Pharmacogenetics in Oncology: A Promising Field

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Abstract: Pharmacogenetics is a rapidly developing field, especially in oncology. In the most ideal situation pharmacogenetics will allow oncologists to individualize therapy based on patients' individual germline genetic test results. This can help to improve efficacy, reduce toxicity and predict non-responders in a way that alternative therapy can be chosen or individual dose adjustments can be made.

Multiple pathways have been studied extensively of which a brief review is presented here. Increased 5FU toxicity is associated with variations in the *DPYD* gene, *TYMS* gene and *MTHFR* gene. Furthermore variations in the *UGT1A* gene and the *ABCB1* gene influence irinotecan metabolism and disposition. Other genetic changes result in reduced DNA repair capacity related to platinum efficacy or reduced cytochrome P450 2D6 activity related to tamoxifen efficacy.

Despite the extensive number of pharmacogenetic studies and promising results, it is still unclear when and how pretreatment genetic screening should be implemented in oncology. Future prospective studies should focus on the effect of pharmacogenetics on patient outcome and combine this with cost effectiveness evaluations. Thus supplying us with predictive models helping in deciding when pretreatment genetic screening is useful.

Keywords: Pharmacogenetics, pharmacogenomics, single nucleotide polymorphism, oncology.

INTRODUCTION

Pharmacogenetics is studying the interindividual differences in drug response at the genetic basis and as such aims to improve drug therapy. Ultimately this will allow a physician to make a more tailor made choice with regard to the type of medication, schedule and dosage in order to create an optimal therapeutic effect. This approach requires extensive knowledge of genetic variations, both inherited and acquired, and also of pathophysiological pathways and pharmacological mechanisms. Different types of genetic variants exist such as single nucleotide polymorphisms (SNPs), deletions, insertions, and tandem repeats.

SNPs are a relatively common type of genetic variation comprising a single nucleotide change, and when occurring in a coding region, causes a single aminoacid change (non-synonymous SNP) or even no aminoacid change (synonymous SNP). In contrast, deletions and insertions usually cause more prominent aminoacid variation and tandem repeats in the promoter region of a gene modulate gene expression. These germline genetic polymorphisms usually have no apparent effect on the phenotype ('silent variation') but can result in an altered amino acid composition and hence in mRNA instability, altered gene expression and different protein structure. This in turn can have effects on enzyme activity and therefore these variations can lead to functional changes in patients using specific drugs or drug target modifications.

Pharmacogenetics is especially important for drugs used in oncology due to the small therapeutic window between efficacy and severe toxicity. This makes a personalized dosing regimen preferable above standard dosing. Initially the studies concerning pharmacogenetics in oncology focused on germ line mutations involved in drug metabolism, e.g. dihydropyrimidine dehydrogenase (DPD) deficiency in patients treated with 5-fluorouracil (5FU). Besides these inherited, interindividual variations, there are also somatic mutations, which are only present in tumor cells and can therefore be specifically targeted, e.g. the EGFR mutation in lung cancer for gefitinib. Discussions on these somatic mutations are not within the scope of this review.

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This review aims at providing an overview of the recent advances in germline pharmacogenetics with regard to oncology and tries to explain some of the blank spots to be filled. To this end a Medline search was performed during October 2008 using the keywords oncology, pharmacogenetics, pharmacogenomics and the specific enzymes [1-3].

DIHYDROPYRIMIDINE DEHYDROGENASE (DPD)

5FU is an anticancer drug used in the treatment of several solid tumors such as colorectal carcinoma and breast cancer. In the 5FU pathway DPD, encoded by the gene *DPYD*, is the rate limiting enzyme converting up to 80% into inactive metabolites. In 1984 Wadman *et al.* [4] made the first postulation connecting DPD deficiency with an excess of thymine and uracil. A case of a 27 year old woman presenting with severe hematological and neurological side effects upon 5FU therapy was described. Urine analysis showed high levels of thymidine and uracil, sustaining the postulation that this may have been caused by DPD deficiency [5]. Shortly thereafter a case of DPD deficiency related to severe 5FU toxicity with an autosomal recessive inheritance pattern was described [6]. After administration of a test dose of 5FU there was a prolonged elimination half time with no observed catabolites. Partial deficiency was also found in the patient's father. Larger studies showed very low prevalences of DPD deficiency; estimates in the Japanese population amount to 1 in 10.000 births [7]; a French group conducted a prospective study in 185 patients who were treated with 5FU, none of which were DPD deficient [8]. After complete sequencing of the *DPYD* gene [9], multiple variants were found [10]. The most important variant seems to be a G to A mutation in the GT 5'splice recognition site of intron 14 (exon skipping mutation) IVS14 + 1G>A (DPYD*2A). Multiple studies described high prevalences of this variant in DPD deficient patients ranging from 28-43% [11-13]. These studies also showed that 55% of DPD deficient patients developed grade 4 neutropenia upon 5FU treatment, compared with 13% of patients with a normal DPD activity. In a group of patients with grade 3-4 toxicity after 5FU administration it was shown that 60% of these cases was DPD deficient of which 28% was carrier of the IVS14+1G>A mutation, this in contrast to the non-DPD deficient cases in which only 1 heterozygote was found [14,15]. Besides this common splice site mutation, multiple other variants have been described such as IVS11 + 1G>T, 731A>C (E244V), 1651G>A (A551T) [16],

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G1601A (DPYD*4), T1679G(DPYD*13) [17]. Another highly prevalent variant seems to be 2846A>T (Asp949Val) [18]. All of these variants in the *DPYD* gene cause decreased DPD activity. However, not all decreased DPD activity cases can be attributed to variation in the *DPYD* gene. Hypermethylation of the *DPYD* promoter region was observed in DPD deficient cases while this was not the case in healthy individuals. Possibly this hypermethylation is involved in regulation of DPD activity [19,20]. However a recent study showed no hypermethylation in 27 patients treated with 5FU of which 17 had serious side effects and none had a known mutation in DPYD gene [21].

DPD deficiency alone is not the sole cause of 5FU related toxicity as shown in a recent study in which 23 patients treated with 5FU whom had serious side effects were screened for DPD deficiency, which was the case in only 7. The other cases had no known cause of their toxicity [22,23]. It is clear that DPD deficiency is related to severe 5FU toxicity and this may lead to pretreatment screening either by genotyping or phenotyping [24,25] . The IVS14+1>G splice site mutation is the most common cause of DPD deficiency. Genetic pretreatment screening of this mutation to prevent severe toxicity may be considered. However because of the low absolute prevalence of this mutation (1.3%), it is unclear if this approach is cost effective [26-28].

THYMIDYLATE SYNTHETHASE (TS)

Besides DPD, thymidylate synthethase (TS) is another important enzyme involved in the 5FU pathway. TS is associated with de novo thymidine synthesis and is the central target of 5FU, since this is a TS-inhibitor. *In vitro* continuous 5FU exposure is associated with TS gene amplification and TS protein over expression causing 5FU resistance [29]. The gene coding for TS, *TYMS*, has a promotor enhancer region (TSER) containing a 28 bp tandem repeat sequence [30] which is important for gene expression and efficiency [31]. Two different alleles have been described with a two repeat sequence and a three repeat sequence. *In vivo* the three repeat sequence (TSER*3) seems to provide greater translational efficiency [32], possibly through higher mRNA levels, compared with the two repeat sequence (TSER*2). TS levels are similar in both healthy and tumor tissue [33]. Because of lower levels of TS and less upregulation of TS the two tandem repeat polymorphism is associated with a better outcome of therapy in patients with colorectal carcinoma treated with 5-FU, with regard to both disease free survival and overall survival(OS) [34,35]. Not all patients with the TSER*3 allele have a worse outcome [36]. This is probably due to another mutation, a G>C SNP in bp 12 of this allele, which causes lower TS activity and thus a comparable phenotype with the TSER*2 allele [37-39]. This SNP is found in 29%-57% of all TSER*3 alleles [40]. Besides these variants, also a 6 bp deletion in the 3' UTR of the *TYMS* gene has been described to be in linkage disequilibrium with the TSER*3 allele and associated with worse prognosis in 5FU treated patients [41,42]. This is caused by increased mRNA instability and lower TS expression [43]. Besides colorectal carcinoma, TS amplification is a prognostic factor for 5FU treatment in bladder and gastric cancer as well [44,45]. *TYMS* genotyping, perhaps in combination with *DPYD* genotyping, can attribute to selecting a subpopulation of patients who will have a better response on 5FU chemotherapy and less severe side effects [46-48]. Recently it was shown that mutations in the promoter region of the *TYMS* gene cause modification of the number of operative binding sites of a transcription factor [49].

METHYLENE TETRAHYDROFOLATE REDUCTASE (MTHFR)

Another enzyme involved in the 5FU pathway is methylene tetrahydrofolate reductase (MTHFR), which is also important in methothrexate (MTX) mechanism of action. It plays a role in folate and methionine metabolism, and hence in DNA synthesis and methylation. MTHFR metabolizes a 5FU substrate (5,10 methylene tetrahydrofolate), and therefore decreased function of this enzyme is associated with enhanced 5FU activity, while MTX sensitivity is reduced [50]. The most prevalent variant in the gene coding for MTHFR is 677C>T (ala>val at codon 222). In the general population about 25% is homozygous for this genotype [51]. This polymorphism is associated with increased toxicity of MTX treatment. In 43 patients with ovarian cancer treated with low dose MTX, 12 patients developed grade 3-4 toxicity. A significant association was found between this toxicity and the TT MTHFR 677 genotype. Grade 3-4 toxicity occurred in 10 of 13 (77%), 1 of 17 (6%) and 1 of 13 (8%) of the TT, CT and CC genotype respectively. Patients with the TT genotype had a 42 times increased risk at developing grade 3-4 toxicity. The homocysteine levels in patients with the TT genotype were significantly higher and correlated with toxicity [52]. Patients treated with 5FU show better results if they have the TT genotype. In 43 advanced colorectal cancer (aCRC) patients treated with 5FU the TT genotype, which was present in 26 patients (5 homozygous), was correlated with better response rates (odds ratio 2.86) [53]. This was also shown in 116 patients with gastric cancer treated with 5FU. In the TT genotype group there was significant longer relapse free survival and overall survival [54]. Other studies show conflicting results, possibly due to interpatient variability in the folate status [55-57]. Another mutation frequently found (1298A>C) does not seem to be associated with enzymatic activity [58]. Despite the extensive studies and knowledge regarding the 5FU pathway (*DPYD, TYMS, MTHFR*), it does not yet seem possible to accurately predict 5FU toxicity and therefore further studies are needed before pharmacogenetic screening should become general practice.

THIOPURINE S-METHYLTRANSFERASE (TPMT)

6 mercaptopurine (6-MP) and 6-thioguanine are anticancer drugs most commonly used for the treatment of acute lymphatic leukemia (ALL). The metabolic pathway of these drugs is regulated through the thiopurine S-methyltransferase enzyme. This enzyme has a dual effect; it inactivates these drugs through a methylation step and has therefore significant impact on the toxicity of thiopurine drugs [59] and it causes conversion of 6-MP into methylthionosine 5-prime monophosphate, a metabolite that inhibits de novo purine synthesis and likely contributes to the cytotoxic effect [60,61] . In 1980 it was first published that TPMT activity differs in the population, probably because of genetic heterogeneity through multiple polymorphisms [62]. Decreased TPMT activity is inversely correlated with 6-MP concentrations in red blood cells and ALL blasts [63,64]. Therefore dose adjustments are necessary in patients with reduced TPMT activity treated with 6-MP to avoid serious side effects [65-67]. Population studies showed that three different phenotypes exist; normal TPMT activity, intermediate TPMT activity (9.6-11.1%) and absent TPMT activity (0.3-0.6%) [68]. To avoid side effects dosage reductions are necessary. Dosage reductions of 50% and 90% respectively are described without causing decrease in efficacy [67,69]. In 1995 a case was published regarding an 8-year-old girl who developed severe hematological toxicity with conventional oral doses of 6MP for treatment of ALL, caused by decreased TPMT activity because of a variation in the *TPMT* gene, referred to as TPMT*2 [60]. This variant is a pro>ala switch (A80P) due to a 238G>C polymorphism. Other variations include TPMT*3A (A154T and Y240C) [70,71]. Both these variations cause amino acid changes which showed enhanced degradation of TPMT protein and hence less catalytic activity [72]. The frequency of individuals with a *TPMT* variant seems to be 10% in Caucasians with the TPMT*3A mutation the most common (8%) [73,74] This was confirmed in other studies [75] although in Asian populations the TPMT*3C allele has been described as the most frequent variant and cause of decreased TPMT activity [76-78].

In total over 20 *TPMT* variant alleles have been described (TPMT*2-24) associated with decreased enzyme activity [79-81].

Over 95% of decreased TPMT activity can be explained by the most frequent variant alleles (TPMT*2 and TPMT*3A-D). Besides increased toxicity because of higher levels of the toxic metabolite 6TGN, increased efficacy was also described, probably due to the fact that the 6MP levels are higher in individuals with a variant allele. Recently cost effectiveness studies have been done regarding pretreatment screening for variant alleles of the *TPMT* gene. Based on these studies the net cost per prevented case of neutropenia equals to 5,300 euros. However, this may be overrated due to underreporting of adverse events [82-84].

Interestingly a recent study showed autophagy as an additional mechanism by which variant TPMT enzymes are degraded. This contributes to the increased toxicity of the 6MP therapy in these patients [85]. Further research has to be done with regard to cost effectiveness of pretreatment screening not only for 6-MP but also for azathioprine which is also metabolized through TPMT.

URIDINE DIPHOSPHATE GLUCURONOSYL TRANSFERASE (UGT)

UGT-1 is the principal enzyme in the glucuronidation pathway of bilirubine and many lipophilic therapeutics including the active metabolite of irinotecan (SN-38), a chemotherapeutic drug commonly used in advanced colorectal carcinoma. Variations in this gene are the cause of Gilbert's syndrome [86,87]. The most important variations linked with impaired glucuronidation are an insertion of a TA element in the promotor region of the *UGT1* gene (UGT1A1*28) and a 3263T>G polymorphism [88,89]. These variants in the *UGT1* gene impair the enzymes function *in vitro* and *in vivo* and thus cause probable effects on the irinotecan metabolism [90]. The UGT1 activity in subjects with a homozygous UGT1A1*28 allele is decreased by 70% [91]. In 2000 the first retrospective study was published describing 118 patients treated with irinotecan for advanced colorectal carcinoma, of which 26 developed serious side effects. Al patients were screened for the various *UGT1* genotypes. UGT1A1*28 (TA(7)TAA) was found in 15% (homozygous) and 31% (heterozygous) versus 3% and 11% respectively in the group without serious adverse effects which indicates that the UGT1A1*28 allele is a significant risk factor for serious adverse effects. Besides the UGT1A1*28 allele, three patients with the UGT1A1*27 allele were described and all three had serious side effects [92]. Multiple other studies confirmed this report that variations in the *UGT1* gene were associated with impaired irinotecan metabolism and hence increased toxicity especially grade 3-4 diarrhea and grade 3-4 neutropenia [93-95]. The prevalence of the UGT1A1*28 allele seems to highest in the African population (45%) and lowest in the Asian population (7-17%). In the Caucasians population prevalences of 22-39% are reported [96-98]. Screening could identify patients with an altered (delayed) SN-38 metabolism and at risk of developing grade 3-4 neutropenia and diarrhea [99]. Screening methods described in 2004 in a group of 75 patients treated with irinotecan showed that genotyping the UGT1A1*28 variation and several variations in the coding sequence prior to starting therapy differentiates between patients who tolerate therapy and those who experience more severe side effects [100]. Although recently it was shown that this does not necessarily lead to dose reductions [101-103]. If pretreatment genotyping is considered not only the UGT1A1*28 polymorphism should be investigated but also UGT1A1*6 and UGT1A1*7, although up to date those two polymorphisms have only been found in the Asian population [104]. In 2005 the FDA altered the package insert of irinotecan, mentioning *UGT1* variations, but up to date no specific recommendations on dosage adjustments can be made.

ATP BINDING CASSETTES (ABCB1, ABCC2 AND ABCG2)

The ATP binding cassettes (ABC) are drug transporters involved in the efflux of substances across the cell membrane. Variable ABC activity may be an important factor to interpatient variability in clearance of chemotherapeutic agents.

The *ABCB1* gene, also known as MDR1 (multi drug resistance) codes for P-glycoprotein. Over expression of this P-glycoprotein is seen in cells displaying resistance to specific anti-cancer therapy [105]. Two synonymous SNPs (C1236T in exon 12 and C3435T in exon 26) and a non-synonymous SNP (G2677T; Ala893Ser) in exon 2, frequently found in the European-American population (up to 62%), the African-American (13%) and the Asian population, appear to be linked in haplotype MDR1*2 [106]. The MDR1*2 haplotype is associated with enhanced drug transporter activity. *In vivo* functional relevance of this haplotype was tested using the P-glycoprotein substrate fexofenadine as a probe of the transporters activity. Analysis showed differences in fexofenadine levels very different between the genotypes with a plasma level-time curve being almost 40% greater in the wild type compared to the MDR1*2 homozygotes [107]. The MDR1*2 haplotype is associated with up regulation of P-glycoprotein and increased activity of the drug transporter [108] and with decreased clearance of the active metabolite of irinotecan (SN38) [109] and thus a lower maximal plasma concentration of glucuronidated SN38 [110]. The C1236T polymorphism is associated with a significantly increased irinotecan exposure and can possibly be used in pretreatment screening for optimizing dosage regimens [111].

Other drug transporters also play an important role in the pharmacokinetics of irinotecan. This includes ABCG2 (breast cancer resistance protein), in which a 421C>A change is of influence on irinotecan disposition [112] and ABCC2 (MRP2), of which the ABCC2*2 haplotype is associated with reduced side effects of irinotecan, especially diarrhea which was evaluated in a cohort of 167 patients receiving irinotecan. The frequency of diarrhea was 10% in the group with the ABCC2*2 haplotype versus 44% in the other patients [113]and haplotype ABCC2*1A is found predominantly in the Japanese population and is also associated with decreased function [114].

GLUTATHIONINE S-TRANSFERASE (GST)

Glutathione S-transferases (GSTs) are a family of enzymes that play an important role in detoxification. Based on their biochemical, immunologic, and structural properties, the GSTs are divided into several classes, (noted as Greek letters α, β and so on). Each class is encoded by a single gene or a gene family. Multiple substrates for these GSTs are known including multiple chemotherapeutic drugs such as carboplatin, cisplatin, cyclofosfamide, doxorubicin and etoposide. Polymorphisms in these genes causing decreased function would be expected to have an increasing effect on efficacy and toxicity of the above mentioned drugs.

GSTP1, which is the gene encoding for GST π, is overexpressed in tumor cells compared to normal tissue [115] and was one of the first genes of this family to be examined. A highly prevalent polymorphism in the *GSTP1* gene is a non-synonymous SNP in exon 5 (313A>G; ile105val), found in 27% of the Asian population and in 40-45% of the Caucasian and black population [116,117]. This polymorphism is associated with better outcome in therapy with oxaliplatin. In 107 patients with aCRC treated with 5FU/oxaliplatin genotypes and disease progression were determined. Patients with the variant genotype had a median survival of 24.9 months while wild type patients had a survival of 7.9 months, which was confirmed in other studies [117,118]. Other polymorphisms in the GST μ and θ gene include deletions GSTM1 and GSTT1, which do not seem to be associated with increased survival in aCRC but in ovarian cancer do cause delayed disease progression [119]. Retrospective analysis of 251 breast cancer patients showed that null genotypes for GSTM1 and GSTT1 caused a reduced hazard of death ratio of 0.59 and if both alleles were deleted it decreased to 0.28 [120]. The decreased function of GST is also correlated with increased toxicity as shown in 64 patients with

gastrointestinal cancer who received oxaliplatin based chemotherapy. Grade 3 neuropathy was more frequent in wild type patients with an odds ratio of 5.75 [121].

EXCISION REPAIR CROSS COMPLEMENTING GROUP 1 (ERCC1)

The *ERCC1* gene is part of the nucleotide excision pathway and is involved in gene specific repair caused by oxaliplatin and other platinum containing compounds [122]. High *in vivo* levels of ERCC1 mRNA are associated with worse outcome in patients with bladder cancer [123]. A silent SNP in exon 4 (496C>T; Asn118Asn) is associated with better survival in non-small cell lung carcinoma (NSCLC) patients treated with docetaxel and cisplatin due to a decreased ERCC1 expression and impaired repair activity. In a group of 62 advanced NSCLC patients the median survival was 10.3 months while the 17 patients with a wild type genotype all reached the 20 month follow up end point [124]. This same polymorphism was also analyzed in 91 patients with aCRC treated with 5-FU/oxaliplatin. The response rate was significantly higher in the patients with a homozygous variant genotype, compared to the heterozygotes and wild type (61.9%, 42.3% and 21.4% respectively) [125]. Very recently, genotypes of 126 aCRC patients of multiple DNA repair genes showed that the 497C>T SNP was associated overall survival in oxaliplatin/5FU treatment [126]. These and some other studies show that enhanced DNA repair cause decreased efficacy of platinum based chemotherapeutics and probably other treatment strategies based on DNA damage, but multiple studies with contradictory results have been published. These contradictory results can in part be explained because of existing linkage disequilibrium between the above mentioned variant and other enzymatic components of this pathway.

EXCISION REPAIR CROSS COMPLEMENTING GROUP 2 (ERCC2)

The *ERCC2* gene is also part of the nucleotide excision repair pathway and codes for the enzyme xeroderma pigmentosum group D (XPD). Multiple important SNPs have been described; two of them (965G>A; Asp321Asn and 2251A>C; Lys751Gln) are associated with reduced DNA repair capacity [127]. Allele frequencies are 0.32 and 0.44 in Caucasians and 0.16 and 0.09 in Blacks and Asians respectively [128]. In 73 patients with aCRC treated with 5FU and oxaliplatin the Lys751Gln polymorphism was associated with better response and longer overall survival. Twenty-four percent of the wild type patients responded versus 10% of the heterozygotes and homozygotes. The median survival was 17.4 months in the wild type patients vs. 12.8 and 3.3 months for the heterozygotes and homozygotes respectively [129,130]. These results could not be reproduced in a study in 109 NSCLC patients treated with cisplatin. No difference in response rate or OS was found [131]. A synonymous SNP (Arg156Arg) was associated with a higher response rate, 52% vs. 26.1% for the variant genotype in patients with advanced gastric cancer [132].

X-RAY CROSS COMPLEMENTING GROUP 1 (XRCC1)

The X-ray cross complementing group 1 is an important component of the base pair excision repair pathway. This pathway influences the efficacy of platinum agents. A SNP in the *XRCC1* gene (1301G>A; Arg399Gln) is associated with altered base excision repair capacity due to changed confirmation [133], increased cancer risk and worse response in patients with aCRC [134]. A Chinese study evaluated 62 patients with gastric cancer receiving oxaliplatin based chemotherapy. In this cohort the median survival of patients with the above mentioned SNP in the *XRCC1* gene was significantly longer if wild type was present [135]. In 61 patients with aCRC treated with 5FU/oxaliplatin 73% of the responders had a wild type genotype while none of the responders had a homozygous variation. Patients carrying at least one variant allele were at a 5.2 fold increased risk to fail 5FU/oxaliplatin chemotherapy [136]. In patients with NSCLC survival was shorter for individuals homozygote for the variant allele [128].

CYP2D6

Tamoxifen is a widely used agent in the treatment of breast cancer. Unfortunately only about half of the estrogen receptor positive breast cancer patients respond to tamoxifen. Pharmacogenetics focuses on the 30-100 times more active metabolites of tamoxifen. The active metabolites of tamoxifen are endoxifen and 4-hydroxy-tamoxifen and are formed by the CYP2D6 enzyme [137,138]. A highly prevalent variation is the CYP2D6*4 allele. A 1846G>A change which results in gene deletion and has a prevalence of 15-20% in Caucasians. This SNP results in absent CYP2D6 activity and probably in reduced tamoxifen efficacy [139-141]. Other important alleles resulting in lower CYP2D6 activity are CYP2D6*3 (2549A del), CYP2D6*5 (gene deletion) and CYP2D6*6 (1707T del). These are the most frequent alleles but over 80 other have been described [142].

The effect of the CYP2D6*4 allele on clinical outcome in breast cancer patients treated with tamoxifen has been evaluated in multiple studies. As expected because the CYP2D6*4 genotype represents a poor metabolizer phenotype, several studies showed higher relapse rates of patients with the CYP2D6*4 genotype treated with tamoxifen [143,144]. In 223 patients with breast cancer women with the CYP2D6*4/4 genotype had worse relapse free time and disease free survival but no difference in overall survival was observed. Hot flashes, one of the side effects of tamoxifen, caused by its active metabolites were not observed in the *4/4 genotype [139]. Contradictory results were published in 2005 describing a subset of patients with estrogen receptor positive breast cancer treated with tamoxifen who carried the CYP2D6*4 allele. This subgroup had better overall survival than those not treated with tamoxifen [140,145]. These contradictory results are possibly caused by selection bias and the concomitant use of CYP2D6 inhibitors such as selective serotonin reuptake inhibitors which are frequently used to treat hot flashes, one of the side effects of tamoxifen. This causes lower levels of endoxifen [146-149].

CONCLUSION

Pharmacogenetics plays an important role in individual drug response and can possibly become just as important in choice and dosage of drugs. Using pharmacogenetics may enable to predict the pharmacodynamics of multiple anticancer drugs such as irinotecan, 5-FU and oxaliplatin. Polymorphisms in important metabolic enzymes, DNA repair enzymes or drug transporters can cause changes in efficacy, toxicity or both. Despite the growing knowledge, pharmacogenetic testing before choosing a treatment regimen has not yet become common practice.

Before routinely pharmacogenetic testing can be implemented more studies are needed to validate results and to asses cost effectiveness. Genetic variation is not the only determinant of drug response and should always be considered in the light of other determinants such as alcohol use, environmental effects and co-medication. Preferably studies should be conducted in which multiple non-genetic determinants are evaluated in combination with genetic determinants. Prospective studies are needed to prove the evidence of pharmacogenetic testing.

Pharmacogenetics is a very promising field, giving us the tools to create tailor made treatment of cancer patients.

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COMPETING INTERESTS

The authors have declared that no competing interests exist.

ABBREVIATIONS

SNP	=	Single nucleotide polymorphism
DPD	=	Dihydropyrimidine dehydrogenase
5FU	=	5-Fluorouracil
TPMT	=	Thiopurine S-methyltransferase
6-MP	=	6-Mercaptopurine
GST	=	Glutathionine S-transferase
ABC	=	ATP binding cassette
TS	=	Thymidylate synthethase
TSER	=	Thymidylate synthethase enhancer region
MTHFR	=	Methylene tetrahydrofolate reductase
MTX	=	Methotrexate
aCRC	=	Advanced colorectal cancer
ALL	=	Acute lymphatic leukemia
UGT	=	Uridine diphosphate glucuronosyl transferase
MDR	=	Multi drug resistance
ERCC	=	Excision repair cross complementing group
NSCLC	=	Non-small cell lung carcinoma
XRCC	=	X-ray cross complementing group
OS	=	Overall survival

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