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REVIEW ARTICLE

Genotypes Affecting the Pharmacokinetics of Anticancer Drugs

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Abstract Cancer treatment is becoming more and more individually based as a result of the large inter-individual differences that exist in treatment outcome and toxicity when patients are treated using population-based drug doses. Polymorphisms in genes encoding drug-metabolizing enzymes and transporters can significantly influence uptake, metabolism, and elimination of anticancer drugs. As a result, the altered pharmacokinetics can greatly influence drug efficacy and toxicity. Pharmacogenetic screening and/or drug-specific phenotyping of cancer patients eligible for treatment with chemotherapeutic drugs, prior to the start of anticancer treatment, can identify patients with tumors that are likely to be responsive or resistant to the proposed drugs. Similarly, the identification of patients with an increased risk of developing toxicity would allow either dose adaptation or the application of other targeted therapies. This review focuses on the role of genetic polymorphisms significantly altering the pharmacokinetics of anticancer drugs. Polymorphisms in *DPYD*, *TPMT*, and *UGT1A1* have been described that have a major impact on the pharmacokinetics of 5-fluorouracil, mercaptopurine, and irinotecan, respectively. For other drugs, however, the association of polymorphisms with pharmacokinetics is less clear. To date, the influence of genetic variations on the pharmacokinetics of the increasingly used monoclonal antibodies has hardly been investigated. Some studies indicate that genes encoding the Fcγ-receptor family are of interest, but more research is needed to establish if screening before the start of therapy is beneficial. Considering the profound impact of polymorphisms in drug transporters and drug-metabolizing enzymes on the pharmacokinetics of chemotherapeutic drugs and hence, their toxicity and efficacy, pharmacogenetic and pharmacokinetic profiling should become the standard of care.

Key Points

Genetic mutations in genes can affect the pharmacokinetics of drugs.

Altered metabolism of drugs can result in a decreased therapeutic response and increased toxicity.

Personalized medicine requires detailed analyses of the patient's genome and phenotypic consequences.

1 Introduction

Cancer treatment is becoming more and more individually based as a result of the large inter-individual differences in treatment outcome and toxicity. Factors responsible for inter-individual variability in pharmacokinetics and pharmacodynamics include drug–drug interactions, ethnicity, age, renal and liver function, comorbidities, nutritional status, smoking, and alcohol consumption. However,

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genetic factors may have an even greater impact on drug efficacy and toxicity [1]. In oncology, genetic variations can be found either in the tumor genome as somatic mutations, influencing the choice of chemotherapeutic treatment or as germline mutations, potentially altering individual drug pharmacology [2].

Pharmacogenetics is the study of the inherited basis of inter-individual differences in the efficacy and toxicity of drugs. Pharmacogenetic screening and/or drug-specific phenotyping of cancer patients eligible for treatment with chemotherapeutic drugs, prior to the start of anticancer treatment, can identify patients with tumors that are likely to be responsive or resistant to the proposed drugs. Patients with an unfavorable clinical or genetic make-up would be candidates for alternative treatment modalities. Similarly, the identification of patients with an increased risk of developing toxicity would allow either dose adaptation or the application of other targeted therapies. Polymorphisms in the human genome, affecting either expression or functionality of enzymes and transporters involved in the distribution and metabolism of anticancer drugs, can influence drug efficacy and toxicity and thereby the treatment outcome of patients.

The metabolism of xenobiotics is often divided into three phases: modification (phase I), conjugation (phase II), and elimination (most often in urine or bile). Phase I drug-metabolizing enzymes, especially members of the cytochrome P450 (CYP) family, are responsible for oxidation, reduction, and hydrolysis of drugs [3]. Phase II drug-metabolizing enzymes, such as glutathione *S*-transferases (GSTs) and uridine diphosphate glucuronosyltransferases (UGTs), mainly inactivate or activate drugs by conjugation reactions [4]. Polymorphisms in these enzymes have frequently been described to influence the pharmacokinetics of several anticancer drugs. Genes encoding key enzymes in the anabolic and catabolic pathway of purine and pyrimidine analogs, such as thiopurine *S*-methyltransferase (TPMT) and dihydropyrimidine dehydrogenase (DPD), are known to contain many polymorphisms and functional mutations affecting the enzymatic activity [5, 6]. Polymorphisms in genes encoding drug efflux transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), can greatly influence gastrointestinal uptake and excretion of anticancer drugs [7]. Monoclonal antibodies (mAbs) are increasingly being used in the treatment of cancer. However, limited information is known about the influence of genetic variations on the pharmacokinetics of mAbs [8].

This review focuses on the role of genetic polymorphisms in altering the pharmacokinetics of anticancer drugs. Table 1 provides an overview of the currently used anticancer drugs, their metabolic pathways, and if a genetic polymorphism significantly alters its pharmacokinetics.Anaplastic lymphoma kinase

2 Cytochrome P450 (CYP)-Mediated Phase I-Metabolizing Enzymes

Phase I reactions are catalyzed by CYP enzymes, a large superfamily of membrane-bound proteins, located predominantly in the endoplasmatic reticulum. The CYP1, CYP2, and CYP3 families are most frequently involved in drug metabolism (Table 2). Several factors may cause inter-individual variations in CYP450 activity: genetic polymorphisms, changes in physiological conditions such as age, sex, and disease, or environmental factors such as smoking, drugs, and certain foods.

The phase I, polymorphic xenobiotic-metabolizing CYP enzymes can be mainly divided into two classes: Class I, composed of CYP1A1, CYP1A2, CYP2E1, and CYP3A4, which are well conserved, do not have many clinically important functional polymorphisms, and are active in the metabolism of precarcinogens and drugs. Class II, composed of CYP2B6, CYP2C9, CYP2C19, and CYP2D6, which are highly polymorphic and active in the metabolism of drugs, but not of precarcinogens [9]. In this review, we discuss all three CYP families, with a special focus on Class II enzymes and their polymorphisms.

2.1 CYP1

In the CYP1 family, only one member, i.e., CYP1A2, has been associated with altered cancer drug metabolism. The CYP1A2 enzyme is involved in the metabolism of more than 20 clinically used drugs and the enzyme accounts for approximately 15 % of the total CYP450 amount in the human liver [10]. In lung cancer patients, the *CYP1A2*1M* variant has been associated with higher maximum plasma concentration values after the intake of 150 mg of erlotinib, suggesting reduced enzyme activity. The impact on drug efficacy and toxicity is so far unknown [11].

2.2 CYP2

The most important polymorphic enzymes in cancer drug metabolism are members of the CYP2 family, i.e., CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP2D6. The CYP2A6 enzyme is involved in the activation of the 5-fluorouracil (5-FU) prodrug tegafur. In a set of 45 Chinese livers with 20 polymorphic variants, the *CYP2A6*4* allele was mainly responsible for decreased in vitro microsomal formation of 5-FU from tegafur, whereas the *CYP2A6*1B* variant was associated with increased in vitro 5-FU formation [12]. In 23 Asian patients treated with

Table 1 Overview of the currently used anticancer drugs, their metabolic pathways, and if genetic polymorphisms significantly alter their pharmacokinetics

Anti-cancer drug	Target	Metabolizing enzymes	Transporters/receptors	Polymorphism-altering pharmacokinetics
Alkylating agents				
Bendamustine	DNA	CYP1A2		No, mainly non-enzymatic
Busulfan	DNA	CYP2C9, CYP2B6, **GSTs**		Yes [159, 160]
Carmustine	DNA			Unknown
Chlorambucil	DNA	**GSTs**		Yes [161]
Cyclophosphamide	DNA	CYP3A4, CYP3A5, **CYP2B6**, **CYP2C19**, GSTs		Yes [32, 162]
Dacarbazine	DNA	CYP1A1, CYP1A2, CYP2E1		Unknown
Estramustine	DNA			Unknown
Hydroxycarbamide	DNA			Unknown
Ifosfamide	DNA	CYP2A6, CYP2B1, **CYP2B6**, CYP2C8, CYP2C9, **CYP2C19**, CYP3A4, CYP3A5, GSTs		Yes [9, 162]
Lomustine	DNA			Unknown
Mechlorethamine	DNA			Unknown
Melphalan	DNA		LAT1, LAT2	No [163]
Temozolomide	DNA			No, mainly non-enzymatic
Procarbazine	DNA	CYP2B6, CYP1A4, CYP3A5		Unknown
Thiotepa	DNA	CYP3A4,CYP3A5 **CYP2B6**		Yes [9]
Treosulfan	DNA			No, mainly non-enzymatic [160]
Antimetabolites				
Azacitidine	DNA/RNA	**CDA**		Yes [164]
Capecitabine	DNA/RNA	**DPD**		Yes [70]
Cladribine	DNA/RNA	dCK		Unknown
Clofarabine	DNA/RNA	**dCK**		Yes [92, 93]
Cytarabine	DNA/RNA	**dCK**	MDR1	Yes [86]
Decitabine	DNA/RNA	**CDA, dCK**		Yes [90, 95]
Fludarabine	DNA/RNA	**dCK**		Yes [91]
Fluorouracil	DNA/RNA	**DPD**, GSTs		Yes [49]
Gemcitabine	DNA/RNA	**CDA, dCK**		Yes [87–89]
Mercaptopurine	DNA/RNA	**TPMT**		Yes [72, 73]
Methotrexate	DNA/RNA	**MTHFR**	SLC, MDR1	Yes [71, 81–84]
Nelarabine	DNA/RNA			Unknown
Pemetrexed	DNA/RNA			Unknown
Tegafur	DNA/RNA	**DPD**, **CYP2A6**, CYP2C8, CYP1A2		Yes [57]
Tioguanine	DNA/RNA	**TPMT**		Yes [165]
Anti-mitotic cytostatics				
Cabazitaxel	Microtubule	CYP3A4		Unknown
Docetaxel	Microtubule	CYP1B1, CYP2B6, CYP3A4, CYP3A5	**MDR1, BCRP**	Yes [98, 105]
Paclitaxel	Microtubule	CYP2C8, CYP3A4, CYP3A5	**MDR1, BCRP**	Yes [98, 105]
Vinblastine	Microtubule	CYP3A4,CYP3A5, GSTs		Unknown
Vincristine	Microtubule	CYP3A4,CYP3A5, GSTs	MDR1	No [166]
Vinorelbine	Microtubule	CYP2D6, CYP2E1, CYP3A4,CYP3A5, GSTs		Unknown

Table 1 continued

Anti-cancer drug	Target	Metabolizing enzymes	Transporters/receptors	Polymorphism-altering pharmacokinetics
Anti-tumor antibacterials				
Bleomycin	DNA/RNA	**BLMH**, GSTs		Yes [167]
Dactinomycin	DNA/RNA	GSTs	**MDR1**	No [168]
Daunorubicin	DNA	GSTs	MDR1	No [108]
Doxorubicin	DNA	CYP2B6, CYP3A4, CYP3A5, CYP2D6, GSTs, UGTs	**MDR1**, BCRP	Yes [106]
Epirubicin	DNA	UGTs	MDR1, SLC	No [107]
Idarubicin	DNA	CYP2D6, CYP2C9, GSTs	MDR1	Unknown
Mitomycin	DNA	GSTs		Unknown
Mitoxantrone	DNA	CYP1B1, CYP3A4, CYP3A5, GSTs	MDR1	Unknown
Topoisomerase inhibitors				
Etoposide	Topoisomerase	CYP1A2, CYP2E1, CYP3A4, CYP3A5, GSTs, UGTs	**MDR1**	Yes [98]
Irinotecan	Topoisomerase	CYP3A4, CYP3A5, **UGTs**	**MDR1**, BCRP	Yes [169]
Teniposide	Topoisomerase	CYP3A4, CYP3A5, UGTs		Unknown
Topotecan	Topoisomerase	CYP3A4, CYP3A5, UGTs	BCRP	No [170]
Anti-hormones				
Abiraterone	Androgen receptor			Unknown
Anastrozole	Aromatase	CYP3A4, CYP3A5, CYP2C8, CYP19A1, **UGTs**		Yes [171]
Bicalutamide	Androgen receptor UGTs		MDR1, **BCRP**	Yes [113]
Enzalutamide	Androgen receptor	CYP2C8, CYP3A4, CYP3A5		Unknown
Exemestane	Aromatase	CYP3A4, CYP3A5, CYP4A11, CYP1A2, CYP19A1, **UGTs**		Yes [172]
Flutamide	Aromatase	CYP1A2		No [9]
Letrozole	Aromatase	CYP3A4, CYP3A5, **CYP2A6**, CYP19A1		Yes [172]
Megestrol	Estrogen receptor			Unknown
Nilutamide	Androgen receptor			Unknown
Tamoxifen	Estrogen receptor	**CYP2D6**, CYP3A5, CYP3A4, CYP2C9, CYP2C19, CYP1B1, UGTs		Yes [173]
Fulvestrant	Estrogen receptor	CYP3A4, CYP3A5		No, mainly non-enzymatic
Tyrosine kinase inhibitors				
Afatinib	EGFR			No, mainly non-enzymatic
Axitinib	VEGF-R 1-3	CYP3A4, CYP1A2, CYP2C19, UGTs	MDR1	No [125]
Bosutinib	BCR-ABL/SRc	CYP3A4	MDR1	No [115]
Crizotinib	ALK	CYP3A4, CYP3A5		Unknown
Dabrafenib	BRAF	CYP2C8, CYP3A4		Unknown
Dasatinib	BCR-ABL	CYP3A4	MDR1, BCRP	No [115]
Erlotinib	EGFR			
Gefetinib	EGFR	CYP3A4, CYP3A5, CYP2D6	MDR1, BCRP	No [28]
Imatinib	BCR-ABL	CYP3A4, CYP3A5, CYP2C8	**MDR1, BCRP, SLC**	Yes [118, 119]
Lapatinib	HER-2	CYP3A4, CYP3A5, CYP2C19, CYP2C8		Unknown
Nilotinib	BCR-ABL	CYP3A4, CYP2C8	BCRP, SLC	No [115]
Olaparib	PARP	CYP3A4		Unknown
Pazopanib	Multi	CYP3A4, CYP1A2, CYP2C8		Unknown

Table 1 continued

Anti-cancer drug	Target	Metabolizing enzymes	Transporters/receptors	Polymorphism-altering pharmacokinetics
Ponatinib	BCR-ABL	CYP3A4		No [115]
Regorafenib	Multi	CYP3A4, UGTs		Unknown
Ruxolitinib	JAK	CYP3A4, CYP2C9		Unknown
Sorafenib	Multi	CYP3A4, **UGTs**	BCRP	Yes [126]
Sunitinib	Multi	CYP3A4, CYP3A5	**MDR1**, BCRP	Yes [174]
Vandetanib	Multi	CYP3A4		Unknown
Vemurafenib	BRAF	CYP3A4		No, mainly non-enzymatic
Biologicals				
Bevacizumab	VEGF			Unknown
Brentuximab	CD30	CYP3A4, CYP2D6		Unknown
Cetuximab	EGFR		**FCGRT**	Yes [145–148]
Ipilimumab	CTLA-4			Unknown
Nivolumab	PD-1			Unknown
Ofatumumab	CD20			Unknown
Panitumumab	EGFR			Unknown
Pembrolizumab	PD-1			Unknown
Pertuzumab	HER-2			Unknown
Rituximab	CD20		**FCGRT**	Yes [138–142]
Trastuzumab	HER-2		**FCGRT**	Yes [143, 144]
Immunomodulants				
Lenalidomide	Bone marrow			No, mainly non-enzymatic
Pomalidomide	Bone marrow	CYP1A2, CYP3A4, CYP2C19, CYP2D6		Unknown
Thalidomide	Bone marrow	**CYP2C19**		Yes [175]
Non-categorized				
Asparaginase (PEG)	L-Asparagine			No [71]
Bortezomib	Proteasome	CYP3A4, CYP2C19, CYP1A2		No [176]
Carboplatin	DNA	**GSTs**		Yes [162]
Cisplatin	DNA	CYP2E1, CYP3A4, CYP3A5, **GSTs**		Yes [177]
Oxaliplatin	DNA	**GSTs**		Yes [98]
Temsirolimus	mTOR	CYP3A4		Unknown
Trabectedin	DNA	CYP3A4, (CYP2C19, CYP2C9, CYP2D6, CYP2E1)		Unknown

The enzymes and transporters for which genetic polymorphisms are known to significantly alter the pharmacokinetics are indicated in bold

ALK anaplastic lymphoma kinase, *BCR-ABL/SRc* breakpoint cluster region protein-Abelson murine leukemia viral oncogene homolog/proto-oncogene tyrosine-protein kinase src, *BRAF* serine/threonine-protein kinase B-Raf, *CD20* cluster of differentiation 20, *CD30* cluster of differentiation 30, *CTLA-4* cytotoxic T-lymphocyte-associated protein 4, *CYP* cytochrome P450, *EGFR* epidermal growth factor receptor, *GSTs* glutathione, *HER-2* human epidermal growth factor receptor 2, *JAK* janus kinase, *mTOR* mammalian target of rapamycin, *multi* various tyrosine kinases, *PARP* Poly (ADP-ribose) polymerase, *PD-1* Programmed cell death protein, *S*-transferases, *UGT* uridine diphosphate glucuronosyltransferase, *VEGF* vascular endothelial growth factor, *VEGFR 1-3* vascular endothelial growth factor subtypes 1-3

irinotecan, oxaliplatin, and tegafur for metastatic gastrointestinal cancer, the *CYP2A6*4*, **7*, and **9* variants were associated with a lower metabolic ratio of tegafur (area under the curve [AUC] ratio of 5-FU to tegafur) [13].

The impact of CYP2A6 polymorphisms (**4A*, **7*, and **9*) on tegafur pharmacokinetics was studied in 58 Japanese patients. Although the CYP2A6 genotype did not affect the AUC of 5-FU, the clearance of tegafur was 58 %

Table 2 Polymorphisms in phase I and phase II metabolic enzymes affecting pharmacokinetics of anticancer drugs

Drugs	Gene	Mutations	dbSNP ID	ESP MAF		ExAC MAF	PK parameters
				African American	European American		
Erlotinib	*CYP1A2*	c.1042+43G>A	rs2472304	0.13	0.56	0.46	Plasma concentrations [11]
Tegafur	*CYP2A6*	CYP2A6*1A					Increased 5-FU formation [178]
		CYP2A6*4A	del				Decreased 5-FU formation [178]
		CYP2A6*4A-H	del				CL, AUC [13, 14]
		CYP2A6*7 (c.1412T>C)	rs5031016	nr	9×10^{-4}	1.1×10^{-2}	CL, AUC [13, 14]
		CYP2A6*9 (c.-48T>G)	rs28399433	0.08	0.06	0.10	CL, AUC [13, 14, 178]
Cyclofosfamide	*CYP2B6*	CYP2B6*6					CL [15–18, 32]
		(c.516G>T)	rs3745274	0.37	0.25	0.27	
		(c.785A>G)	rs2279343	nr	nr	0.06	
Busulfan	*CYP2C9*	CYP2C9*2 (c.430C>T)	rs1799853	0.03	0.13	0.09	Decreased CL [19]
Cyclophosphamide	*CYP2C19*	CYP2C19*2 (c.681G>A)	rs4244285	0.17	0.15	0.19	Reduced CL [16, 20, 179, 180]
		CYP2C19*3 (c.636G>A)	rs4986893	5×10^{-4}	2×10^{-4}	6×10^{-3}	
Gefitinib Tamoxifen	*CYP2D6*	CYP2D6*2xN	duplication				Endoxifen plasma concentrations [21–23, 28]
		CYP2D6*3 (c.775delA)	rs35742686	4.5×10^{-3}	1.7×10^{-2}	1.3×10^{-2}	Gefitinib plasma concentrations [29, 30]
		CYP2D6*4 (c.506-1G>A)	rs3892097	0.07	0.19	0.17	
		CYP2D6*5	del				
		CYP2D6*6 (c.454delT)	rs5030655	2×10^{-3}	9×10^{-3}	7.9×10^{-3}	
		CYP2D6*9 (c.841_843del)	rs5030656	5.9×10^{-3}	2.7×10^{-2}	1.9×10^{-2}	
		CYP2D6*10 (c.100C>T)	rs1065852	0.12	0.22	0.25	
		CYP2D6*17 (c.320C>T)	rs28371706	0.17	1.8×10^{-2}	1.8×10^{-2}	
		(c.886C>T)	rs16947	0.49	0.34	0.34	
Busulfan Chloorambucil Melphalan	*GSTA1*	GSTA1*B (c.-135T>C)	rs3957357	nr	nr	nr	Reduced CL busulfan [32, 33]
Thiotepa	*GSTP1*	GSTP1 (c.341C>T)	rs1138272	0.02	0.08	0.06	Reduced CL thiotepa and tepa [34]
Irinotecan	*UGT1A1*	UGT1A1*6 (c.211G>A)	rs4148323	0.01	0.01	0.02	Reduced CL SN-38 [36–38, 42]
		UGT1A1*28[a]	rs8175347				

AUC area under the curve, *CL* clearance, *ExAc* Exome Aggregation Consortium, *ESP* Exome Sequencing Project, *MAF* minor allele frequency, *nr* not reported, *PK* pharmacokinetic, *5-FU* 5-fluorouracil

[a] UGT1A1*28 occurs with a frequency of 0.26–0.31 in Caucasians, 0.42–0.56 in African Americans, and only 0.09–0.16 in Asian populations [181]

lower in patients with two variant alleles of CYP2A6 than in patients with the wild-type or 1 variant allele [14].

The CYP2B6 enzyme converts cyclophosphamide to its active form 4-hydroxycyclophosphamide. The most common functionally deficient allele is *CYP2B6*6*. A total of 644 plasma samples collected over a 5-year period, from 49 B-cell non-Hodgkin lymphoma (NHL) patients aged ≤18 years receiving cyclophosphamide (250 mg/m^2), were used to characterize a population pharmacokinetic model. Polymorphisms in genes including CYP2B6 and CYP2C19 were analyzed. The presence of at least one *CYP2B6*6* variant allele was associated with a lower cyclophosphamide clearance, as compared with homozygous wild-type patients, but there was no impact on clinical outcome [15]. However, several other reports have shown that the **6* allele is associated with a higher rate of cyclophosphamide 4-hydroxylation [16–18]. The overall effect of *CYP2B6*6* expression on the pharmacokinetics and therapeutic efficacy/toxicity of cyclophosphamide seems difficult to predict and would depend on whether the dominant effect is reduced enzyme expression or increased specific enzyme activity.

Patients with the *CYP2C9 *1/*2* or **2/*2* genotype undergoing hemopoietic stem cell transplantation may have decreased metabolism of busulfan as compared with patients with the wild-type genotype. However, other genetic and clinical factors may also influence the metabolism of busulfan [19]. The CYP2C19 enzyme plays a role in the metabolism of cyclophosphamide, ifosfamide, tamoxifen, and thalidomide. A splice site mutation in exon 5 (*CYP2C19*2*) and a premature stopcodon in exon 4 (*CYP2C19*3*) represent the most predominant null alleles [10]. With regard to cyclophosphamide and CYP2C19 activity, poor metabolizers are theoretically expected to have a reduced response and low toxicity upon therapy with cyclophosphamide, as a result of decreased CYP2C19-mediated activation. However, for *CYP2C19*2* and *CYP2C19*3*, no effect on the pharmacokinetics of cyclophosphamide was observed in two larger trials conducted in Japanese and European patients [16, 20]. This might be owing to the fact that cyclophosphamide is activated via multiple CYP enzyme pathways.

The *CYP2D6* gene is the best-studied member of the CYP family, with over 40 variant alleles [10]. In breast cancer patients, CYP2D6 plays an important role in the activation of tamoxifen into endoxifen. In several studies, clear associations were found between *CYP2D6* status and plasma endoxifen concentrations [21–23]. However, a clear exposure-response effect remains controversial. In two of the largest prospective-retrospective studies from BIG 1-98 and ATAC, no association was found between the *CYP2D6* genotype and breast cancer recurrence, although genotyping was performed in tumor DNA and massive departures from the Hardy–Weinberg equilibrium have been noted [24–26]. These controversial findings and the partial contribution of the genotype in explaining inter-individual variability in plasma concentrations of endoxifen imply that tailored tamoxifen treatment may not be fully realized through pharmacogenetics of metabolizing enzymes alone [27].

Lung cancer patients designated as *CYP2D6* poor metabolizers might theoretically have increased concentrations of gefitinib as compared with individuals designated as CYP2D6 extensive metabolizers. However, other genetic and clinical factors may also influence concentrations of gefitinib. The pharmacokinetics and pharmacogenomics were not associated with significantly different toxicities, response rates, or survival times with gefitinib [28, 29].

2.3 CYP3

The CYP3A subfamily is involved in the metabolism of more than 50 % of clinically used drugs, including several anticancer drugs such as cyclophosphamide, ifosfamide, thiotepa, etoposide, teniposide, docetaxel, paclitaxel, irinotecan, toremifene, vinblastine, vincristine, vinorelbine, gefitinib, imatinib, and erlotinib. The enzyme activity of CYP3A ranges widely among subjects, and its activity is largely affected by non-genetic factors such as age, endogenous hormone levels, health status, and environmental stimuli. Although approximately 40 allelic variants have been described for CYP3A4, it has been found that genetic variability in CYP3A alone is insufficient to explain its widely ranging enzyme activity and therefore is not indicated in clinical practice [30]. Recently, it was demonstrated that the *CYP3A4*22* (rs35599367:C>T) and the *CYP3A5*3* (rs776746:A>G) polymorphisms have a small but clinical insignificant impact on the pharmacokinetics of sunitinib, but so far no other studies have demonstrated an impact on the pharmacokinetics of anticancer drugs [31].

3 Non-CYP Phase II-Metabolizing Enzymes

Several clinical relevant gene polymorphisms associated with phase II drug metabolism and pharmacokinetics of anticancer drugs have been reported in the literature. The GST enzyme family and UGT enzymes have been most intensively studied (Table 2).

3.1 Glutathione *S*-Transferase

Four subfamilies of GSTs exist, namely, GSTA, GSTM, GSTP, and GSTT. GSTA1 plays an important role in the

detoxification of, busulfan, melphalan, and chlorambucil. *GSTA1*B* might be of clinical relevance in busulfan treatment because two studies in children demonstrated that the presence of *GSTA1*B* reduced the clearance of busulfan up to 30 % [32, 33]. In clinical practice, this might require dose adjustments of busulfan, at least in children, based on the *GSTA1*B* genotype.

In 124 Caucasian patients treated with high-dose chemotherapy for metastatic breast, ovarian, and testicular tumors, the clearance of thiotepa and tepa was predominantly affected by the *GSTP1 C341T* polymorphism, which had a frequency of 9.3 %. This allele variant increased non-inducible thiotepa clearance by 52 % and decreased tepa clearance by 32 % in heterozygous patients, which resulted in an increase in combined exposure to thiotepa and tepa of 45 % in homozygous patients [34].

3.2 Uridine Diphosphate Glucuronosyltransferases

The UGT enzymes are a superfamily of enzymes responsible for the glucuronidation of target substrates. The transfer of glucuronic acid renders xenobiotics and other endogenous compounds water soluble, allowing for their biliary or renal elimination. Unconjugated hyperbilirubinemias, such as Gilbert's syndrome and Crigler–Najjar syndrome, have been found to be associated with polymorphic variants of *UGT1A1*, especially with *UGT1A1*28* [35]. Currently, over 113 different *UGT1A1* variants have been described throughout the gene. These variants can confer reduced or increased activities, as well as inactive or normal enzymatic phenotypes.

Irinotecan is converted to its active metabolite SN-38. SN-38 is further metabolized to SN-38-glucuronide by various hepatic and extrahepatic UGT1A isozymes, mainly UGT1A1. Impaired glucuronidation activity of the UGT1A1 enzyme has been linked with elevated levels of SN-38, leading to toxicities. *UGT1A1*28* involves an extra TA repeat in the UGT1A1 promoter region and is the variant most frequently contributing to interpatient variability in irinotecan pharmacokinetics and toxicities. This information led to the revision of the irinotecan label by the US Food and Drug Administration. Both the **28* and **6* alleles have been well studied in regard to pharmaceutical toxicities. In particular, both alleles have shown associations with the development of irinotecan toxicities [36–38]. *UGT1A1*28* occurs with a frequency of 0.26–0.31 in Caucasians, and 0.42–0.56 in African Americans, and only 0.09–0.16 in Asian populations [39, 40]. *UGT1A1*6* has allele frequencies in Japanese, Korean, and Chinese populations of 0.13, 0.23, and 0.23, respectively [41].

Several studies hypothesized that patients with the *1/*1 genotype would tolerate a higher dose than the standard recommended dose of 180 mg/m^2, while patients with the *28/*28 genotype would require dose reduction. A prospective genotype-guided phase I study in colorectal cancer patients receiving irinotecan monotherapy indeed demonstrated a maximum tolerated dose (MTD) of 850 mg, 700 mg, and 400 mg in patients with the *1/*1 genotype, *1/*28 genotype, and *28/*28 genotype, respectively. Interestingly, although the irinotecan AUC increased according to the different MTDs in each genotype group, the mean SN-38 AUC levels were comparable across the different MTDs in each genotype group [42].

A similar, genotype-guided dose escalation study in colorectal patients receiving FOLFIRI (5-FU, folinic acid, irinotecan) identified the MTD of irinotecan to be 370 mg/m^2 and 310 mg/m^2 in patients with the *1/*1 genotype and *1/*28 genotype, respectively. Patients with the *28/*28 genotype were excluded [43]. Recently, it was demonstrated that high-dose irinotecan (260 mg/m^2) FOLFIRI combined with bevacizumab did not improve the overall response rate in metastatic colorectal cancer patients with the *1/*1 or *1/*28 genotype [44]. Whether irinotecan dose escalation in wild-type UGT1A1 patients contributes to improved clinical outcome is therefore questionable.

4 Enzymes of Purine and Pyrimidine Metabolism

Structural analogs of nucleobases and nucleosides are used in the treatment of cancer, viral infections, and inflammatory diseases. These nucleobase and nucleoside analogs are inactive prodrugs that are taken up by the cell via specific nucleobase or nucleoside transporters and subsequently phosphorylated intracellularly to their pharmacologically active triphosphate form [45]. The incorporation of nucleoside triphosphate analogs into DNA causes termination of DNA elongation and often also resistance to proofreading exonucleases. Some of these analogs also inhibit key enzymes (e.g., ribonucleotide reductase, thymidylate synthase, or dCMP deaminase) involved in the generation of purine and pyrimidine nucleotides for RNA and DNA synthesis. Opposing the activation of these purine and pyrimidine analogs are enzymes that inactivate or degrade the parent compounds or one of its anabolic products. Thus, a deficiency of a key enzyme in the anabolic or catabolic pathway of these purine and pyrimidine analogs will not only affect the clinical efficacy and toxicity of the drug but is also likely to alter the pharmacokinetics of the drug (Table 3).

5-FU and its oral prodrug capecitabine (Xeloda®, F. Hoffmann-La Roche AG, Basel, Switzerland) are two of the most frequently prescribed chemotherapeutic drugs for the adjuvant and palliative treatment of patients with cancers of the gastrointestinal tract, breast, and head and neck [46, 47]. Both 5-FU and capecitabine need to undergo

Table 3 Genotypes affecting pharmacokinetics of drugs targeting purine and pyrimidine metabolism

Drugs	Gene	Mutations	dbSNP ID	ESP MAF		ExAC MAF	PK parameters
				African American	European American		
5-FU Capecitabine Tegafur	*DPYD*	c.1905+1G>A	rs3918290	9.0×10^{-4}	5.8×10^{-3}	5.2×10^{-3}	V_{max}, $t_{1/2}$, AUC, CL [58, 59, 61, 182]
		c.1679T>G	rs55886062	0	6×10^{-4}	3.5×10^{-4}	CL [61]
		c.2846A>T	rs67376798	9.0×10^{-4}	5.5×10^{-3}	2.6×10^{-3}	CL [61]
		c.2579delA	rs746991079	nr	nr	3.3×10^{-5}	V_{max} (uracil) [62]
		c.1129-5923C>G	rs75017182	nr	nr	nr	V_{max} (uracil) [62]
	DPYS	c.1506delC	rs147965145	2.6×10^{-3}	0	2.4×10^{-4}	T_{max}, C_{max}, AUC [66]
	UPB1	c.254C>A	rs34035085	1.5×10^{-2}	0	1.4×10^{-3}	Altered uracil flux [68]
Capecitabine	*MTHFR*	c.655C>T (C677T)	rs1801133	0.12	0.35	0.30	$t_{1/2}$ [70]
Thiopurines	*TPMT*	TMPT*2 (c.238G>C)	rs1800462	0	2.3×10^{-3}	1.4×10^{-3}	TGN [77, 78]
		TPMT*3B (c.460G>A)	rs1800460	1.0×10^{-2}	3.7×10^{-2}	2.7×10^{-2}	
		TMPT*3C (c.719A>G)	rs1142345	5.3×10^{-2}	4.2×10^{-2}	3.7×10^{-2}	
Methotrexate	*MTHFR*	c.665C>T (C677T)	rs1801133	0.12	0.35	0.30	CL, serum concentrations MTX [183, 184]
		c.1286A>C	rs1801131	0.16	0.31	0.30	Serum concentrations MTX [184]
	ARID5B	c.1200-6044T>C	rs4948502	nr	nr	nr	Serum concentrations MTX [185]
		c.734-5030T>C	rs4948496	nr	nr	nr	Serum concentrations MTX [185]
		c.276+7693C>A	rs4948487	nr	nr	nr	Serum concentrations MTX [185]
	ABCC2	c.1234A>G	rs765027508	nr	nr	8.2×10^{-6}	$t_{1/2}$ [186]
		Knockout model					AUC [187]
	SLCO1B1	c.521T>C	rs4149056	3.6×10^{-2}	0.16	0.13	Serum concentrations MTX, AUC, CL [185, 188]
		c.388A>G	rs2306283	0.23	0.40	0.48	Serum concentrations MTX, AUC, CL [188]
		c.1865+248G>A	rs4149081	nr	nr	nr	CL [189]
		c.1865+4846T>C	rs11045879	nr	nr	nr	CL[189]
		Hap*5					CL[190]
		Hap*15					CL [190]
		Hap*23					CL [190]
		Hap*31					CL [190]
Gemcitabine	*CDA*	Hap*3 (c.208G>A)	rs60369023	nr	nr	2.9×10^{-4}	AUC, CL, C_{max} [88]
		THU induced[a]					AUC, CL [191]
	CNTN4	c.2398+70G>T	rs4685596	nr	nr	nr	AUC, C_{max} [87]
	ALOX5AP	c.495-204A>G	rs4769060	nr	nr	nr	AUC, *Vss*, C_{max} [87]
		c.495-523T>C	rs3935645	nr	nr	nr	*Vss*, C_{max} [87]
		c.341+12C>A	rs3803277	0.44	0.44	0.49	*Vss*, C_{max} [87]
	DMD	c.1331+127G>A	rs5928065	nr	nr	nr	AUC, *Vss* [87]
	HEXDC	c.15T>G	rs1141463	0.38	0.30	0.35	AUC, *Vss* [87]
Decitabine	*CDA*	mRNA expression activity					Plasma concentrations decitabine [95]

AUC area under the curve, *ExAc* Exome Aggregation Consortium, *CDA* cytidine deaminase, *CL* clearance, C_{max} maximum plasma concentration, *ESP* Exome Sequencing Project, *MAF* minor allele frequency, *nr* not reported, *PK* pharmacokinetic, *TGN* thioguanine nucleotides, $t_{1/2}$ elimination half-life, V_{max} maximum enzymatic conversion capacity, *Vss* volume of distribution at steady state, *5-FU* 5-fluorouracil

[a] CDA deficiency was achieved in mice by treatment with tetrahydrouridine [191]

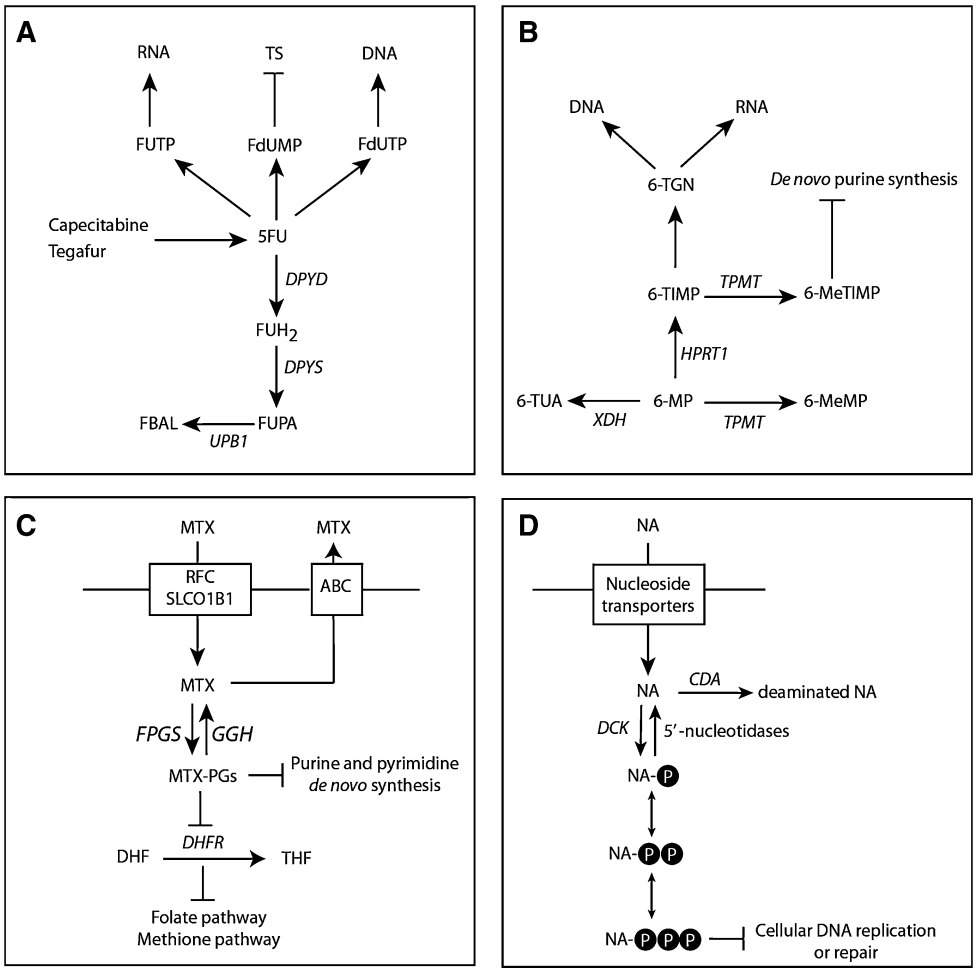

Fig. 1 Metabolism of drugs interfering with purine and pyrimidine synthesis. **a** Metabolism of fluoropyrimidine-containing drugs. **b** Thiopurine metabolism. **c** Methotrexate metabolism. **d** Nucleoside metabolism. *ABC* adenosine triphosphate-binding cassette family of transporters, *CDA* cytidine deaminase, *DCK* deoxycytidine kinase, *DHF* dihydrofolate, *DHFR* dihydrofolate reductase, *DPYD* dihydropyrimidine dehydrogenase, *DPYS* dihydropyrimidinase, *FBAL* fluoro-β-alanine, *FGPS* folylpolyglutamate synthase, *FUH_2* 5-fluoro-dihydrouracil, *FUPA* fluoro-β-ureidopropionate, *GGH* γ-glutamyl hydrolase, *HPRT1* hypoxanthine-guanine phosphoribosyltransferase, *MTX* methotrexate, *MTX-PGs* MTX-polyglutamate, *NA* (deoxy)nucleoside analogs, *RFC* reduced folate carrier, *SLCO1B1* solute carrier organic anion transporter B, *THF* tetrahydrofolate, dehydrogenase/oxidase, *TPMT* thiopurine-*S*-methyltransferase, *UPB1* β-ureidopropionase, *XDH* xanthine, *5-FU* 5-fluorouracil, *6-MeMP* 6-methylmercaptopurine, *6-MeTIMP* 6-methylthioinosine monophosphate, *6-MP* 6-mercaptopurine, *6-TGN* 6-thioguanine nucleotides, *6-TIMP* 6-thioinosine monophosphate, *6-TUA* 6-thiouric acid

enzymatic activation to fluoropyrimidine nucleotides to exert their cytotoxic effects (Fig. 1a). However, the degradation of 5-FU plays a significant role as more than 80 % of 5-FU is catabolized by DPD [48]. 5-FU has a narrow therapeutic index and an increased exposure to 5-FU, owing to a reduced activity of DPD, can thus result in severe or even lethal toxicity [49]. For DPD activities within the normal range, conflicting results have been published as to whether a correlation exists between the DPD activity and the clearance of 5-FU [50–52]. Compelling results, however, have shown that patients with a partial or complete DPD deficiency have a reduced capacity to degrade 5-FU and are at risk of developing severe 5-FU-associated toxicity [53]. To date, many mutations and polymorphisms have been described in the gene encoding DPD (*DPYD*) and ample evidence has been provided that carriers of the c.1905+1G>A, c.1679T>C, c.2846A>T, and c.1129-5923C>G/hapB3 variant have a strongly increased risk of developing toxicity [6, 54–57].

In a two-compartment model with Michaelis–Menten elimination, the mean *V*max value was 40 % lower in patients heterozygous for the c.1905+1G>A mutation in *DPYD* compared with controls [58]. Non-compartmental analysis showed that the mean AUC was 1.5-fold and 1.3-fold higher in carriers of the c.1905+1G>A mutation treated with 300 mg/m^2 and 450 mg/m^2, respectively, when compared with controls. The mean terminal half-life of 5-FU was 2.1-fold and 1.7-fold longer at 300 mg/m^2 and

450 mg/m^2, respectively, compared with controls [58]. Furthermore, a clinical pharmacological study of a patient with a complete deficiency owing to homozygosity for the c.1905+1G>A mutation in *DPYD* demonstrated minimal catabolism of 5-FU, with a tenfold longer half-life of 5-FU compared with patients with a normal DPD activity [59, 60]. A decreased clearance of plasma 5-FU concentrations was also noticed for carriers of the c.2846A>T and c.1679T>G mutations [61]. In addition, an oral uracil loading test to identify DPD-deficient patients showed altered pharmacokinetics of uracil in patients who were carriers for the c.1905+1G>A, c.2846A>T, c.2579delA, c.1679 T>G, or c.1129-5923C>G mutation [62].

Patients with a complete dihydropyrimidinase (*DPYS*) deficiency, the second enzyme of the pyrimidine degradation pathway, present with strongly elevated levels of dihydropyrimidines and moderately elevated levels of uracil and thymine [63]. Patients with a partial DHP deficiency also show an impaired flux through the pyrimidine degradation pathway and are prone to the development of severe toxicity after the administration of 5-FU [64–67]. The identification of a healthy individual showing altered catabolism of uracil due to heterozygosity for a mutation in UPB1 suggests that also patients with a β-ureidopropionase deficiency, the third enzyme of the pyrimidine degradation pathway, might be at risk of developing 5-FU toxicity [68, 69]. Although methylenetetrahydrofolate reductase (MTHFR) is not involved in the degradation of capecitabine, a borderline decrease in the elimination-half-life of capecitabine was observed for the c.677C>T mutation in *MTHFR* [70]. The c.677C>T mutation in *MTHFR* reduces the enzyme activity and presumably increases the level of 5,10-methyleneterahydrofolate, a substrate of thymidylate synthase. Thus, a direct causal relationship between *MTHFR* genotype and apparent elimination half-life of capecitabine is not likely.

6-Mercaptopurine (6-MP) is an analog of guanine and hypoxanthine, which is widely used in the treatment of patients with inflammatory bowel disease and patients with acute lymphoblastic leukemia [71, 72]. The principal cytotoxic and immunosuppressive effects of thiopurine drugs are caused by incorporation of thioguanine nucleotides into DNA or RNA (Fig. 1b). Opposing the principal enzyme of the anabolic pathway, hypoxanthine-guanine phosphoribosyl transferase, are the two catabolic enzymes xanthine oxidase and TPMT. Xanthine oxidase is responsible for oxidation of 6-MP into the inactive metabolite 6-thiouric acid, whereas TPMT methylates 6-MP to form the inactive metabolite 6-MP. Therefore, TPMT plays a pivotal role in the production of active thiopurine metabolites by diverting a proportion of available substrates away from the anabolic pathway of thiopurines to generate methylated metabolites. To date, more than 35 variants in the gene encoding TPMT have been associated with decreased TPMT activity [72]. Three variants TPMT*2, TMPT*3A, and TMPT*3C account for 80–85 % of intermediate or low enzyme activity in the Caucasian population [5]. Individuals who are heterozygous carriers or homozygous for an inherited functional mutation in *TPMT* have an increased risk of developing life-threatening myelosuppressive effects of thiopurines. Patients who are heterozygous for a TPMT deficiency require a lower dose of thiopurines (30–50 % of the regular dose) and substantial reduced doses (>tenfold) or the use of alternative agents is recommended in patients homozygous for a TPMT deficiency [72, 73]. Upfront screening of patients for variants in *TPMT*, followed by a dose reduction in heterozygous or homozygous carriers of a variant, reduced hematological events during thiopurine treatment of inflammatory bowel disease [74]. Furthermore, a similar treatment efficacy was obtained in carriers treated with a reduced thiopurine dose as compared with that observed in controls [74].

The oral bioavailability of 6-MP is very low owing to extensive intestinal and hepatic metabolism by xanthine oxidase [75]. The maximum concentration of 6-MP in plasma is observed approximately 1.3 h after oral administration of 6-MP and the elimination half-life is approximately 1.8 h [76]. One approach to ensure optimal dosing of thiopurines is to monitor the thiopurine metabolites in erythrocytes [72]. A population pharmacokinetic model has been developed to predict the concentrations of thioguanine nucleotides in erythrocytes in pediatric patients with acute lymphoblastic leukemia and the most influential covariate examined proved to be the *TMPT* genotype [77]. In a physiologically based pharmacokinetic model, the predicted thioguanine nucleotides in erythrocytes in patients with heterozygous or homozygous variants in the TPMT gene were twofold and tenfold higher, respectively, compared with those observed in patients with wild-type TMPT [78].

Methotrexate (MTX) is most frequently used for the treatment of patients with rheumatoid arthritis as well as patients with acute lymphoblastic leukemia. Nevertheless, MTX can cause severe dose-limiting adverse events and organ toxicities [79]. MTX is a structural analog of folic acid and it enters the cell via the reduced folate carrier (solute carrier family 19 member 1B1, SLC19A1) or the solute carrier organic anion transporter B1 (SLCO1B1) (Fig. 1c). In the cytoplasm, MTX is polyglutamated by folylpolyglutamate synthase, which enhances its retention in the cell. This process can be reversed by the enzyme γ-glutamyl hydrolase. MTX and MTX-polyglutamate inhibit dihydrofolate reductase, which catalyses the conversion of dihydrofolate into tetrahydrofolate. Because reduced folates are required for both the de novo thymidylate and

purine synthesis, inhibition of dihydrofolate reductase results in direct inhibition of both pathways (Fig. 1). In addition, methotrexate polyglutamate metabolites also bind directly and inhibit thymidylate synthase and aminoimidazolecarboximide ribonucelotide formyltransferase (purine de novo pathway) [80]. Efflux of MTX from the cell occurs via members of the adenosine-5′-triphosphate-binding cassette (ABC) family of transporters, including ABCB1 [81]. Genetic variations in pharmacokinetic genes involved in MTX metabolism can be major determinants of clinical response and toxicity (Table 3) [71, 81–84].

Deoxycytidine kinase (dCK) is responsible for the initial activation of a number of clinically important anticancer drugs such as cytarabine, gemcitabine, decitabine, fludarabine, and clofarabine (Fig. 1d). Impaired dCK expression or activity in cells results in resistance to these drugs, whereas overexpression of dCK in dCK-deficient cell lines increased the sensitivity of dCK-activated deoxynucleoside analogs, indicating that dCK plays a key role in their metabolism and pharmacological activities [45]. Cytidine deaminase is an important determinant of the efficacy and cytotoxicity of cytarabine, gemcitabine, and decitabine because these deoxynucleoside analogs are readily deaminated and thereby inactivated by cytidine deaminase [85]. The pharmacokinetics of cytarabine [86], gemcitabine [87–89], decitabine [90], fludarabine [91], and clofarabine [92, 93] have been thoroughly investigated in cancer patients. To date, limited information is only available regarding the potential impact of altered levels of the cytidine deaminase gene (*CDA*) on the pharmacokinetics of gemcitabine [87–89, 94] and decitabine [95].

5 Drug Transporters

Polymorphisms in genes encoding drug efflux transporters, such as P-gp and BCRP, can influence uptake and excretion of anticancer drugs (Table 4). This contributes to the inter-

Table 4 Polymorphisms in drug transporter genes affecting pharmacokinetics of anticancer drugs

Drugs	Gene	Mutations	dbSNP ID	ESP MAF		ExAC MAF	PK parameters
				African American	European American		
Docetaxel	*ABCB1*	c.1236T>C	rs1128203	0.22	0.43	0.54	CL [1]
		c.3435T>C	rs1045642	0.23	0.48	0.50	CL [192]
Paclitaxel	*ABCB1*	c.1236T>C	rs1128203	0.22	0.43	0.54	AUC [193]
		c.2677T>A/G	rs2032582	nr	nr	0.54	AUC [193]
Etoposide	*ABCB1*	c.3435T>C	rs1045642	0.77	0.47	0.50	CL [194]
Doxorubicin	*ABCB1*	c.1236T>C	rs1128203	0.22	0.43	0.54	C_{max} [106]
		c.2677T>A/G	rs2032582	nr	nr	0.54	CL [106]
	SLC22A16	c.146A>G	rs714368	0.36	0.22	0.25	AUC [195]
		c.312T>C	rs6907567	0.36	0.22	0.25	AUC [195]
Irinotecan	*ABCB1*	c.1236T>C	rs1128203	0.22	0.43	0.54	AUC, CL [110]
		Hap*2					CL [111]
Bicalutamide	*ABCG2*	c.421C>A	rs2231142	0.03	0.11	0.12	AUC, T_{max}, C_{max}, $t_{1/2}$, CL plasma concentrations [113]
Topotecan	*ABCG2*	c.421C>A	rs2231142	0.03	0.11	0.12	F [196]
Imatinib	*ABCB1*	c.1236T>C	rs1128203	0.22	0.43	0.54	C_{min}, CL, F [116, 117]
		c.2677T>A/G	rs2032582	nr	nr	0.54	CL, F [117]
		c.3435T>C	rs1045642	0.23	0.48	0.50	CL, F [117]
		Hap*4					C_{min} [116]
	ABCG2	c.421C>A	rs2231142	0.03	0.11	0.12	C_{min}, CL [118, 119]
	SLC22A1	c.480C>G	rs683369	0.05	0.22	0.17	CL, C_{min} [128]
Gefitinib	*ABCG2*	c.421C>A	rs2231142	0.03	0.11	0.12	$C_{ss,min}/C_{1,min}$ [123]
Sunitinib	*ABCB1*	c.2677T>A/G	rs2032582	nr	nr	0.54	CL [31]

The drug accumulation at the steady-state was assessed as the ratio of $C_{ss,min}$ to $C_{1,min}$, where $C_{ss,min}$ was the average pretreatment concentration on days 8, 15, 22 and 28, and $C_{1,min}$ was the pretreatment concentration before the second dose

AUC area under the curve, *ExAc* Exome Aggregation Consortium, *ESP* Exome Sequencing Project, *CL* clearance, C_{max} maximum plasma concentration, C_{min} trough plasma concentration, $C_{ss,min}/C_{1,min}$, *F* oral bioavailability, *MAF* minor allele frequency, *nr* not reported, *PK* pharmacokinetic, T_{max} time to maximum plasma concentration, $t_{1/2}$ elimination half-life

individual variability in pharmacokinetics and, as a consequence, to large differences in treatment response between cancer patients [7, 96].

P-gp is a member of the ABC superfamily of membrane transporters and is involved in the active transport of lipophilic and amphipathic molecules through lipid membranes [97]. P-gp is encoded by the multidrug resistance 1 (*MDR1*) gene (*ABCB1*), located at chromosome 7q21. A number of polymorphisms described in this gene significantly influence the pharmacokinetics of several anticancer drugs. There are three main polymorphisms influencing the activity of P-gp; the c.2677G>T/A single nucleotide polymorphism (SNP) in exon 21 leads to a change in the amino acid sequence from Ala (G) to Ser (T) or Thr (A), possibly resulting in increased P-gp function [98, 99]. The second polymorphism is in exon 26 at wobble position c.3435C>T, resulting in a more than twofold lower P-gp expression in the duodenum [100]. The third one is also a synonymous SNP, at c.1236T in exon 12, which does not directly affect expression of P-gp but may have an indirect effect such as altering RNA stability for P-gp [101].

BCRP, also called mitoxantrone resistant protein (MXR) or placenta-specific ABC transporter, is another member of the ABC transporter superfamily. BCRP is encoded by the *ABCG2* gene located at chromosome 4q22 [102]. A functional SNP (c.421C>A) in exon 5 has been identified, resulting in a Gln (C) to Lys (A) amino acid substitution, which proved to be associated with decreased BCRP expression levels and altered substrate specificity [103].

Docetaxel and paclitaxel are cytotoxic taxanes inhibiting mitosis leading to cancer cell death, which are mainly used in the treatment of breast, ovarian, and lung cancer [104]. For taxanes, the *ABCB1* gene is considered one of the best candidates to become a biomarker underlying variations in clinical responses and toxicity owing to pharmacokinetic differences [105].

Doxorubicin, an anthracycline widely used as mono- or combination therapy in the treatment of solid tumors including breast cancer, is also the substrate of P-gp and BCRP [106]. Significantly altered clearance and lower plasma concentration of doxorubicin was observed in patients harboring any of the three above-described polymorphisms in *ABCB1*. For c.421C>A in *ABCG2*, no significant influence on doxorubicin pharmacokinetics was observed [106]. Pharmacokinetics of other anthracyclines, such as epirubicin and daunorubicin, were not altered by polymorphisms in drug transporter genes [107, 108].

Irinotecan, a topoisomerase I inhibitor, plays a major role in the treatment of colorectal cancer as monotherapy or in combination with 5-FU [109]. Elimination pathways of irinotecan are partially mediated by P-gp and BCRP. A study investigating polymorphisms in genes encoding these transporters showed that only the polymorphism c.1236C>T in *ABCB1* was associated with significantly increased exposure to irinotecan and its active metabolite SN-38 in individuals homozygous for the T allele [110]. In addition, a significant association has been observed for *ABCB1* haloptype*2 containing both c.1236C>T, c.2677G>T/A, and c. 3435C>T, with reduced renal clearance of irinotecan [111].

Bicalutamide, a non-steroidal pure anti-androgen that competitively blocks the growth-stimulating effects of androgens, is used in the treatment of prostate cancer as monotherapy or in combination with a luteinizing hormone-releasing hormone analog [112]. P-gp and BCRP are involved in the disposition of bicalutamide. The pharmacokinetic parameters of bicalutamide did not show any significant differences between *ABCB1* genotype groups for the three main polymorphisms previously described [113]. However, for *ABCG2* it was shown that the c.421C>A polymorphism influenced plasma concentrations of bicalutamide with subjects homozygous for the c.421AA genotype exhibiting significantly higher plasma concentrations than those with the c.421CC or c.421CA genotype [113].

Tyrosine kinase inhibitors (TKIs) are a relatively new class of oral targeted anticancer therapy. TKIs are designed to compete with adenosine-5′-triphosphate in the tyrosine kinase receptor mutated and/or over-expressed in cancer tissues, thereby blocking the signaling important for tumor growth [114]. Most TKIs are transported by P-gp and BCRP, thus polymorphisms in genes encoding these transporters are likely to influence the pharmacokinetics of TKIs. Most studied in this respect is the first approved TKI; imatinib, used in the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors [115]. However, conflicting results have been reported as to whether *ABCB1/ABCG2* polymorphisms affect the pharmacokinetics of imatinib [116–122]. For *ABCG2*, the results are more consisted, with the c.421C>A SNP resulting in significant lower plasma concentrations and changes in the clearance of imatinib [118, 119]. Another first-generation TKI gefitinib, a selective epidermal growth factor receptor inhibitor used in the treatment of non-small-cell lung cancer, showed higher drug accumulation in patients with c.421C>A SNP in *ABCG2* [123]. No relationship with gefitinib AUC was found with polymorphisms in either *ABCB1* or *ABCG2* [28]. For the newer second- and third-generation TKIs, axitinib, bosutinib, nilotinib, dasatinib, sorafenib, and ponatinib, the substrate affinity for both efflux transporters is lower than measured for imatinib. Therefore, their efficacy is not significantly affected by polymorphisms in genes encoding these transporters [115, 124–126]. Increased clearance of sunitinib, a multi-targeted TKI used in the treatment of renal cell carcinoma, has been shown for homozygote genotypes of c.2677G>A/T SNP in *ABCB1* [31].

Another increasingly recognized group of transporters involved in the pharmacokinetics of anticancer drugs are the influx transporters of the solute carrier family, also known as the human organic cation transporter 1 (hOCT1), encoded by the *SLC22A1* gene [127]. hOCT1 is expressed in several tissues and organs where its activity contributes to the uptake and elimination of endogenous small organic toxic by-products and drugs. The c.480C>G polymorphism in this gene is the most studied one in relation to pharmacodynamic effects, but only for imatinib has an association been found between genotype and clearance [128].

6 Immunoglobulin-Metabolizing Enzymes

Monoclonal antibodies (mAbs) are increasingly being used in the treatment of cancer, owing to their high specificity and activity, combined with the expanding knowledge on specific tumor targets [129]. mAbs are immunoglobulins produced with recombinant DNA technology and can be fully human, humanized chimeric (human/murine), or murine [130].

The response to mAbs may be difficult to predict owing to several sources of variability, partly explained by inter-individual variability in pharmacokinetics [131]. mAbs are hydrophilic high-molecular-weight proteins and their pharmacokinetic properties are therefore different from conventional chemical agents. mAbs used in cancer treatment are, or derive from, human immunoglobulin G (IgG). Therefore, the pharmacokinetic properties of mAbs are similar to those of IgG [131]. The IgG structure can be divided into two identical binding portions (Fab) and a crystallizable portion (Fc). The Fc portion binds to the neonatal Fc receptor (FcRn) expressed on phagocytic cells of the reticuloendothelial system, which is involved in IgG protection from intracellular catabolism [132]. Intracellular catabolism is the main route for elimination of IgGs and mAbs with a Fc portion [133]. Knock-out mice that do not produce FcRn have a much higher IgG elimination (lower half-life) than wild-type mice [134].

FcRn is encoded by *FCGRT*, a gene located on chromosome 19 [135]. To date, little is known about potential polymorphisms of this gene influencing the pharmacokinetics of mAbs [8]. A variable number of tandem repeats (VNTR) in the *FCGRT* promotor region has been described and immunoglobulin therapy proved to be more efficient in VNTR3/VNTR3 homozygous patients than in VNTR2/VNTR3 patients [136]. For cetuximab, a significant lower distribution clearance was shown in VNTR3/VNTR3 patients compared with VNTR2/VNTR3 [8].

In addition, cells of the reticuloendothelial system express various types of Fcγ-receptors, which are also expected to play a role in the elimination of mAbs, through internalization and degradation by lysosomes in these cells after binding of the mAb to the Fcγ-receptors [137]. Two of these Fcγ-receptors are FcγRIIA and FcγRIIIA and several studies described the influence of a polymorphisms in *FCGR2A* or *FCGR3A*, the genes encoding the FcRIIA and FcRIIIA receptors, respectively, on therapy outcomes for rituximab [138–142], trastuzumab [143, 144], and cetuximab [145–148]. The G to A point mutation described in the *FCGR2A* gene generates two FcγRIIA allotypes, with either a histidine (H) or arginine (R) at amino acid position 131. The T to G substitution described in *FCGR3A* generates two FcγRIIIA allotypes, with either a phenylalanine (F) or valine (V) at amino acid position 158 in the membrane-proximal Ig-like loop. Human IgG binds more strongly to cells homozygous for FcγRIIA-131H and FcγRIIIA-158V than to cells homozygous for FcγRIIA-131R and FcγRIIIA-158F [149, 150].

Cetuximab, a chimeric immunoglobulin monoclonal antibody that targets the epidermal growth factor receptor, is used in the treatment of metastatic colorectal cancer in combination with chemotherapy or as monotherapy [151]. Several studies explored the role of *FCGR* polymorphisms in the treatment outcome of cetuximab, but have conflicting results. In some studies, FcγRIIIA-158F/F was correlated with response and a longer progression-free survival [146], while in other studies FcγRIIIA-158V/V was associated with longer progression-free survival [147] or no difference on progression-free survival at all was observed [145, 148]. For FcγRIIA-131 H/H, in two out of three studies, a better disease control rate and progression-free survival was observed than those for FcγRIIA-131 R/R [147, 148, 152].

Rituximab, a chimeric immunoglobulin monoclonal antibody that targets the B-cell-surface antigen CD20, is used in the treatment of diffuse large B-cell lymphoma in combination with chemotherapy or as monotherapy [153]. For rituximab, several studies showed that FcγRIIIA-158V/V patients had a longer progression-free survival than F carriers [138–142].

Trastuzumab, a humanized immunoglobulin monoclonal antibody that targets the human epidermal growth factor receptor (HER2), is a major therapeutic agent in the treatment of HER2-positive breast cancer in combination with chemotherapy or as monotherapy [154]. Some studies on trastuzumab show a similar effect as observed with rituximab, with a better clinical response for FcγRIIIA-158V/V patients [143, 144], while others could not confirm these results [155].

For cetuximab, rituximab, and trastuzumab, the underlying mechanism of *FCGR* polymorphisms was speculated to be pharmacodynamic, owing to a more efficient FcγRIIa/FcγRIIIa-dependent cytotoxicity. However, because these receptors are also involved in the elimination of mAbs, it can be hypothesized that these polymorphisms

also impact mAb clearance. For infliximab, a mAb that is not used in cancer treatment but instead is frequently used to control inflammatory diseases, a higher infliximab elimination rate constant in FcγRIIIA-158V/V patients was observed than in F carriers, leading to a faster infliximab underexposure and relapse of disease [156]. These findings can also explain why in vitro studies on rituximab showed a much stronger correlation, with the concentration leading to 50 % of maximal lysis about fourfold lower for FcγRIIIA-158V/V patients than for F carriers, than found in vivo [157].

7 Conclusions

Cancer treatment is becoming more and more individually based to increase drug efficacy and reduce adverse responses to therapy. Pharmacogenetic screening and/or drug-specific phenotyping of cancer patients eligible for treatment with chemotherapeutic drugs, prior to the start of anticancer treatment, can not only identify patients with tumors that are likely to be responsive or resistant to the proposed drugs but also patients prone to develop severe toxicity. Ample evidence is now available that polymorphisms in *DPYD*, *TPMT*, and *UGT* can profoundly affect the pharmacokinetics of 5-FU, mercaptopurine, and irinotecan, respectively [158]. Considering the common use of these three drugs in the treatment of cancer patients, the severe toxicity in patients carrying functional polymorphisms in these genes, it would be preferable to screen these patients prior to the start of the therapy. For most other chemotherapeutic drugs, however, the association of gene mutations and pharmacokinetics is less clear, which may be because of a minor impact of genetics compared with non-genetic factors such as diet, co-medication, health status, and renal and liver function. These agents may be candidates for dose individualization by a phenotype-based approach such as therapeutic drug monitoring.

In the past decades, huge progress has been made in the rapid characterization of SNPs, enabling the clinical application of pretreatment pharmacogenetic screening. However, the scarcity of information on functional characteristics of many SNPs indicates the need for future research, allowing pharmacogenetic and pharmacokinetic screenings to become the standard of care.

Compliance with Ethical Standards

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