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Clinical Pharmacology: Pharmacogenetics: Opportunities for Patient-Tailored Anticancer Therapy

Part 2: Pharmacogenetic Variability in Drug Transport and Phase I Anticancer Drug Metabolism

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. List currently identified candidate genes involved in phase I metabolism that are potential pharmacogenetic markers in anticancer therapy.
2. Describe the general effect on standard treatment of allelic variants of the candidate genes and the implications for individualized treatment.

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ABSTRACT

Equivalent drug doses in anticancer chemotherapy may lead to wide interpatient variability in drug response reflected by differences in treatment response or in severity of adverse drug reactions. Differences in the pharmacokinetic (PK) and pharmacodynamic (PD) behavior of a drug contribute to variation in treatment outcome among patients. An important factor responsible for this variability is genetic polymorphism in genes that are involved in PK/PD processes, including drug transporters, phase I and II metabolizing enzymes, and

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drug targets, and other genes that interfere with drug response. In order to achieve personalized pharmacotherapy, drug dosing and treatment selection based on genotype might help to increase treatment efficacy while reducing unnecessary toxicity.

We present a series of four reviews about pharmacogenetic variability in anticancer drug treatment. This is the second review in the series and is focused on genetic variability in genes encoding drug transporters (*ABCB1* and *ABCG2*) and phase I drug-metabolizing enzymes (*CYP2B6*, *CYP2C8*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *DPYD*, *CDA* and *BLMH*) and their associations with anticancer drug treatment outcome. Based on the literature reviewed, opportunities for patient-tailored anticancer therapy are presented. *The Oncologist* 2011;16:820–834

Introduction to the Series

We present a series of four reviews about pharmacogenetic variability in anticancer phase I and II drug metabolism, drug transport, and pharmacodynamic drug effects. The first review focused on the molecular biological background and methodologies and technologies in pharmacogenetic research. This second part in the series deals with pharmacogenetic variability in drug transport and anticancer phase I drug metabolism, and emphasizes opportunities for patient-tailored pharmacotherapy based on the current knowledge in the field of pharmacogenetics in oncology. The level of evidence of the reviewed studies was graded according to the levels reported in Table 1.

Drug Transport by ATP-Binding Cassette Transporters

The ATP-binding cassette (ABC) transporters are a family of transmembrane proteins that use ATP-derived energy to actively transport a variety of substrates across cell membranes. Thereby, they are heavily involved in the absorption and disposition of many clinically used drugs, including anticancer drugs. Based on the sequence homology of ABC transporters, seven subfamilies (ABCA to ABCG) are distinguished, two of which—ABCB1 (P-glycoprotein [P-gp]) and ABCG2 (breast cancer resistance protein [BCRP])—are discussed.

Table 1. Levels of evidence

Level of evidence	Type of evidence
1	Evidence obtained from meta-analyses or randomized controlled trials
2	Evidence obtained from nonrandomized controlled trials
3	Evidence from cohort or case–control studies
4	Evidence from descriptive studies or case reports
5	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Adapted from http://www.cancer.gov.

P-gp (ABCB1)

P-gp (ABCB1) is expressed in the intestine, liver, kidney, brain, and placenta, with highly varying expression levels among individuals [1–3]. The substrate affinity of P-gp is broad, and many anticancer drugs are transported by P-gp, including etoposide, teniposide, doxorubicin, vinblastine, vincristine, daunorubicin, irinotecan, paclitaxel, and docetaxel [4].

The gene encoding P-gp is *ABCB1*, which contains various functional polymorphisms that range in allele frequency among various ethnicities [4–8]. A widely investigated single nucleotide polymorphism (SNP) in *ABCB1* is 3435C>T (Ile1145Ile; *ABCB1*6*), which is in strong linkage disequilibrium with another silent SNP, 1236C>T (Gly412Gly; *ABCB1*8*) and the triallelic variant 2677G>T/A (Ala893Ser/Thr) [7, 9]. The combination of these three SNPs (i.e., haplotype) is also designated as *P-gp*2* [7]. There is debate about the functional effect of 3435C>T. Some studies reported that this SNP affects mRNA stability and results in lower mRNA expression and thereby lower protein levels [5, 10–12], whereas others reported higher expression levels and enhanced activity of P-gp [7, 13, 14].

With regard to *ABCB1* polymorphism and irinotecan treatment outcome, the homozygous *P-gp*2* variant haplotype was shown to be associated with lower renal clearance of irinotecan and its active metabolite SN-38 [8] and showed a lower area under the plasma concentration–time curve (AUC) of SN-38 glucuronide in 2677TT/3435TT individuals than in wild-type patients [15]. Furthermore, 3435TT was significantly associated with grade 3 diarrhea in 107 patients with non-small cell lung cancer (NSCLC) given irinotecan and cisplatin [15].

Besides irinotecan, taxanes are also substrates for P-gp. In 62 patients with NSCLC treated with docetaxel and cisplatin, 3435TT allele carriers also more frequently (33%) experienced grade ≥2 diarrhea than heterozygous (4%) and wild-type (11%) patients [16]. The pharmacogenetic anal-

ysis from the Scottish Randomised Trial in Ovarian Cancer 1 (SCOTROC1) trial, however, did not demonstrate a relationship between genetic polymorphism in *ABCB1* and toxicity or treatment outcome in 914 patients with ovarian cancer who had received either docetaxel or paclitaxel combined with carboplatin [17].

Polymorphism in *ABCB1* has also been investigated in patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). In the treatment of childhood ALL according to Berlin-Frankfurt-Münster protocols, a matched case–control study in white patients showed a lower rate of central nervous system relapse for 3435C>T variant allele carriers than for wild-type patients [18]. Similarly, in 405 white AML patients receiving etoposide, mitoxantrone, or daunorubicin, a significantly shorter overall survival duration and higher probability of relapse were observed in 3435C>T wild-type patients than in hetero- or homozygous patients [14]. In contrast, a smaller study in Asian patients with AML reported a higher response rate and 3-year event-free survival rate for patients with the wild-type genotype [19].

In conclusion, polymorphisms in *ABCB1* have been shown to possibly affect treatment outcome with chemotherapy, especially irinotecan. However, some of the observed associations with clinical outcome for other anticancer drugs were not always consistent. This might result from differences in ethnicity, population size, and type of treatment regimen in the various populations that have been studied. For this reason, genetic polymorphism in *ABCB1* is currently not suitable yet for patient-tailored anticancer therapy. The study results obtained, however, should encourage the conduction of additional pharmacogenetic studies. Given the highly polymorphic character of *ABCB1* in differing among ethnicities, a haplotype analysis that includes additional genetic variants in *ABCB1* besides the above-mentioned SNPs might help to better predict treatment outcome with P-gp (anticancer) drug substrates.

BCRP (ABCG2)

One of the most important ABC transporters of the ABCG family is ABCG2, also known as BCRP. ABCG2 is highly expressed in the gastrointestinal tract, liver, kidney, brain, heart, and placenta [20]. Anticancer drugs that are known substrates for ABCG2 include, among others, mitoxantrone, methotrexate, SN-38, topotecan, imatinib, and gefitinib, but as for P-gp, substrate affinity of ABCG2 is very broad and it transports many other drugs as well [21].

Multiple polymorphisms in *ABCG2* have been identified that may modulate the functional activity of ABCG2 [22–24]. Particularly relevant SNPs in *ABCG2* appear to be 421C>A (Gln141Lys) and the nonsense SNP 376C>T

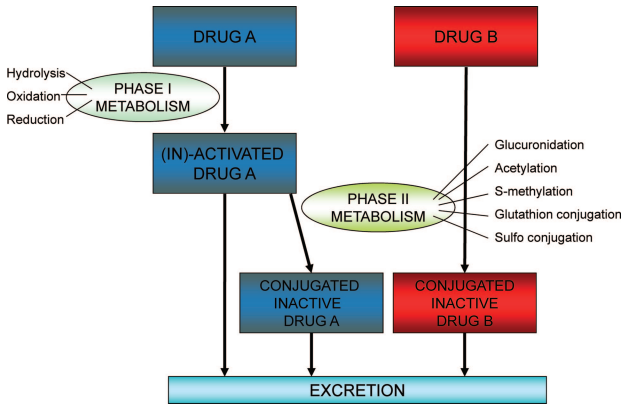

Figure 1. Phase I and phase II drug metabolism. Phase I drug-metabolizing enzymes mediate drug oxidation, reduction, or hydrolysis reactions, by which drugs may be activated or inactivated. This may be followed by phase II reactions to further increase solubility and thereby facilitate excretion from the body. Preceding phase I reactions are not a prerequisite.

(Gln126stop). Until now, the nonsense SNP 376C>T has only been identified in Japanese individuals [25–27]. The allele frequency of 421C>A is also higher in Japanese than in white subjects (30% versus 10%). 421C>A has been reported to affect the translation efficiency of ABCG2 and to result in lower ABCG2 (placental) protein expression [25, 26]. Indeed, additional in vitro research showed greater drug accumulation and less drug resistance for patients with the 421C>A polymorphism [27–29]. However, in white [30] and Asian [31] patients treated with irinotecan, 421C>A did not significantly affect the pharmacokinetics of irinotecan or its metabolites, although one of two homozygous mutated allele carriers showed extensive accumulation of SN-38 and SN-38 glucuronide [30].

The clinical effect of 421C>A has also been investigated in patients treated with the tyrosine kinase inhibitors imatinib and gefitinib. One study in 82 patients with gastrointestinal tumors treated with imatinib showed no significant pharmacokinetic effect [32], whereas another study in 67 patients did show a 22% lower clearance of imatinib in 421C>A heterozygous patients [33]. Likewise, in gefitinib-treated patients, 421C>A was associated with a higher accumulation of gefitinib [34] and with grade 1 or 2 diarrhea [35]. However, in that study, the majority of heterozygous patients did not develop any diarrhea, and the single homozygous patient had no noticeable toxicity. Moreover, this association was not confirmed in a similar, but Asian, study population [36].

Overall, despite preclinical evidence that 421C>A functionally impairs *ABCG2* activity, a significant association with toxicity was only observed in white patients treated with gefitinib. With other anticancer drugs, the clinical relevance of 421C>A in *ABCG2* appears to be thus far

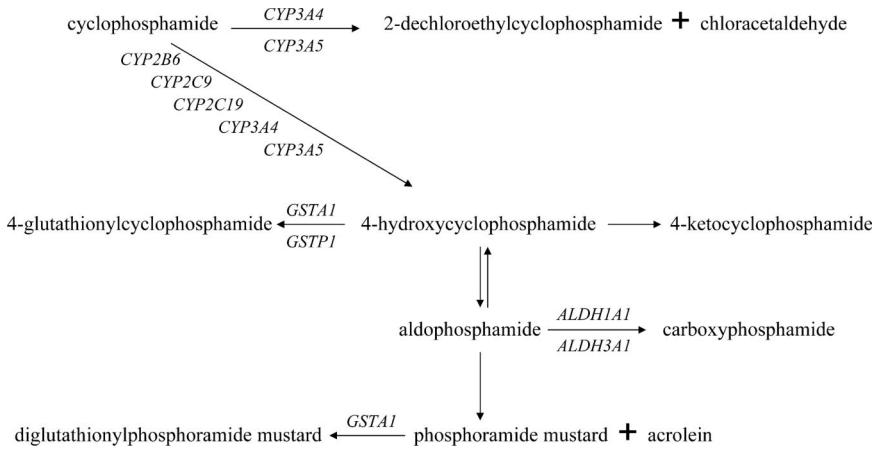

Figure 2. Biotransformation of cyclophosphamide. The biotransformation of cyclophosphamide involves multiple drug-metabolizing enzymes that are subject to genetic polymorphism, which in turn may affect the disposition of cyclophosphamide and its metabolites. However, because of the fact that its metabolism is regulated by several phase I and phase II enzymes, a genetic defect in a single gene might go unnoticed because other metabolic enzymes may serve as escape metabolic routes.

of limited importance. Additional trials among various geographic populations are awaited to evaluate the exact clinical relevance of polymorphisms and haplotypes of *ABCG2*, especially in patients treated with gefitinib.

Phase I Anticancer Drug Metabolism

Phase I drug-metabolizing enzymes mediate drug oxidation, reduction, and hydrolysis reactions, by which drugs may be activated or inactivated (Fig. 1). In addition, phase I metabolism generally increases the polarity of a drug, and thereby facilitates excretion from the body. Phase I reactions may be followed by phase II reactions to further increase solubility; however, preceding phase I reactions are not a prerequisite. Typical phase II reactions are glucuronidation, acetylation, S-methylation, and glutathione- or sulfo-conjugation of drugs. Genetic polymorphism in phase I metabolism may modulate the pharmacokinetics and disposition of drugs and thereby affect the toxicity and efficacy of treatment, and is discussed in the following sections.

Oxidizing Phase I Metabolizing Enzymes

The cytochrome P450 (CYP450) system is involved in oxidation reactions. The CYP450 genes particularly involved in anticancer therapy are *CYP2B6*, *CYP2C8*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, and *CYP3A5*.

CYP2B6

Cyclophosphamide and ifosfamide undergo extensive metabolism by CYP450. CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 are involved in the activation as well as inactivation of cyclophosphamide and ifosfamide (Fig. 2). CYP2B6 activates cyclophosphamide to 4-hydroxycyclophosphamide, whereas CYP2B6 inactivates the CYP3A4-derived hydroxylated active form of ifosfamide, 4-hydroxy-ifosfamide [37, 38]. In addition, thiotepa is a minor substrate for, but acts also as an inhibitor of, CYP2B6 [39, 40].

Multiple functional polymorphisms in *CYP2B6* exist [41–45]. A commonly occurring genetic variant is *CYP2B6*6*, which is compromised of two SNPs, 516G>T (Q172H) and 785A>G (K262R). In vitro investigations on the functional effect of *CYP2B6*6* showed inconsistent findings—on the one hand greater enzyme activities were reported [46, 47], but on the other hand, lower enzyme activities was reported as well [41, 48, 49]. This inconsistency in study results is possibly an effect of other (still unknown) mutations linked to these SNPs, creating various haplotypes with different enzyme activities.

The relationship between *CYP2B6*6* and the pharmacokinetics of cyclophosphamide was investigated in several studies. Greater CYP2B6-mediated activation of cyclophosphamide to 4-hydroxycyclophosphamide for 516G>T variant allele carriers has been observed [50, 51], as well as a higher clearance and shorter half-life of cyclophosphamide for *CYP2B6*6* homozygous mutant patients than for wild-type patients [52]. These findings, however, could not be confirmed by others in a cohort of 124 patients with solid tumors [53]. Despite the fact that a few studies reported a significant pharmacokinetic effect of cyclophosphamide by *CYP2B6*6*, no significant associations with adverse events [54, 55], disease-free survival or overall survival [56] were observed in cancer patients treated with cyclophosphamide combination chemotherapy. Therefore, the clinical relevance of *CYP2B6*6* appears to be limited in cyclophosphamide treatment. However, because cyclophosphamide is a

substrate for several subfamilies of the CYP450 system (Fig. 2), an effect of a genetic defect in a single gene might go unnoticed because other metabolic enzymes may serve as escape metabolic routes. A combined analysis that would include multiple genes involved in the pharmacological pathway could possibly help to clarify the broad range in drug response for compounds that are substrates for multiple metabolizing enzymes.

CYP2C8

CYP2C8 is an important inactivating enzyme of the taxane paclitaxel [57]. Several polymorphisms have been identified, such as *CYP2C8*2* (805A>T, Ile269Phe), *CYP2C8*3* (416G>A, Arg139Lys and 1196A>G, Lys399Arg), and *CYP2C8*4* (792C>G, Ile264Met) [58–60].

Although in vitro results showed a lower metabolism of paclitaxel by up to 15% for *CYP2C8*3* [59, 60] carriers, no effect of *CYP2C8* genetic polymorphism on the clearance of unbound paclitaxel was observed in patients treated with paclitaxel [61, 62]. Moreover, a study in 914 patients receiving either docetaxel or paclitaxel combined with carboplatin showed that *CYP2C8* polymorphisms were not associated with toxicity or efficacy of treatment [17].

In conclusion, polymorphisms in *CYP2C8* have thus far not been demonstrated to affect paclitaxel treatment outcome and are therefore not yet suitable for patient-tailored therapy with paclitaxel.

CYP2C9

CYP2C9 metabolizes, among others, the anticancer agents cyclophosphamide, etoposide, ifosfamide, and tamoxifen, and the experimental anticancer drug indisulam (E7070). *CYP2C9* harbors many allelic variants, of which at least two SNPs, *CYP2C9*2* (430C>T, Arg144Cys) and *CYP2C9*3* (1075A>C, Ile359Leu), are known to decrease CYP2C9 enzyme activity [63–65]. Despite these significant in vitro observations, four recent studies in patients with cancer did not demonstrate a significant effect of *CYP2C9* polymorphism on the pharmacokinetics of cyclophosphamide [51, 53, 66] or tamoxifen [67]. In addition, no relationship between *CYP2C9* genotype and survival was observed in patients with breast cancer treated with tamoxifen [68, 69]. However, a study in 67 patients treated with the experimental anticancer drug indisulam revealed a lower elimination rate of 27% and a significantly higher risk for severe neutropenia in heterozygous *CYP2C9*3* carriers [70].

To conclude, allelic variants of *CYP2C9* do not appear to affect treatment outcome with cyclophosphamide or tamoxifen, but possibly do affect indisulam treatment outcome. This suggests that a substrate-specific pharmacogenetic effect might be present. Further studies are awaited to draw definite conclusions.

CYP2C19

Besides cyclophosphamide, ifosfamide, and tamoxifen, thalidomide is also a substrate for CYP2C19 and is activated by CYP2C19-mediated hydroxylation [71]. There are two SNPs in *CYP2C19* that lead to the poor metabolizer phenotype. These are 681G>A (*CYP2C19*2*), which results in a splicing defect, and 636G>A (*CYP2C19*3*), which introduces a premature stop codon. Both allelic variants have no residual activity left, and approximately 99% of the CYP2C19 poor metabolizer phenotype is explained by these two SNPs [72]. Thus far, only one study investigated *CYP2C19* polymorphism in relationship to response to treatment with thalidomide. In 92 patients with multiple myeloma treated with thalidomide, extensive metabolizers experienced a significantly higher response rate (63%) than *CYP2C19*2*-induced poor metabolizers (33%) [73]. Further studies are awaited.

With regard to cyclophosphamide and CYP2C19 activity, poor metabolizers are theoretically expected to have a poor response and low toxicity probability upon therapy with cyclophosphamide, because its CYP2C19-mediated activation is eliminated. Indeed, one study in 60 white cancer patients showed a *CYP2C19*2*-dependent lower clearance of cyclophosphamide at doses $<1{,}000$ mg/m^2 [66]; however, no effect on the pharmacokinetics of cyclophosphamide for *CYP2C19*2* and *CYP2C19*3* was observed in two larger trials conducted in Japanese [52] and European [53] patients, and no relationship with clinical outcome was reported [54].

In summary, *CYP2C19*2* and *CYP2C19*3* result in a CYP2C19 poor metabolizer phenotype. Their clinical relevance appears limited in cyclophosphamide treatment, but not in thalidomide treatment. Additional investigation is required before definitive conclusions can be drawn.

CYP2D6

The enzyme CYP2D6 is particularly important in the treatment of breast cancer patients with tamoxifen. CYP2D6 oxidizes tamoxifen to 4-hydroxytamoxifen, the antiestrogen potency of which is 50 times higher than that of tamoxifen itself [74]. Furthermore, the conversion of N-desmethyltamoxifen to endoxifen is primarily mediated by CYP2D6. The potency of endoxifen is also higher than that of tamoxifen, and comparable with the binding affinity and suppression of estradiol-stimulated cell proliferation of 4-hydroxy-tamoxifen [75]. Thus, theoretically, CYP2D6 poor metabolizers are expected to benefit less from therapy with tamoxifen because of a lower rate of formation of the active substrate.

CYP2D6 is highly polymorphic. Multiple allelic variants have been described, of which, some result in lower, or even absent, enzyme activity [76]. Furthermore, copy number variants of *CYP2D6* exist with either two, three, four, five, or 13 gene copies, which consequently lead to the ultrarapid metabolizer phenotype. The most abundant and functionally important SNPs are *CYP2D6*4* (1846G>A), resulting in a splicing defect, *CYP2D6*5*, characterized by complete *CYP2D6* gene deletion, *CYP2D6*6* (1707delT), resulting in a frameshift at amino acid 118, and *CYP2D6*10* (100C>T), which markedly reduces enzyme activity [77–80].

A few studies in patients with breast cancer treated with tamoxifen showed that plasma levels of endoxifen are lower in CYP2D6 poor metabolizers than in extensive metabolizers. Besides genetic variants, potent inhibitors of CYP2D6, such as paroxetine or fluoxetine, also led to lower levels of endoxifen [67, 81, 82]. Moreover, several retrospective clinical trials demonstrated a shorter time to recurrence or shorter survival time for women with the poor metabolizer phenotype [68, 83–89]; however, this could not be confirmed in other retrospective studies [90–93]. Prospective evaluations are currently lacking. Plausible explanations for inconsistent findings among the various studies are, among other things, the retrospective study design; incomplete *CYP2D6* genotyping; a lack of stratification for coadministration of no, weak, or strong CYP2D6 inhibitors; the inability to account for drug compliance; and differences in patient selection, duration of treatment, and dose of tamoxifen. In addition, some studies analyzed tumor DNA whereas others used germline DNA. Notwithstanding, the concordance rate between tumor and germline DNA for *CYP2D6* appears to be 100% [88, 89].

In conclusion, poor metabolizers as a result of genetic defects appear to benefit less from treatment with tamoxifen, though inconsistent findings have been reported. Treatment with tamoxifen is also negatively affected by simultaneous use of potent CYP2D6 inhibitors. Well-defined prospective trials are needed, with complete *CYP2D6* genotyping, that are supported by pharmacokinetic analyses. These trials should additionally differentiate the strengths of coadministered inhibitors of CYP2D6 for tamoxifen [94], to establish the exact role of *CYP2D6* polymorphism in tamoxifen treatment.

CYP3A4 and CYP3A5

The CYP3A subfamily is highly expressed in the liver and small intestine, and metabolizes >50% of clinically used drugs, including several anticancer drugs such as etoposide, teniposide, docetaxel, paclitaxel, irinotecan, toremifene, vinblastine, vincristine, vinorelbine, cyclophosphamide, ifosfamide, thiotepa, gefitinib, and erlotinib [95–97]. Enzyme activity of CYP3A ranges widely among subjects, and besides genetic polymorphism, its activity is largely affected by nongenetic factors such as age, endogenous hormone levels, transcription factor activity, health status, and environmental stimuli [98, 99].

To date, approximately 40 allelic variants have been described for *CYP3A4*, of which some reduce its activity, such as *CYP3A4*6*, *CYP3A4*8*, and *CYP3A4*17* [100]. In addition, a common SNP, −392A>G (*CYP3A4*1B*, *CYP3A4-V*), appears to influence CYP3A4 expression as a result of altered nuclear protein binding affinity to the polymorphic element [101]. In *CYP3A5*, the main SNP of interest is 6986G>A (*CYP3A5**3), which leads to a splicing defect that results in severely lower enzyme activity. Most white people are homozygous for this genetic defect and consequently live with a CYP3A5 deficiency [102, 103].

Docetaxel is metabolized by CYP3A4 and CYP3A5 up to 93% [104]. Therefore, variability in CYP3A enzyme activity is hypothesized to affect the metabolism of docetaxel and hence its toxicity and possibly efficacy.

Although two studies showed a higher clearance of docetaxel for the *CYP3A4*1B* variant allele in patients treated with docetaxel [105, 106], this was not observed by others [107]. For paclitaxel, a taxane as well, no associations were observed with *CYP3A* genotype and treatment outcome [17, 61, 108].

In treatment with cyclophosphamide-based chemotherapy, controversial results have been reported with regard to *CYP3A4*1B* and treatment outcome. Two studies reported a shorter (disease-free) survival time for variant allele carriers [56, 109], whereas this could not be confirmed by others [53, 54].

With regard to other anticancer drugs, in one study in 42 patients with advanced NSCLC treated with irinotecan and carboplatin, *CYP3A4*1B* was not associated with toxicity [110]; however, a nonsignificant association with skin rash grade ≥2 for *CYP3A4*1B* and *CYP3A5*3* was observed in a prospective study in 80 cancer patients receiving erlotinib monotherapy [111].

Obviously, further research is warranted. It can be concluded though that genetic variability in *CYP3A* alone is insufficient to explain its widely ranging enzyme activity [112]. Possibly, CYP3A4 phenotypic approaches, although often more costly, might serve as better predictors of treatment outcome.

Additional Oxidizing Phase I Metabolizing Enzymes

Other typical phase I oxidation enzymes are monoamine oxidase (MAO), cyclooxygenase (COX), alcohol dehydro-

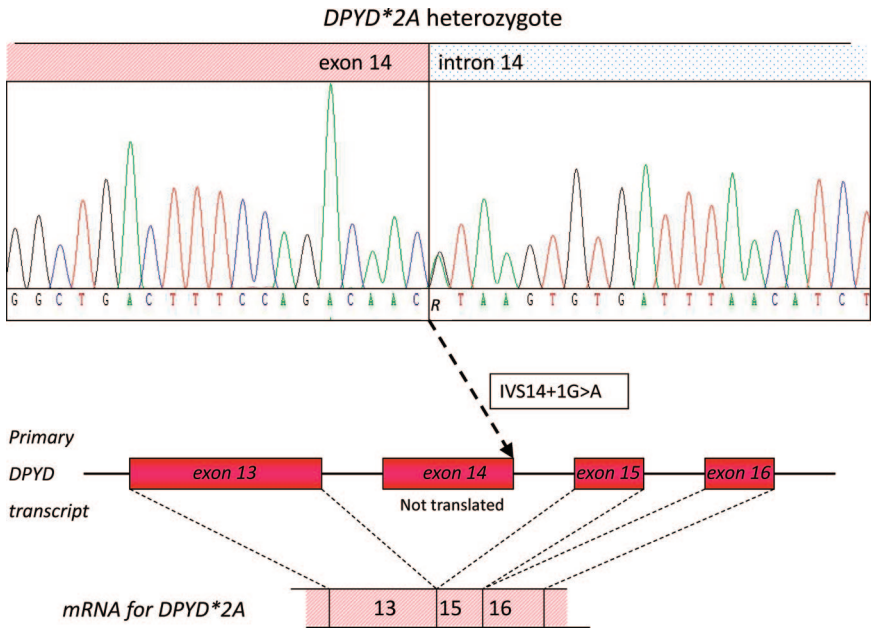

Figure 3. Functional effect of *DPYD*2A* (IVS14+1G>A). The polymorphism *DPYD* IVS14+1G>A is a single nucleotide polymorphism that is located at the first position of intron 14. This polymorphism results in complete skipping of exon 14 during the process of pre-mRNA splicing, which thereby creates a truncated protein with absent dihydropyrimidine dehydrogenase activity.

genase (ADH), and aldehyde dehydrogenase (ALDH). The enzymes MAO and COX are not involved in the biotransformation of anticancer drugs, but there is an increasing interest in COX inhibitors in the prevention and treatment of cancer [113–115]. In addition, polymorphisms in *ADH* have been associated with a higher risk for developing cancer, especially in high alcohol consumers [116, 117].

ALDH oxidizes acetaldehyde (a metabolite of alcohol) and also oxidizes cyclophosphamide and ifosfamide. A study in 124 white patients treated with high-dose chemotherapy showed that two polymorphisms in *ALDH* (*ALDH1A1*2* and *ALDH3A1*2*) did not affect the pharmacokinetics of cyclophosphamide; however, a significantly higher risk for liver toxicity and hemorrhagic cystitis was observed [53, 54]. Notwithstanding, this association was not observed in Asian patients [55]. Besides differences in ethnicity, this discrepancy might also be a result of differences in patient selection or treatment regimen, and therefore additional studies are warranted before definitive conclusions can be drawn.

Reducing, Hydrolyzing, and Deaminating Phase I Metabolizing Enzymes

Dihydropyrimidine dehydrogenase (DPD) is a phase I reduction enzyme and a key detoxification enzyme of fluoropyrimidines. Other inactivating enzymes of anticancer drugs are cytidine deaminase (CDA) for gemcitabine and cytarabine and bleomycin hydrolase (BLMH) for bleomycin.

DPD

The primary step in the 5-fluorouracil (5-FU) degradation pathway is mediated by DPD [118, 119]. Furthermore, DPD also inactivates the 5-FU oral prodrugs capecitabine and tegafur. About 3%–5% of the population has a (partial) DPD deficiency, which increases the risk for 5-FU–induced severe toxicity in these individuals [120]. Currently, >50 polymorphisms in *DPYD*, the gene encoding DPD, have been identified [121]. The most predominant polymorphism associated with DPD deficiency is IVS14+1G>A (*DPYD*2A*). This SNP results in complete skipping of exon 14 during pre-mRNA splicing, and consequently creates a truncated protein that has no residual activity left (Fig. 3) [122–124]. Another polymorphism in *DPYD* that negatively affects DPD enzyme activity, mainly by interfering with cofactor binding, is 2846A>T (Asp949Val) [125–127].

Table 2 provides an overview of various clinical studies that investigated the effect of *DPYD*2A* and 2846A>T on treatment outcome with fluoropyrimidines. Multiple case reports have been described, reporting on patients with severe, even lethal, toxicity following 5-FU–based chemotherapy who proved to be polymorphic for *DPYD*2A* [123, 128–136]. In addition, others showed that *DPYD*2A* was

Table 2. Clinical pharmacogenetics of dihydropyrimidine dehydrogenase (*DPYD*)

Gene	Location	SNP variant	Amino acid change	Effect on protein	Allele frequency in whites (*n* of patients)	Type of cancer/ affected drug	Relation with toxicity	Relation with efficacy	Patient cohort	Level of evidence[a]	Reference
DPYD	Intron 14	IVS14+1G>A (*DPYD*2A*)	Deletion of 55 amino acids	Exon 14 skipping; truncated, nonfunctional protein [122, 159]	1.1% (487)	Advanced carcinomas/ 5-FU	60% of HET grade 3 or 4 toxicity (2 HET without severe toxicity received initially reduced 5-FU doses)	NA	Prospective	2	[138]
					1% (683)	CRC, GI, UP, breast/5-FU	46% of HET grade 3 or 4 toxicity	NA	Prospective	2	[141]
					0.6% (252)	CRC/5-FU	2 of 3 HET grade 3 or 4 toxicity, third patient safe on a 50% dose reduction in cycle 2	NA	Prospective	2	[120]
					0.5% (105)	Breast/ capecitabine	Single HET deceased	NA	Prospective	2	[140]
					0.6% (568)	CRC/ capecitabine	71% of HET grade 3 or 4 diarrhea, 100% grade 3 or 4 overall toxicity	No association	Retrospective	3	[142]
					0.5% (851); 14% in toxicity grade 3 or 4 cohort ($n = 25$)	White controls and cancer patient cohort with severe toxicity upon 5-FU treatment	24% of the 25 patients with severe toxicity attributable to *DPYD*2A*	NA	Retrospective	3	[137]
					-	Various types of cancer/5-FU or capecitabine	Severe toxicity associated with *DPYD*2A*	NA	Case reports	4	[123, 128–136]
DPYD	Exon 22	2846A>T	Asp949Val	Reduced enzyme activity[160]	1% (487)	Advanced carcinomas/5-FU	60% of HET grade 3 or 4 toxicity	NA	Prospective	2	[138]
					0.4% (656)	CRC, GI, UP, breast/5-FU	60% of HET grade 3 or 4 toxicity	NA	Prospective	2	[141]
					1.6% (252)	CRC/5-FU	75% of HET grade 3 or 4 toxicity	NA	Prospective	2	[120]

[a]Adapted from http://www.cancer.gov. See also Table 1.
Abbreviations: 5-FU, 5-fluorouracil; CRC, colorectal cancer; GI, gastrointestinal; HET, heterozygous mutant patients; NA, not analyzed; SNP, single nucleotide polymorphism; UP, unknown primary.

present in approximately 25% of patients presenting with severe toxicity following treatment with fluoropyrimidines [135, 137]. Moreover, several retro- and prospective population trials consisting of hundreds of patients per trial showed that, on average, >70% of all patients polymorphic for *DPYD*2A* developed severe, including lethal, toxicity following treatment with 5-FU or capecitabine [120, 138–143].

Similarly, the polymorphism 2846A>T in *DPYD* is also associated with severe toxicity to fluoropyrimidines, as demonstrated by multiple cohort studies [120, 138, 141, 142]. Though *DPYD* 2846A>T is slightly less predictive of severe toxicity than *DPYD*2A*, the majority of patients polymorphic for 2846A>T still develop severe toxicity following 5-FU–based treatment. Moreover, the simultaneous presence of both variant alleles (*DPYD*2A* and 2846A>T) in an individual, a rarely (<1 in 1,000 patients) occurring phenomenon, however, was shown to be lethal in multiple cases shortly after the start of fluoropyrimidine treatment [120, 129].

In conclusion, these data demonstrate the clinical significance of *DPYD*2A* and 2846A>T in fluoropyrimidine treatment, suggesting prospective screening prior to the start of therapy to avoid severe toxicity in patients with the variant genotype. Possibly, initial fluoropyrimidine dose reductions of 50% in *DPYD*2A* and 25% in 2846A>T heterozygous patients followed by further dose titration upon clinical tolerability could be a safe and effective strategy [142] that needs to be assessed in additional, prospective clinical trials.

CDA

The enzyme CDA inactivates gemcitabine to 2′,2′-difluorodeoxyuridine and inactivates cytarabine as well. Two nonsynonymous SNPs in *CDA*, 79A>C (Lys27Gln) and 208G>A (Ala70Thr) were shown to reduce CDA enzyme activity [144–147]. The 208G>A SNP, however, is likely to occur only in Japanese and Korean subjects, and has not yet been detected in African, white, and Chinese Americans [148]. A few studies evaluated the predictive value of these SNPs in gemcitabine treatment (Table 3). A study in 256 Japanese patients treated with gemcitabine-based chemotherapy showed a higher AUC and maximum concentration of gemcitabine in patients heterozygous polymorphic for 208G>A. In addition, 208G>A was associated with grade ≥3 neutropenia in patients who were coadministered 5-FU

Table 3. Clinical pharmacogenetics of cytidine deaminase (*CDA*) and bleomycin hydrolase (*BLMH*)

Gene	Location	SNP variant	Amino acid change	Effect on protein	Allele frequency in whites (*n* of patients)	Type of cancer/ affected drug	Relation with toxicity	Relation with efficacy	Patient cohort	Level of evidence[a]	Reference
CDA	Exon 1	79A>C	Lys27Gln	Reduced enzyme activity [144, 145]	36% (65)	NSCLC/ gemcitabine	WT associated with grade 3 or 4 neutropenia and thrombocytopenia	WT longer TTP and OS	Prospective	2	[146]
					–	Metastatic vesical cancer/ gemcitabine	Heterozygous carrier severe toxicity leading to death	–	Case report	4	[152]
CDA	Exon 2	208G>A	Ala70Thr	Reduced enzyme activity [147, 149]	3.7% (256)	Carcinoma/ gemcitabine	Variant allele higher risk for grade 3 or 4 neutropenia with combination chemotherapy	NA	Prospective	2	[149]
					–	Pancreas carcinoma/ gemcitabine	Severe toxicity in HOM	–	Case report	4	[150]
					–	Pancreas carcinoma/ gemcitabine	Severe toxicity in HOM		Retrospective	4	[151]
BLMH	Exon 11	1450A>G	Ile443Val	Might influence enzyme activity [154]	32% (304)	Testicular germ cell cancer/ bleomycin	NA	HOM shorter OS and PFS	Retrospective	3	[158]

[a]Adapted from http://www.cancer.gov. See also Table 1.
Abbreviations: HOM, homozygous mutant patients; NA, not analyzed; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; SNP, single nucleotide polymorphism; TTP, time to progression; WT, wild-type patients.

and a platinum analog [149]. Furthermore, homozygosity for this SNP in Japanese patients has been associated with severe toxicity to gemcitabine [150, 151].

For 79A>C, one case report of a patient with lethal toxicity following treatment with gemcitabine was described, who proved to be heterozygous polymorphic for 79A>C but wild-type for 208G>A. Additional phenotyping in that patient showed a 75% lower CDA enzyme activity than in nontoxic controls [152]. However, it appears unlikely that 79A>C alone caused CDA deficiency in that patient because no effect on the pharmacokinetics of gemcitabine for 79A>C has been observed in Japanese [149] and white [153] patients. Moreover, a study in 65 chemotherapy-naïve NSCLC patients treated with gemcitabine and cisplatin showed that wild-type 79A>C patients more frequently experienced grade ≥3 neutropenia and thrombocytopenia and had a longer time to progression and overall survival time as well [146].

In summary, inconsistent findings have been reported for 79A>C in *CDA*, showing positive and negative associations with clinical outcome with gemcitabine. This might be partly a result of differences in patient selection, treatment regimen, and ethnicity, but as yet undetected polymorphisms might also possibly play a role. However, for *CDA* 208G>A, clear associations with severe toxicity from gemcitabine have been shown in Japanese patients. Caution and possibly initial dose reductions of gemcitabine for at least homozygous 208G>A carriers appear indicated. *CDA* 208G>A has the potential to become a predictive marker in gemcitabine treatment in Japanese patients, and this requires additional studies for independent confirmation.

BLMH

BLMH is the primary enzyme in the inactivation of bleomycin. The enzymatic activity of BLMH is, among other things, regulated by its C-terminal region [154–156]. A SNP that is located in this C-terminal region, 1450A>G, was shown in vitro to affect bleomycin-induced chromatid breaks per cell [157]. Moreover, a retrospective study in patients with testicular germ cell cancer treated with bleomycin showed shorter progression-free and overall survival times for homozygous 1450A>G variant allele carriers [158]. To determine whether this SNP is of clinical relevance, further (pre-)clinical studies on the functional effect of *BLMH* 1450A>G and on its effect on the clinical pharmacokinetics, toxicity, and efficacy of bleomycin are required.

Conclusion: Implications for Clinical Practice—Opportunities for Patient-Tailored Anticancer Therapy

Based on the literature reviewed, genetic polymorphisms in at least four candidate genes involved in phase I metabolism could potentially serve as pharmacogenetic markers in anticancer therapy to enable more safe, and possibly more effective, anticancer pharmacotherapy. These are *DPYD*2A* and

Table 4. Pharmacogenetics: Opportunities for patient-tailored anticancer therapy

Drug	Allelic variant	General effect observed in standard treatment	Highest level of evidence	Pharmacogenetic-based drug dose or treatment suggestions for future clinical trials
5-Fluorouracil/capecitabine	*DPYD*2A*	Higher risk for severe toxicity in variant allele carriers	2	50% dose reduction in heterozygous mutant patients, with further dose titration
5-Fluorouracil/capecitabine	2846A>T in *DPYD*	Higher risk for severe toxicity in variant allele carriers	2	25% dose reduction in heterozygous mutant patients, with further dose titration
Tamoxifen	*CYP2D6* genetic variants	Less clinical benefit in CYP2D6 poor metabolizers	3	Prospective validation of pharmacogenetic effect; possible dose or treatment adjustments in poor metabolizers
Gemcitabine	208G>A in *CDA*	High risk for severe toxicity in homozygous mutant patients	2	If data can be prospectively confirmed, dose reductions may need to be applied to prevent severe toxicity
Bleomycin	1450A>G in *BLMH*	Less clinical benefit in homozygous mutant patients	3	Prospective validation of pharmacogenetic effect Possibly treatment adjustment in homozygous mutant patients

2846A>T in *DPYD* in fluoropyrimidine treatment, *CYP2D6* polymorphism in breast cancer patients receiving tamoxifen, *CDA* 208G>A (which, however, appears to only occur in Asians) in gemcitabine treatment, and possibly 1450A>G in *BLMH* in patients treated with bleomycin (Table 4).

As determined in several studies, *DPYD*2A* and 2846A>T in *DPYD* consistently showed significant relationships with severe, possibly lethal, toxicity following treatment with standard-dose fluoropyrimidines, with a level of evidence of 2. Initial dose reductions ≥50% in *DPYD*2A* and ≥25% in 2846A>T heterozygous polymorphic patients, both followed by further dose titration upon clinical tolerability, are recommended.

Despite some inconsistent findings, genetic polymorphism in *CYP2D6* appears to negatively affect survival in the treatment of breast cancer with tamoxifen, because of a lower rate of formation of active metabolites of tamoxifen in *CYP2D6* poor metabolizers. Whether this genetic subgroup of patients should be given higher doses of tamoxifen or another type of treatment, such as, for example, aromatase inhibitors, is currently unknown. Additional, prospective studies, preferentially supported by pharmacokinetic analyses, will help to address these important questions.

With gemcitabine treatment, *CDA* 208G>A homozygous patients, in particular, but also *CDA* 208G>A heterozygous patients, appear to be predisposed for severe gemcitabine toxicity. If this finding can be independently confirmed by additional, prospective studies, the question arises of whether or not severe gemcitabine toxicity is preventable by initial dose reductions in at least *CDA* 208G>A homozygous variant allele carriers without negatively affecting treatment response.

For bleomycin, a single retrospective study in patients with testicular germ cell cancer treated with bleomycin-based chemotherapy reported that patients homozygous polymorphic for 1450A>G in *BLMH* experienced shorter overall and progression-free survival times (level of evidence, 3). Prospective studies should evaluate whether these findings can be confirmed. If so, the question evolves of whether or not this genetically defined subgroup of patients would benefit more from another type of chemotherapeutic regimen that does not include bleomycin.

Overall, genetic polymorphism in candidate genes involved in phase I metabolism has been shown to potentially affect the pharmacokinetics of anticancer drugs, and the toxicity and efficacy of treatment. A few selected candidate polymorphisms are, or at least have the potential to become, predictive markers for anticancer treatment outcome. These results should encourage the continuation of pharmacogenetic research in anticancer therapy, in an effort to implement personalized medicine in daily clinical practice.

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