are cisplatin, carboplatin and oxaliplatin. Crosslinks between guanine bases are induced by cisplatin, carboplatin and oxaliplatin. Cisplatin and carboplatin form an identical crosslink, whereas the oxaliplatin crosslink is structurally very different in the adduct [5]. The formation of platinum–DNA adducts that result in DNA crosslinks inhibit transcription, block replication and lead to the death of cancer cells. Hence, survival is expected to be longer in patients with higher levels of platinum–DNA adducts. Of the platinum compounds, cisplatin is most widely known as a scaffolding of combination chemotherapy in NSCLC. The combination of cisplatin with a third-generation cytotoxic drug (e.g., vinorelbine, gemcitabine, paclitaxel or docetaxel) is the standard chemotherapy for first-line treatment of advanced-stage (stage IIIB or IV) NSCLC [6]. The International Adjuvant Lung Cancer Trial (IALT) found a modest benefit of 4.1% in 5-year overall survival among 1867 patients treated with adjuvant cisplatin-based chemotherapy [7]. However, drug resistance and the detrimental effects of chemotherapy may reduce the quality of life of patients. Therefore, a plateau has been reached in the efficacy of chemotherapy.

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"...the repair/removal of DNA adducts has been demonstrated to be the 'trigger' that leads to cisplatin resistance because NER-deficient cells are hypersensitive to cisplatin."

DNA adducts of cisplatin are mainly removed by the nucleotide excision repair (NER) pathway. This is one of the four DNA repair mechanisms that has a role in the control of the progression of the cell cycle and apoptosis via DNA damage checkpoints. The NER pathway can be divided into two distinct subpathways. These are called

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the transcription-coupled repair (TCR) pathway (which repairs transcription-blocking lesions in transcribed DNA strands of active genes) and the global genomic repair pathway (which repairs the lesions in the nontranscribed strand of active genes and the nontranscribing genome) [3,8]. In the TCR pathway, damage is detected by the elongating RNA polymerase II complex when it encounters a lesion [9]. Thus, the tumors are sensitive to cisplatin if the TCR pathway is deficient [8]. Therefore, the repair/removal of DNA adducts has been demonstrated to be the 'trigger' that leads to cisplatin resistance because NER-deficient cells are hypersensitive to cisplatin. The reduced capacity to repair DNA may be expected to lead to an increased response and prolongation of survival for the cisplatin-based chemotherapy.

“...pharmacogenetic studies for the SNPs of ERCC1 may be used as predictive and prognostic markers of outcome for NSCLC patients treated by cisplatin-based chemotherapy.”

Of the proteins involved in the excision of damaged base(s) in the TCR pathway, excision repair cross-complementation group 1 (ERCC1) is a rate-limiting enzyme [1,10], which forms a heterodimer with xeroderma pigmentosum F (XPF) [3]. The ERCC1/XPF complex is responsible for the incision that cleaves the damaged strand at the 5'-end of the DNA lesion, particularly those induced by interstrand crosslinks. Therefore, ERCC1 is important for the repair of platinum-DNA adducts. The IALT-Bio program recently demonstrated that patients with ERCC1-negative (low-expression) tumors derived a substantial benefit from adjuvant cisplatin-based chemotherapy compared with ERCC1-positive (high-expression) tumors [11]. Other studies observed a decreased risk of death in patients with ERCC1-negative tumors as compared with patients with ERCC1-positive tumors after cisplatin-based adjuvant chemotherapy [2]. ERCC1 overexpression is also associated with resistance to cisplatin-based chemotherapy in NSCLC patients [12]. The capacity for DNA repair on the

basis of low or high expression of ERCC1 can be a determinant of the sensitivity to cisplatin-based chemotherapy in NSCLC patients.

Furthermore, the two common SNPs of *ERCC1*; one at codon 118C/T (which is associated with differential mRNA levels and protein levels) and C8092A (which is located in the 3'-UTR of the gene and which may affect *ERCC1* mRNA stability) have been recognized [13,14]. The SNP at codon 118 of *ERCC1* can influence the resistance/sensitivity of platinum [15]. Studies demonstrated that *ERCC1* codon 118C/T was correlated with time-to-disease progression and treatment response, as well as survival in cisplatin-based chemotherapy in NSCLC patients [1,16–19]. Contrary to expectation, it has been reported that patients with wild-type *ERCC1* C/C had a significantly longer survival and time to progression than those harboring non-wild-type *ERCC1* [19]. As to the reason, there was no significant difference between ERCC1 protein expression levels and the *ERCC1* SNP. With respect to function, the increase in protein expression in codon 118 of *ERCC1* has also been associated with diminished survival [16]. The C8092A SNP has been associated with overall survival, response and outcome in patients with advanced NSCLC treated by cisplatin-based chemotherapy [1,20]. Other studies demonstrated no significant association between outcome, treatment response and overall survival in the two SNPs of *ERCC1* [4,21]. Therefore, pharmacogenetic studies for the SNPs of *ERCC1* may be used as predictive and prognostic markers of outcome for NSCLC patients treated by cisplatin-based chemotherapy.

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