Review

Pharmacogenomics in Lung Cancer Chemotherapy: A Review of What the Oncologist Should Know

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Abstract. *Lung cancer is the leading cause of cancer-related death around the world; the addition of chemotherapy to treatment of this disease has been shown to significantly increase progression-free survival and overall survival. Despite newer chemotherapies, it is important to personalize the care (treatment and dose) upon each single patient's susceptibility for controlling and reducing adverse side-effects, at best. The present review describes the current status of pharmacogenomics studies regarding germline DNA variants that may alter response and tolerability to chemotherapeutic agents used to treat lung cancer, including perspective studies.*

Pharmacogenomics is an emerging branch of pharmacology that studies individual genetic variability in response to drugs, drug-induced gene expression modulation and the identification of new pharmacological targets based on the knowledge of genetic information. In fact, the human genome sequencing revealed that a single gene may have a number of differences in sequence at the nucleotide level, defined as polymorphism by combination of the Greek words poly (meaning multiple) and morph (meaning form). It is very important to analyze the correlation between patients' genotypes and phenotypes in order to define the relationship between individual polymorphisms and the alterations resulting by using drugs and to explain why the same therapy can have different results in different individuals. In particular, the aim of a pharmacogenomics analysis is singling-out any mutation that can affect the drug's therapeutic effects or the predisposition to undesired effect's occurrence (1). It is known that individual variation in drug response is due to factors such as age, sex, body weight, physical fitness, illnesses, level of liver and kidney functionality, diet, alcohol and tobacco use, but recent studies have reported that polymorphism of genes encoding proteins involved in the transport, metabolism and action of drugs influences in a more prominent way the outcome of chemotherapy (2-4) and toxicity. The problem of toxicity due to adverse drug reaction (ADR), despite being a major one, is often underestimated: it reportedly causes 7% of all hospitalizations in Europe, while in the USA it causes about 106,000 deaths and costs about 380 million dollars every year. It is estimated that the total cost to the community of damages caused by ADRs equals annually the cost of all pharmacological treatments (5). Chemotherapy-related ADRs seem to increase the global hospital cost by around 1,9% and the drug cost by 15% (6).

Such a variety of gene polymorphisms eventually reflects in a remarkable inter-individual variability both in chemotherapy response and toxicity, as no reliable and easily-evaluable markers are currently known to predict the drug treatments' efficacy and toxicity in neoplastic diseases. However, nowadays some peculiar polymorphisms have been identified that could cause significant side-effects and affect the tolerability and compliance to chemotherapy; in particular, in the present review we evaluated all studies demonstrating that genetic variants of polymorphisms significantly change the medical outcome in response to the administered drug in the Non Small Cell Lung Cancer (NSCLC). The patented methodologies, presented herein shed light on their identification and, consequently, mode of clinical approach. Thanks to developments in molecular

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genetics, there are currently several techniques that allow the identification of known genetic alterations directly, by examining the differences in the DNA nucleotide sequence. In particular, semi-automated methods have been patented for genotyping, based on the polymerase chain reaction (PCR), permitting the identification of polymorphisms in a very simple and fast way. For instance, a 2006 patent allows analysis of the fragments by an automated capillary electrophoresis system that can separate, detect and analyse up to 16 capillaries of fluorescently labelled DNA fragments in one run (7); another patent in 2002 defined a method of sequencing DNA, based on the detection of base incorporation by the release of pyrophosphate (PPi) (8), while an older patent application, nowadays in use, describes the methodology of allelic discrimination based on chemistry (9). A more recent invention provides a method to produce a reduced representation of a genome for sequencing and DNA polymorphism detection (10).

Pharmacogenomics Analysis: Rationale

The ultimate purpose of a pharmacogenomics analysis is to carry-out a preliminary analysis of the individual patient's genetic characteristics to predict the therapeutic effect and toxicity of the employed drug, thus allowing for optimization and personalization of the chemotherapy treatment (11). Such a personalization is surely a prominent goal especially in the oncological field. For instance, as several studies have shown, the administration of the same dose of an anti-blastic drug in a patient population often results in a wide toxicity range with lethal consequences in some cases (12). Moreover, such drugs have a low therapeutic index, *i.e.* the ratio between the lowest effective and the highest tolerated doses, the latter of which is generally employed; this entails a high risk of developing adverse effects in the sub-population of genetically predisposed individuals that show an altered drug metabolism (13). Gene characterization of each patient would surely help identify the most suitable treatment protocol (14).

To this day, the dosing of chemotherapy drugs is still based on the patient's body surface correlated with the circulating blood volume and glomerular filtration rate, but not with their pharmacokinetics. Cancer patients are practically treated with a trial-and-error approach, by generally applying the treatment and operating a standard dose reduction in case of toxicity (15).

Lastly, recent studies have shown that the number of polymorphisms in various genes affects therapy efficacy (16). Drugs are involved in a series of complex metabolic pathways, in which several proteins intervene, any of which may carry mutations that can cause an alteration of its effect; the interaction among all such polymorphisms crucially conditions the treatment's final outcome.

Methods

We performed a computerized systematic literature search in electronic databases: PubMed, Embase, Cochrane Library, SCOPUS, OVID, Springer.

Studies eligible for this analysis were updated using the search terms, NSCLC, chemotherapy, patents, polymorphism, pharmacogenomics analysis and GSTP1, XRCC1, ERCC1, MRP2, MDR1, ABCB1, TTSER, MTHFR, CYP. The inclusion criteria were as follows: (i) Only patients with advanced NSCLC were considered; (ii) All trials had to include a treatment of platinum-based agent, *i.e.* gemcitabine, vinorelbine, taxanes, pemetrexed; (iii) Only studies of outcome and toxicity related to polymorphism were discussed and not studies on the correlation risk of developing lung cancer due to single polymorphisms; (iv) Only trials reported in English were included; (v) Patents were downloaded from: http://www.delphion.com/fcgi-bin/patsearch, www.google.com/patents, www.uspto.gov, www.freepatentsonline.com, and www.wipo.int/pctdb/en/search-simp.jsp, www.freshpatents.com.

Chemoterapeutic Agents in Lung Cancer and Polymorphic Variants Correlated with Their Metabolism and Effect

Cisplatin

The activity of platinum (pt) derivatives can be greatly affected by polymorphisms that can alter the activity or expression level of proteins intervening in the biochemical ways in which this class of antiblastic drug is involved. Both the activity and toxicity of platinum derivatives can be affected by polymorphisms in genes that encode proteins in the following three processes.

Transmembrane Drug Transport

Most implied in the efflux mechanism of platinum derivatives is MRP2 (Multidrug resistance-associated protein 2) from the superfamily of ATP-binding cassette (ABC) proteins, whose components are integral membrane glycoproteins working as pumps. The *ABCC2* gene and the encoded protein MRP2 are normally located in hepatocytes, as well as in kidney epithelium and in intestinal enterocytes, and are, therefore, deputed to play an important role in the disposal of drugs (17). Different expression or activity of *ABCC2* gene seems to influence systemic exposure to cisplatin (18). Two polymorphisms are known: 2366C>T consisting of the substitution of a thymine for a cytosine in position 2366 in exon 18 and 4348G>A, caused by the substitution of an adenine for a guanine in position 4348 in exon 31; both variations have been observed to be possibly associated to reduced functionality of the same transporter (19). In a recent study, in advanced and metastatic lung

cancer treated with cisplatin, three functional polymorphisms of *ABCC2* (C-24T, G1249A and C3972T) were significantly associated with a better treatment response (C-24T promoter) and an increased risk of overall toxicity in particular hematological toxicity like severe thrombocytopenia (C3972T exon 28) (20). This finding was confirmed by another trial on 113 lung cancer patients treated with platinum-based chemotherapy showing the polymorphic status of MRP2 C-24T that might be a predictive marker for treatment response (21).

There is also a recent patent application disclosing the detection of polymorphism in the ABCC2 gene that can be realized efficiently in a short time and at low cost (22).

Drug Inactivation

The inactivation process of platinum takes place through its conjugation with reduced glutathione (GSH) in a reaction catalysed by the Glutathione S-transferase (GST) enzyme, protecting the cell from damage and assisting the detoxifying process. At least three of the genes that code for GST have been shown to have functional polymorphisms and are frequently present in general populations: Glutathione S-transferase M1 (*GSTM1*), Glutathione S-transferase T1 (*GSTT1*) and Glutathione S-transferase P1 (*GSTP1*) (23). The role of GST in the detoxification of antitumor agents suggests the possible implication of GST polymorphisms to the chemotherapeutic response. In particular a GST overexpression is reported to be associated to phenomena of innate or acquired resistance to platinum derivatives; reportedly, the *GSTP1* subclass is the most involved in such a process. The main *GSTP1* polymorphism is 313 A>G, which implies the substitution in exon 5 of adenine in position 313 with a guanine. The polymorphic status of *GSTP1* 342 A>G might be the predictive marker for the treatment response of advanced NSCLC patients due to decreased detoxification of chemotherapeutic agents. In NSCLC, *GSTP1* variant genotypes (Ala/Val or Val/Val) had a significantly better survival compared to patients who had the wild type genotype (Ala/Ala; p=0.037) (24). *GSTP1* also seems to influence the toxicity of chemotherapy: patients carrying the homozygous mutant GSTP1 GG genotype were at considerable risk for severe platinum-associated polyneuropathy (18% *vs*. 3% in wild-type *vs*. heterozygous mutant patients, respectively; p=0.01) (25); however, *GSTP1**B and *GSTP1* 105 Val haplotypes were associated, in a statistically significant way, with toxicity, and particularly with neutropenia reduction (26). Patients with deficient-type GSTM1 were superior responders to platinum drugs than those carrying wild-type *GSTM1* (p=0.014) (27). The *GSTT1* –/– and *GSTM1* null genotype were significantly associated with overall survival and found to be independent prognostic factors for shorter lung cancer survival (28-29). A 2004 patent application relates to a high throughput assay for detecting the presence of clinically significant GST polymorphic alleles in a patient (30).

Mechanisms of Platinum-DNA Adducts Repair

DNA repair occurs in three important ways: by excision of the damaged base with Base-Excision Repair (BER), by excision of the nucleotide with Nucleotide-Excision Repair (NER), and by repair of the mismatches with Mismatches Repair (MMR). The DNA repair protein XRCC1 is an important component of the BER system. The NER process involves a complex of binding proteins such as Xeroderma pigmentosum complementation group C (XPC), Xeroderma pigmentosum complementation group A (XPA) and replication protein A (RPA) recruiting the Xeroderma pigmentosum complementation group D (XPD) enzyme, also known as excision repair cross-complementing group 2 (ERCC2). Also relevant are the proteins allowing for the removal of the damaged thread, such as Xeroderma pigmentosum complementation group G (XPG) and the Xeroderma pigmentosum complementation group F (XPF)/ Excision repair cross-complementing group 1 (ERCC1) complex (31).

Both the BER and NER mechanisms are involved in the repair process of all Pt-DNA adducts, those produced by cisplatin as well as carboplatin or oxaliplatin. The MMR system, on the other hand, is capable of discriminating between different types of adducts, thereby providing the basis for the efficiency of oxaliplatin in cisplatin/carboplatin-resistant tumors (32).

X-Ray Repair Cross-Complementing Group 1 (XRCC1)

The XRCC1 protein is critical for repairing DNA damage induced by the platinum-based anticancer drugs, suggesting that XRCC1-mediated DNA repair capacity may markedly impact the efficacy of platinum-based therapy against NSCLC; thus, it is possible that XRCC1 could be a future predictive marker of response to treatment in advanced-stage disease patients (33).

Two principle polymorphisms have been described for the encoding gene of XRCC1: the main one consists of a substitution of an adenine for a guanine in position 28152 (28152 G>A) in exon 10, which leads to amino-acidic substitution of a glutamine for an arginine in codon 399 (Arg399Gln) (34) and Arg194Trp polymorphism.

The Arg399Gln polymorphism shows an allele frequency of 14-39% based on the population considered; in particular, in the Caucasian population the varying allele shows a 32-36% frequency (35). Such a polymorphism involves the interaction domain of XRCC1, thus altering its capability to assemble the complex needed to efficiently repair the lesion. Several studies have in fact shown that the Arg399Gln variant is associated with increased levels of DNA damage, clearly due to a decreased capability of the mutated enzyme

to repair lesions (36). A study performed on 103 patients with NSCLC treated with a platinum-based therapy has shown that polymorphism-carrying patients have a lower survival rate (37). In the BIO-FAST Trial a polymorphism in homozygous XRCC1 (Arg399Gln) showed a prognostic role in patients treated with first line based-cisplatin chemotherapy (38). In a recent meta-analysis, *XRCC1*399Gln was less favorably associated with both response rate and overall survival to chemotherapy (39).

Other polymorphisms are also involved in chemotherapy toxicity: patients carrying at least one variant of the XRCC1 Arg399Gln allele have a 2.5-fold increased risk of grade 3 or 4 gastrointestinal toxicity when treated with first-line cisplatin-based chemotherapy (40).

Yuan *et al*. found that the *XRCC1* Arg194Trp allelic variant in Asian patients was particularly associated with the response to platinum-based therapy (41).

Excision Repair Cross-Complementing Group 1 (ERCC1)

ERCC1 is a component of the NER system. Several studies have shown that this protein's expression level should apparently be correlated to the cell sensitivity to the platinum derivatives' activity. An International Adjuvant Lung Cancer Trial (IALT) understudy showed cisplatin-based adjuvant therapy to significantly prolong the survival rate in ERCC1-negative patients (42). A study by Lord *et al*., in patients with locally-advanced or metastatic disease, showed that a low ERCC1 expression is associated to a significant improvement of the survival rate in patients treated with cisplatin and gemcitabine (43). Cobo *et al*. showed that *ERCC1* mRNA levels predict the response to cisplatin-based treatment in metastatic patients (44). In patients receiving adjuvant chemotherapy after surgical resection for lung neoplasms, the relapse rate was lower in *ERCC1*-positive subjects compared to *ERCC1*-negative, and in patients with C8092 A polymorphism. Frequent *ERCC1* polymorphism is the variation of an adenine for a cytosine in position 8092 (8092C>A); this variant shows an allele frequency of 27%. This polymorphism seems as well to have a good predictive value on a platinum-derivative-based therapy outcome. In a study by Zhou *et al*., performed on 128 patients with advanced-stage NSCLC treated with a platinum-derivative-based therapy (cisplatin/carboplatin), individuals with wild-type C/C genotype had better survival rates (45). In another study, carriers of at least one polymorphic allele showed higher gastrointestinal toxicity with chemotherapy (46). Also in multivariate analysis, *ERCC1* expression and C8092A polymorphism were independent prognostic factors in chemotherapy-naive stage I patients (47).

One of the *ERCC1* polymorphisms is 19007 C>T, due to the transition from cytosine to thymine in position 19007, leading to alteration of a codon that encodes for the same amino acid asparagine (Asn) but is translated at a slower speed, thus reducing the gene expression. This polymorphism has a 55-60% frequency (48) and, affecting ERCC1 expression, can play a positive predictive role on a platinum-derivative-based therapy outcome. In a study on 109 NSCLC patients, carriers of this variant were found to have a better survival rate (49).

There are patents providing compositions and methods to analyze polymorphisms in the *ERCC1* and *XRCC1* genes for determining a patient's cancer risk and treatment response (50-51).

Methylenetetrahydrofolate Reductase (MTHFR)

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme involved in the transformation of 5-10 methylene-tetrahydrofolate to 5 methyltetrahydrofolate, needed as a methyl giver for the remethylation of homocysteine in methionine with the intervention of vitamin B12. Alongside severe MTHFR deficiency, another common gene polymorphism due to the substitution of a thymine for a cytosine in nucleotide 677 (C677T) causing substitution of a valine for an alanine in the final protein and a 50% reduction of MTHFR enzyme activity, has been identified. Such a variant entails high homocysteine levels in the bloodstream, especially after the administration of methionine (52).

Another mutation in the *MTHFR* gene, known as genetic variant A1298C, consists of the transition from adenine to cytosine in position 1298 leading to the substitution of a glutamate with an alanine. This genetic variant is associated with high homocysteine levels and low folate levels in plasma when combined with the C677T mutation (53). MTHFR has been related to response at platinum-based chemotherapy in NSCLC. A recent meta-analysis confirmed that MTHFR 677TT homozygote carriers had a better response to platinum-based chemotherapy. Patients in treatment with homozygous mutations for *MTHFR* C677T had a significantly increased PFS (progression free survival) compared to patients with wild-type or heterozygous mutations (54). A single nucleotide polymorphism of *MTHFR* has also been associated with an increased risk of toxicity, like irradiation pneumonia developing in lung cancer patients treated with radiation therapy to the chest wall (55).

Finally, there is finally a patent disclosing a primer set for specifically amplifying a target region in the *MTHFR* gene by a nucleic acid amplification method (56).

Gemcitabine

Although many reports about single nucleotide polymorphisms (SNPs) in the family of ABC transporters have been published, the impact of polymorphisms on pharmacokinetics and pharmacodynamics of gemcitabine remains to be defined (57). More studies report multidrug resistance 1 (MDR1) overexpression to be associated with

sensitivity to gemcitabine (58). MDR1 plays a major role in drug resistance by impairing the intracellular retention of multiple anticancer drugs. The most studied SNP is the C3435T located in exon 26. This polymorphism has been found to have a role in the function of the permeability glycoprotein (P-gp) responsible for substance elimination by the cell membrane by hydrolysis of ATP; multiple studies showed that this polymorphism was significantly correlated with drug response (58). The overall response to treatment of homozygotes for the wild-type (C/C) allele in *MDR1* C3435T was significantly better than in heterozygotes (C/T) (59) and mutant homozygotes (T/T) (95% confidence interval (CI): 1.44-3.68; I=0.0005) (60). The *MDR1* 2677 polymorphism seems to be correlated with an increase in grade 3 toxicities in the mutated group (39%) and an increase in both progression-free and global survival in patients that had had gemcitabine as an adjuvant for other cancers (61).

Of note, there is a patent for determining haplotypes or diplotypes of the 5' regulatory region of *MDR1* (multidrug resistance 1) gene (62). Another recent patent consists of a single nucleotide polymorphism (SNP) detection kit for G2677T/A of *MDR1* (multidrug resistance gene 1) (63).

Taxanes

The overexpression of ABC-transporter genes such as *MDR-1*, is a factor of non-response to taxane-based chemotherapy due to increased toxicity originating from a longer exposure to the drug, due, in turn, to a reduced elimination rate (64). Overexpression of P-gp1/*ABCB1* is in fact associated with poor prognosis in several tumor types. Moreover, polymorphisms in cytochromes *P450* (3 A4, 3 A5, 2 C8), that are implied in the hepatic metabolism of taxanes, can determine an increase in drug concentration due to lack of elimination and thus an unacceptable toxicity level (65). Both genes *CYP3A4* and *CYP3A5* are polymorphic and several allele variants have been described. Only two allele variants that are in linkage disequilibrium, namely *CYP3A4**1B and *CYP3A5**3, are common to several ethnicities and have functional relevance (66). As far as the *CYP3A4**1B is concerned, it seems to modify the ability to metabolize some CYP3A substrates. *CYP3A5**3 instead seems to be the most common *CYP3A5* allele and is associated with decreased enzyme activity. In a study published in the Journal of Clinical Oncology (JCO), gaps in allelic distribution for genes involved in paclitaxel disposition or DNA repair between Japanese and US patients were observed. In this exploratory analysis, genotype-related associations with patient outcomes (progression free survival) were observed for CYP3A4*1B (p=0.04), however, this association should be interpreted in the context that only African-American patients harbored this allele (67). A 2010 patent describes a method for predicting a subject's response to at least one CYP3A4-metabolized compound; with the method comprising the detection of the allelic status of one or more polymorphisms in a nucleic acid sample of the subject (68).

Pemetrexed

Pemetrexed (Alimta) is a multi-target agent converted to a series of polyglutamate-derived metabolites by folylpolyglutamate synthetase. They inhibit three folate-dependent enzymes: thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARF1) (69). Several studies are focused on the effects of pemetrexed on thymidylate synthase. TS is an important target for pemetrexed-based chemotherapy. Its overexpression is correlated to TS-target chemotherapy resistance. Polymorphic tandem repeats located in the TS enhancer region (TSER) have been shown to influence the expression of TS. Three-fold tandem repeats (TSER*3) give larger *in vitro* TS expression than two-fold tandem repeats. In a Korean study, survival was significantly longer with pemetrexed in patients with high *TS* expression genotypes (second Nief's classification) (70) 3RGCC/3RGCC or 3RGGC/3RGGC compared to the other groups (PFS: 5.2 months *vs*. 3.7 months, p=0.03; OS: 31.8 months *vs*. 18.5 months, p=0.001) (71). In advanced non-small cell lung cancer patients treated with pemetrexed-based chemotherapy with the *TS* 2R/2R, 2R/3C or 3C/3C genotypes, median PFS times and response rate were significantly longer than those of patients with the 2R/3G, 3C/3G or 3G/3G genotypes (I=0.036 and I=0.044, respectively) (72). Prospective data are needed to confirm the impact of TSER on the outcome after TS-target therapy (73). There is a recent patent directed to a method of predicting a response to a chemotherapeutic regimen based on loss of heterozygosity at the thymidylate synthase locus in cancer tissue (74).

A 2009 study published by JCO on patients treated with Alimta in a second-line treatment for lung cancer has investigated polymorphisms in *MTHFR*. Homozygous mutant patients with *MTHFR* C677T have a significant increase in PFS compared to wild-type homozygous mutant patients, while homozygous mutant patients with *MTHFR* A1298C have shorter PFS as a trend (p=0.06) (75). In an Italian study, a multivariate analysis confirmed the independent prognostic significance of *MTHFR*-C677T both in risk of disease progression (CC-CT genotypes hazard ratio [HR] 1.94, 95%CI: 1.15-3.28; p=0.012) and death (HR 2.00, 95% CI: 1.12-3.54; p=0.018) (76).

Vinorelbine

Vinorelbine is a semi-synthetic vinca alkaloid, mainly metabolized by *CYP3A4* and *CYP3A5* (77). *CYP3A5* is a highly polymorphic gene: the widespread allele *CYP3A5**3 causes a reduced expression, hence a lower drug

Table I. *Portrayal of the most important polymorphisms identified, their functional effect, the anticancer drugs involved and expected event(s).*

Gene polymorphism	Functional effect	Anticancer drugs involved	Observed event
MRP2 C2366T (16)	T allele is associated with decreased transporter activity	Cisplatin	Polymorphism associated with better treatment response
MRP2 C4348A (16)	A allele is associated with decreased transporter activity	Cisplatin	Polymorphism associated with better treatment response
MRP2 C-24T (17)	T allele is associated with decreased transporter activity	Cisplatin	Polymorphism associated with better treatment response
MRP2 C3972T (17)	T allele is associated with decreased transporter activity	Cisplatin	Polymorphism associated with better treatment response and increased toxicity
MRP2 G1249A (17)	A allele is associated with decreased transporter activity	Cisplatin	Polymorphism associated with better treatment response
GSTP1 A313G (20)	G allele is associated with decreased enzyme activity	Cisplatin	Polymorphism associated with better survival and increased toxicity
GSTP1 A342G (19)	G allele is associated with decreased enzyme activity	Cisplatin	Polymorphism associated with better survival and increased toxicity
GSTM1 gene deletion (23)	Loss of function	Cisplatin	Polymorphism associated with better response to platinum drugs
GSTT1 gene deletion (24)	Loss of function	Cisplatin	Polymorphism associated with shorter survival
XRCC1 G28152A (31-37)	A allele is associated with decreased DNA repair activity	Cisplatin	Polymorphism associated with lower OS and response rate
ERCC1 C8092A (41-44)	A allele is associated with decreased DNA repair activity	Cisplatin	Polymorphism associated with better survival and increased toxicity
ERCC1 C19007T (45-46)	C allele is associated with decreased DNA repair activity	Cisplatin	Polymorphism associated with better survival
MTHFR C677T (48-52,70-74)	T allele is associated with decreased enzyme activity	Cisplatin, pemetrexed	Polymorphism associated with better response to platinum; Homozygous mutant shows increased PFS
MTHFR A1298C (49, 70)	C allele is associated with decreased enzyme activity	Cisplatin, pemetrexed	Homozygous mutant has shorter PFS
MDR1 C3435T (56-57,77)	T allele is associated with decreased transporter activity	Gemcitabine, vinorelbine	Polymorphism associated with worse response to gemcitabine; Lower risk of progression in patients treated with Vinorelbine
MDR1 G2677T (80)	T allele is associated with decreased transporter activity	Gemcitabine, vinorelbine	Polymorphism associated with increased toxicities and better OS and PFS in patients treated with Gemcitabine; Better response to Vinorelbine
CYP3A4*1B (89)	Polymorphism associated with decreased enzyme activity	Paclitaxel, vinorelbine	Polymorphism associated with response
CYP3A5*3 (88, 73)	Polymorphism associated with decreased enzyme activity	Paclitaxel, vinorelbine	Polymorphism associated with response
TTSER 28 bp VNTR (2R/3R) (68)	3R allele is associated with increased TS expression (increased enzyme activity)	Pemetrexed	Survival observed was significantly longer in patients with high expression genotype

metabolism in the liver (78). In a study by Pan *et al*. in 59 NSCLC patients, the CYP3A5*3 polymorphism seemed to be associated to responses to vinorelbine treatment. No significant difference in toxicity and survival was observed according to SNP genotype in lung cancer patients (79). Vinorelbine is also a substrate for P-gp membrane transporters (MDR1, ABCB1). *MDR1* polymorphisms can cause alterations in the drug's absorption and elimination (80). *MDR1* 3435CC polymorphisms appear to be related to lower risk of progression in advanced non small cell cancer treated with vinorelbine (81). In a 2008 study published in Respiration, *ABCB1* C3435T polymorphism was associated to a better response to vinorelbine-based chemotherapy for lower P-gp expression levels (82). This study was in agreement with some reports but in disagreement with others, thus further studies should be

carried on with large patient cohorts to confirm these results (83-84). There is a patent disclosing the detection of this gene polymorphism having an influence on pharmacokinetics in a DNA sample from a subject and predicting the influence of the gene polymorphism on the kinetics of a drug in the subject (85).

Conclusion

Pharmacogenomics provide a polygenic, global approach in the genome study, by simultaneously analysing multiple gene polymorphisms or multiple mutations within a single gene. The pharmacogenomics analysis, aimed at inquiring the effect of single polymorphisms on the treatment's outcome is still fundamental in situations in which the alteration of even a single gene can play a crucial role, such as the predisposition to developing toxic effects.

Integrating results from pharmacogenetics and pharmacogenomics studies surely is a valuable strategy to be developed in the coming years in order to finally achieve individualization of the anti-blastic therapy and thus obtain the highest efficacy and lowest toxicity from each treatment. Polymorphic variants of enzymes involved in the metabolism of chemotherapeutics agents used in lung cancer should be investigated (Table I).

Current and Future Developments

Randomized clinical trials are required in order to define not only the correlation with toxicity, but also with the outcome. In fact, the effectiveness of therapy may be influenced by genetic characteristics of the tumor cells because of their high genetic instability often developing additional somatic genetic alterations that lead to genotype differences that are not found in non-neoplastic germ cells. The pharmacogenomics studies, on the other hand, are based mainly on an analysis of the germ genetic characteristics obtained from peripheral blood samples. Thus, the purpose of these studies is to define a personalized therapy, which gives the maximum clinical benefit with minimal occurrence of side effects. Today, such an approach seems as a distant goal because it is necessary to consider various factors that may influence the chemotherapy response, such as mode of drug administration, administration of other drugs/chemotherapeutic agents, demographic and clinical characteristics of patients, ethnicity issues, influence of environmental factors (alcohol, smoking, diet), all of which interfere with the standardization of the data obtained from this type of analysis.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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