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REVIEW ARTICLE

Polymorphisms of genes encoding drug transporters or cytochrome P450 enzymes and association with clinical response in cancer patients: a systematic review

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Abstract

Purpose Not all patients respond well to cancer chemotherapy. One of the most important factors contributing to treatment response (efficacy and toxicity) is genetic determinant. The current systematic review aims to provide current status of the information on the genetic contribution of genes encoding drug transport proteins and drug metabolizing enzyme, cytochrome P450 (CYP), and relationship with clinical outcomes of cancer chemotherapy.

Methods The literature search was performed through PubMed and ScienceDirect databases. One hundred and four research articles that fulfilled the inclusion criteria and had none of the exclusion criteria were included in the analysis.

Results Various studies reported conflicting results for the polymorphisms of the major genes and association with treatment outcomes in patients with various types of cancer. Nevertheless, among the investigated gene polymorphisms, it appears that the 1236C>T, 3435C>T and 2677 G>T/A SNPs of the drug transporter gene ABCB1 were the most promising determinants of clinical outcomes. Although both 1236C>T and 3435C>T polymorphism are synonymous SNPs, several studies have demonstrated that not all synonymous SNPs are silent. Therefore, using the haplotype (1236C>T, 2677G>T, and 3435C>T) analysis rather than a single SNP may be a more useful approach for phenotype prediction. Some of the patients with variants of CYP genes were associated with unsatisfactory treatment response (efficacy and toxicity), suggesting that these variants may be associated with either reduction or absence of CYP enzyme activity.

Conclusions The controversial results may be due to several factors including difference in populations studied, sample size, tumor sites and stages, chemotherapeutic drug regimens, and evaluation parameters for efficacy and/or toxicity. Before the information can be successfully applied to individualized cancer chemotherapy, further studies should be focused on these promising genetic markers and their association with clinical outcomes using standardized protocols.

Keywords Drug transporter · Cytochrome P-450 · Polymorphism · Treatment outcome · Response · Systematic review

Introduction

Cancer is one of the leading causes of mortality worldwide. Surgery is the primary treatment for managing early-stage and locally advanced stage disease. Nevertheless, complete tumor removal is not successful in several types of cancer. Resistance of most tumors to available anticancer drugs also further aggravates poor prognosis [1].

The ATP-binding cassette (ABC) transporter encodes the multidrug efflux pump P-glycoprotein (P-gp) and is involved in pumping intracellular drugs out of the cells. This protein family acts as a resistance factor to anticancer drugs [2]. The solute carrier (SLC) family on the other hand facilitates drug entry into cells. This protein family encodes membrane-bound transporters [3]. For example, SLCO1B1 or solute carrier

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organic anion transporter family member 1B1 is a major influx transporter expressed on the basolateral membrane of human hepatocytes which mediated the active metabolite of irinotecan [4]. Various members of the ABCB, ABCC, and ABCG subfamilies, i.e., ABCB1 (multidrug resistance-1: MDR1), ABCG2 (breast cancer resistance protein: BCRP) or ABCC2 (multidrug resistance-associated protein-2: MRP2) play important roles in conferring multidrug resistance in cancer cells, as well as alteration of clearance of chemotherapy drugs with enhanced toxicity [2]. This likely results in poor prognosis of response to chemotherapy.

There is an increasing interest factors contributing to inter-individual variability in drug efficacy and toxicity leading to variability in clinical responses [5]. This is of particular concern in cancer chemotherapy as most anticancer agents exhibit low selectivity against cancer cells and narrow therapeutic index. A small increase in plasma drug concentrations may lead to toxicity, while a small decrease in plasma concentrations may reduce clinical efficacy [6]. Investigation of factors associated with variability in chemotherapeutic outcomes and improving strategies to personalized medicine to maximize efficacy and minimize toxicity is currently of great research interest [7]. One of the most important factors is polymorphisms of genes involved in the pharmacokinetic processes (absorption, distribution, metabolism, and excretion). The majority of drug metabolism reactions are catalyzed by the cytochrome P450 (CYP) enzymes [6]. Polymorphisms of genes that encode drug metabolizing enzymes and drug transporters can markedly affect drug efficacy and toxicity [8]. Single-nucleotide polymorphisms (SNPs) in genes involved in metabolism and transport of chemotherapeutic drugs have been shown to significantly affect response to therapy and critically predict clinical outcomes [9]. For example, the rs3212986 variant of CYP2A6 gene has been associated with good clinical response to cisplatin/S-1 combination therapy with prolonged overall survival time. Additionally, the polymorphism of the transporter gene ABCC2-24C>T has been shown to improve response to platinum-based chemotherapy in non-small cell lung cancer [10]. Nevertheless, association studies of the polymorphisms of these genes in cancer patients and response to chemotherapeutic drugs remain conflicting and controversial with inconclusive results. The present study aims to provide a thorough and systematic review of current information on association between polymorphisms of drug transporters or CYP enzymes and chemotherapeutic response.

Methods

Search strategy

The electronic databases PubMed and ScienceDirect were searched during 1982–2018 for relevant published articles with regard to the association between pharmacogenetics in pharmacokinetics and chemotherapeutic response in cancer patients. The following combination keywords were applied: cancer AND pharmacogenetics/polymorphism/genetic variation/single nucleotide polymorphisms, AND drug transporters/cytochrome P450/CYP, AND anticancer drug/chemotherapeutic drug response/outcome. Both free text and MeSH search for keywords were used. The search was restricted to human studies. Two independent reviewers were responsible for completing the title search, title, abstract, full text screening, and full-text extraction.

Inclusion and exclusion criteria

The inclusion criteria of this systematic review were as follows: (1) full-text research articles published in English, and (2) articles related to studies of association between polymorphisms of drug transporters and CYP genes and chemotherapeutic drug response in all type's cancer patients. The exclusion criteria were: (1) comments, reviews, editorials, and conference abstracts, (2) articles with insufficient data, and (3) articles with duplication of previous publications.

Data extraction

Both independent authors were extracted the data from all included publications using predefined tables which included items as follows: first author, publication year, type of cancer, sample size, chemotherapeutic regimens, genotyping method, name of genes, and clinical outcomes (tumor response, survival time, toxicity, and others). *Tumor response* was defined as treatment response determined according to (1) *extent of tumor necrosis*; patients with $< 90\%$ necrosis were classified as poor responders and those with $\geq 90\%$ as good responders, (2) Response Evaluation Criteria in Solid Tumors (RECIST) and WHO criteria [11, 12], (3) percentage of tumor lesion, (4) reduction of BCR/ABL fusion gene transcripts, (5) percentage of blast cells in the bone marrow aspirates and biopsy including absolute neutrophil and platelets count, (6) Becker's Criteria [13], (7) Sokal score [14], (8) percentage of prostate-specific antigen, or (9) reduction of serum PSA from baselines. Survival time was defined as (1) overall survival (OS: the time from diagnosis until death from any cause or last known date alive or the time from the first cycle of chemotherapy to death or last follow-up day or the date of surgery to the date of death or the cut-off date of follow-up, (2) progression-free survival (PFS: the time interval between start of chemotherapy or surgery until the date of disease progression, (3) event-free survival (EFS: the interval from the date of treatment to the date of a confirmed relapse, persistence of the disease or death from any cause or the time between diagnosis and the event of interest, (4) disease-free survival (DFS:

the initiation of therapy to first recorded date of progression, death, or last follow-up evaluation, or (5) recurrence free survival time (RFS: the time from surgical treatment to diagnosis of the recurrence of a cancer. As one research article may report at least one type of study (polymorphisms of drug transporter or CYP enzyme or both), the term "study" rather than "article" is used in this systematic analysis.

Results

Study selection

A total of 585 research articles related to polymorphisms of genes encoding drug transporter or CYP enzyme and chemotherapeutic response in cancers were retrieved from PubMed and ScienceDirect. Duplicated literatures were not found, and 161 articles met the predefined eligibility criteria following screening of title and abstract. After full-text screening, 57 articles were excluded, and 104 articles were finally included in the analysis (Fig. 1). The main reasons for article exclusion were: (1) not related to gene polymorphism or interested gene ($n=401$), (2) review articles ($n=31$), (3) no information provided on treatment response or outcome ($n=29$), (4) not studies in cancer patients ($n=15$), (5) letter to editor article ($n=1$), (6) commentary article ($n=1$), (7) editorial article ($n=1$), (8) no information provided on the association between gene polymorphism and treatment response ($n=1$), and (9) non-English article ($n=1$).

Study characteristics

Of the 104 articles included in the analysis, 55 (12,401 patients), 34 (28,720 patients, unidentified sample size in one study) and 15 (2402 patients) articles were related to gene polymorphisms of drug transporters, CYP enzymes, and both, respectively. Thirty-nine, 11, 5, 5, 3, 1, 1, 1 and 2 studies, respectively, were related to the investigation of

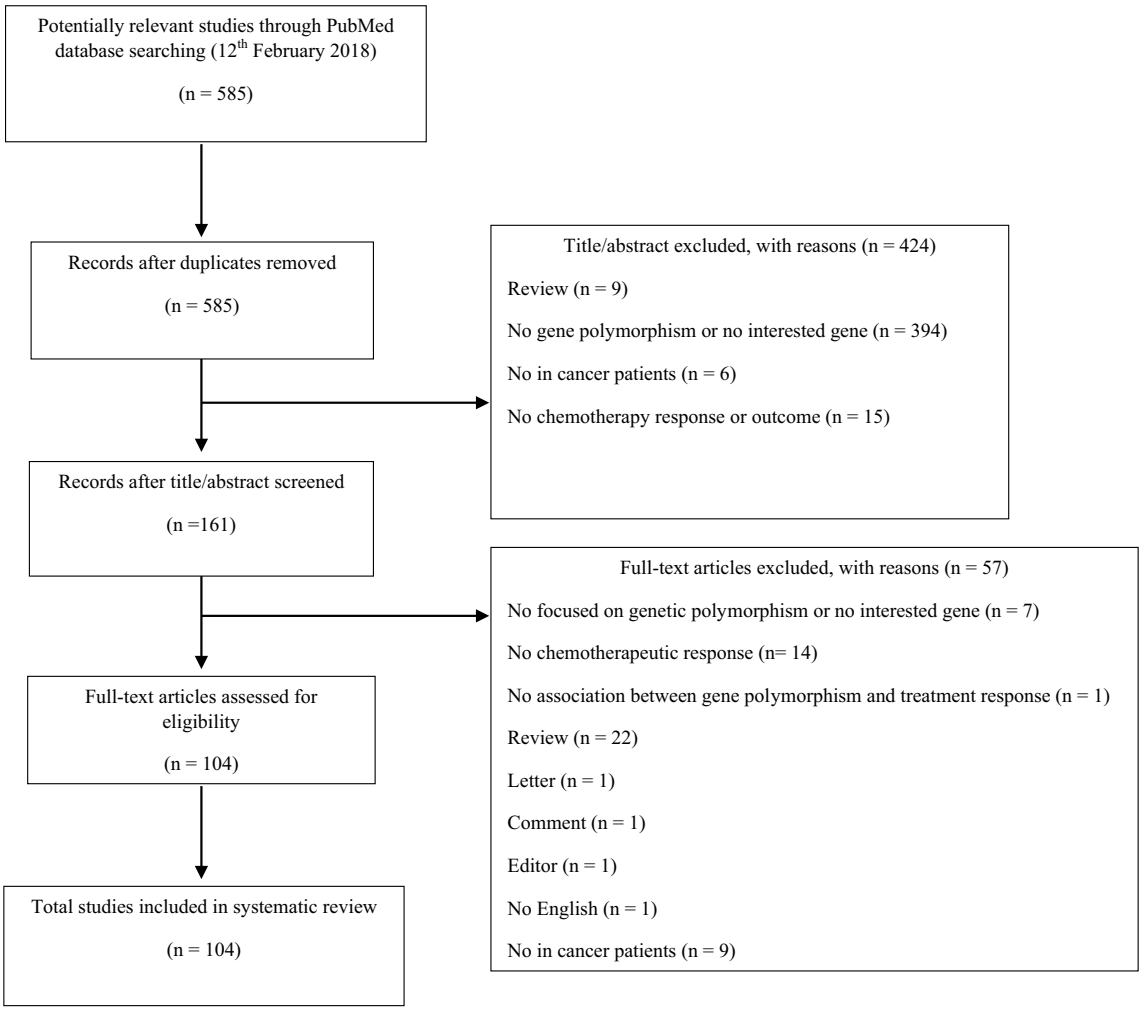

Fig. 1 Flowchart of study selection

association between clinical treatment outcomes and polymorphisms of the ATP-binding cassette transporter (ABC transporter) genes ABCB1, ABCG2, ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, ABCC10, and others. One, 4, 2, 1, 1, 1, 1, 5, 1 and 3 studies, respectively, were related to the investigation of the association between clinical treatment outcomes and polymorphisms of the solute carrier transporter (SLC) genes SLC15A2, SLC19A1, SLC22A1, SLC22A4, SLC22A16, SLC23A2, SLC29A1, SLCO1B1, SLCO1B3, OCT, and others. For CYP enzymes, 1, 1, 5, 6, 8, 1, 3, 1, 1, 1, 3, 2, 7, 6, 14 and 1 studies, respectively, were related to the investigation of association between clinical treatment outcomes and polymorphisms of CYP1A1, CYP1A2, CYP2A6, CYP3A4,CYP3A5, CYP17A1, CYP19A1, CYP24A1, CYP39A1, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and combination of CYP2C19/CYP2D6 genes. Table 1 summarizes the number of studies related to the three groups of genes at each SNPs. Association between ABC transporter, SLC transporter and CYP gene polymorphisms and clinical treatment outcomes (tumor response, survival time, and toxicity) is summarized in Online Resource (Supplementary Tables 1, 2, 3, respectively).

Association between polymorphisms of ATP-binding cassette transporter genes and clinical outcomes

ABCB1 gene

ABCB1 (P-glycoprotein, multidrug resistance 1) is a transmembrane protein that encodes a P-glycoprotein (P-gp) which acts as an energy-dependent drug efflux pump that decreases intracellular drug accumulation, thereby decreasing the effectiveness of many chemotherapeutic agents [15]. P-gp is expressed not only in cancer cells, but also in normal tissues such as kidney, liver, small and large intestine, brain, testis, adrenal gland, and pregnant uterus. Its expression influences the activity and distribution of different drugs [16]. The ABCB1 1236C>T, 2677G>T/A, and 3435C>T SNPs are three most common nonsynonymous and synonymous SNPs studied [6, 17–45].

1236C>T SNP: The 1236C>T SNP is the synonymous polymorphism found in exon 12 with no change in the encoded amino acid sequence of P-gp but surprisingly, may influence P-gp expression and/or function [16]. Several studies have demonstrated that not all synonymous SNPs are silent. They can induce modifications in protein expression, conformation, or function [46, 47]. It is possible that the glycine encoded by the synonymous 1236C>T SNP decreases the translational activity and may have an indirect effect on the mRNA stability in homozygous variants allele [42]. Unfortunately, all the included studies did not provide supporting data regarding this possible direct influence of the ABCB1 1236C>T polymorphism on P-gp function and/or expression level [22, 25, 30, 33, 36, 40, 42]. Two studies reported significant association between TT genotype and poor tumor response to chemotherapeutic drugs in patients with bone cancer compared with wild-type genotype [22, 25]. This may be explained by the increase in drug efflux from tumor cell and/or increase in drug elimination from the body, leading to a decrease in plasma drug concentrations and thus clinical efficacy [22, 25]. A significant association between 1236C>T polymorphism and progression-free survival (PFS) was also found in patients with advanced non-small cell lung cancer (NSCLC) patients after treatment with platinating agents and paclitaxel [36]. Moreover, two studies reported significant association between patients with bone cancer with TT genotype and short overall survival (OS) after doxorubicin plus cisplatin, methotrexate, and vincristine treatment compared with those with wild-type genotype [22, 25]. Similarly, the T allele (CT or TT genotype) in patients with prostate cancer was significantly associated with short OS after docetaxel/thalidomide combination therapy compared with wild-type genotype [40]. However, two studies reported association between T allele and long OS in patients with osteosarcoma and de novo natural killer-acute myeloid leukemia (NK-AML) after treatment with cisplatin/adriamycin, methotrexate, vincristine, and cyclophosphamide/daunorubicin [6, 33]. These conflicting results could be due to the increase in efflux pump associated with variant alleles which resulted in the decrease in chemotherapeutic drug efficacy [40]. The cancer cells such as prostate tumor cells overexpress *ABCB1* gene and, therefore, polymorphisms may determine the efflux activity rather than expression differences when the transporter protein is already up-regulated [40]. In some cancers like leukemia, on the other hand, the observed improvement in patients' survival time may be due to the decrease in drug efflux in cancer cells resulting in higher intracellular drug concentrations and anticancer effect [33]. A single study demonstrated that TT genotype was significantly associated with a decrease in docetaxel clearance in breast, lung, and prostate patients compared to wild-type genotype [42]. The homozygous synonymous C1236T polymorphism may have an indirect effect on mRNA stability and influence downstream mRNA splicing, processing, and translational regulation. More information is needed to identify the molecular biological characteristics of C1236T that result in altering P-gp function [48]. With regard to drug toxicity, significant association between TT genotype and a threefold decrease in the risk of neutropenia was reported in renal cancer patients who carried TT genotype after treatment with sunitinib compared with CT or TT genotype [30]. The homozygous variants allele of 1236C>T polymorphism resulted in an increased clearance of sunitinib and its active metabolite, thus decreasing drug exposure and toxicity [49].

Table 1 Summary of the number of the study in ABC transporter, SLC transporter and CYP gene polymorphisms

Gene	SNP	No. of studies	Gene	SNP	No. of studies
ABC transporter genes			SLC23A2	rs2681116 and rs13037458, rs4987219 and rs1110277	1
ABCB1	1236C>T	10	SLC29A1	rs324148	1
	2677G>T/A	14		rs9394992	1
	3435C>T	22	SLCO1B1	*5	1
	1199G>T/A	2		rs11045879 and rs4149081	1
	49303A>G (IVS9-44A>G or rs10276036)	1		rs11045879, rs4149081, rs11045818, rs10841753, rs11045872, rs17328763 and rs11045787	1
	rs10276036	1			
	rs4148737	1			
	rs7787082	1		rs4149056	1
	rs2235015	1		rs2291075	1
	rs6979885	1		rs2306283	1
	rs3213619	1	SLCO1B3	rs11045585	1
	rs60023214	1	OCT2 (SLC22A2)	rs195854	1
	rs60023214	1			
	rs4728709	1	TMEM205	rs896412	1
	ABCB1 haplotype	11	OCTN1	rs1050152	1
	SLC22A1/ABCB1 combination haplotype	1	hOCT1 (SLC22A1)	rs2282143	1
ABCG2	421C>A (Q141K or rs2231142)	7		M420del (rs35191146)	1
			Cytochrome P450 genes		
	34G>A (V12M or rs2231137)	3	CYP1A1	*2A	1
	421C>A/34G>A haplotype	1	CYP1A2	rs2069521 and rs4646425	1
	rs2231164	1	CYP2A6	*1	1
	rs13120400	1		*4, *7, *9, or *10	1
	rs4148157	1		Two-variant alleles (V/V)	1
	rs3109823	1		rs60823196	1
	rs12505410/rs2725252 haplotype	1		rs138978736	1
ABCC1	G2168A (R723Q or rs4148356)	1		H1, H3, H4 and H5 haplotypes	1
	G2168A	1			
	1684T>C	1	CYP3A4	*1B	3
	rs246240 and rs2238476	1		*3 (rs4986910)	2
ABCC2	−24C>T (rs717620)	4		rs4646437	1
	3972C>T	1	CYP3A5	*3 (rs776746)	8
	−24TT/3972TT	1	CYP17A1	rs2486758 (T>C)	1
	−24CC/3972CC	1	CYP19A1	rs60271534	1
	rs3740065	1			
ABCC3	rs4148416	1		rs700518	1
	rs4148416	1			
	211C>T (rs4793665)	1		rs4646	1
			CYP24A1	rs3787554 (C>T)	1
ABCC4	T1393C	1		rs2762939 (C>G)	1
	A934C	1	CYP39A1	rs7761731	1
ABCC5	rs939338	1			
ABCC10	rs2125739	1	CYP1B1	*3 (4326C>G)	1
ABCA5	rs536009	1			
Others ATP-binding cassette transporter genes					

Table 1 (continued)

Gene	SNP	No. of studies	Gene	SNP	No. of studies
ATP1B2 and ATP8B3	rs1642763 and rs8100856	1	CYP2B6	*2 (64C>T or rs8192709)	1
				*4 (785A>G or rs2279343)	1
				*5 (1459C>T or rs3211371)	2
ATP1A1 and ATP8B3	rs975351 and rs7249302	1		*6 (rs3745274)	2
				*8 (415A>G or rs12721655)	1
				*9 (516G>T or rs3745274)	1
SLC transporter genes			CYP2C8	*2 (805A>T)	1
SLC15A2	rs2257212	1		*3(416G>A or rs11572080)	2
SLC19A1	RFC(G>A)	1		*3 (K399R or rs10509681)	2
	IVS4(2117) C>T, IVS5(9148) C>A and exon6(2522) C>T	1		*4 (792C>G)	1
			CYP2C9	*2 (C430T or rs1799853)	4
SLC19A1	IVS2(4935) G>A	1	CYP2C9	*3 (A1075C)	4
	$G_{80}A$	1		rs17885098	1
	rs1051266	1	CYP2C19	*2	5
SLC22A1	rs683369	1		*3	2
	IVS6-878C>A (rs3798168)/1222A>G (rs628031)/ IVS7 + 850C>T haplotype	1		*17	2
			CYP2D6	Extensive metabolizers	5
SLC22A4	rs460089	1		Intermediate metabolizer	5
	rs460089/ rs2631365(SLC22A5)	1		Poor metabolizer	12
SLC22A16	T1226C	1	Combination of CYP2C19*2/CYP2D6*3, *4, *5, *6		1
	A146G, T312C and T755C	1			

2677G>T/A SNP: The 2677G>T/A polymorphism is a nonsynonymous and triallelic variant with the change of Ala at codon 893 to Ser/Thr change in exon 21 (ABCB1*10). It is located on the intracellular side of P-gp after transmembrane region 10 [50]. The occurrence of T allele is far more frequent than A allele [51]. The 2677G>T/A SNP was shown to be associated with the function of P-gp [21]. In addition, the C3435T polymorphism which is in linkage disequilibrium with C2677T SNPs was also shown correlated with altered P-gp activity [46]. Green et al. [19] reported significant association between homozygously mutated (T/T and T/A) and improved tumor response to paclitaxel in ovarian cancer patients compared with wild-type (GG or GT) genotype. It is possible that the G2677T/A SNP influences P-gp efflux activity and reduces the efflux of drug from the cancer cells or decreases elimination of drug from the body. These altogether result in higher plasma drug concentrations and cancer cells and, thus, improvement of tumor response [19]. In one study in patients with de novo AML, however, wild-type allele was significantly associated with an increased probability of complete remission after idarubicin/cytarabine combination therapy compared with those with or without one G-allele [21]. However, no association between P-gp activity of various genotypes (variant alleles or wild-type) on complete remission rate was observed. This is probably explained by the characteristics of chemotherapeutic drugs given, whether they are substrates or non-substrates of P-gp. Cautious interpretation is, therefore, needed when applying the results to different clinical situations [21].

Significant association between non-GG or variant genotypes and short event-free survival (EFS) was reported in patients with de novo AML after treatment with idarubicin/cytarabine combination therapy compared with wild-type genotype (GG) [21]. Additionally, two studies [38, 44] reported significant association between TT genotype and short EFS compared with wild-type (GG), GT, and other genotypes. When applying the multivariate model to the study [44], however, no such significant association was found. Similar to the study reported by Sissung et al. [40], patients carrying the variant alleles GT, GA and TT were significantly associated with short OS compared with wild-type genotype. Moreover, the heterozygous A allele was significantly associated with short OS and time to progression (TTP) in breast cancer patients after doxorubicin/

cyclophosphamide combination therapy compared with GT genotype [43]. One possible explanation is higher expression of ABCB1 in apical villi of enterocytes in patients with TT genotype for the 2677G>T/A SNP [52] which results in an increased drug efflux in the intestinal lumen with subsequently lower systemic drug exposure. Two studies [33, 35], on the other hand, demonstrated conflicting results. Significant association between T/A allele (GT, TA, and TT genotypes) and long OS and decreased recurrent rate was reported in patients with de novo NK-AML and ovarian cancer after daunorubicin/AraC and paclitaxel/carboplatin combination therapy, respectively compared with wild-type (GG) genotype. Reduction of P-gp expression was reported in the placenta of Japanese women carrying T/A alleles of the 2677G>T/A SNP compared with homozygous wild-type (GG) genotype [53]. This may lead to a reduction in drug efflux, higher intracellular drug accumulation and, consequently, improved responses to chemotherapy. Moreover, the TT genotype of the 1236T>C, 2677G4T>A and 3435C>T SNPs was associated with the decrease in imatinib clearance in patients with gastrointestinal stromal tumor or chronic myeloid leukemia compared with homozygous wild-type genotype [54]. Hepatic drug clearance study showed that patients with prostate, breast, lung, bladder, gastrointestinal stromal cancers and chronic myeloid leukemia (CML) with TT genotypes had a significantly lower rate of P-gp-mediated drug clearance than those with wild-type (GG) genotype [55]. The TT genotype was also significantly associated with an increased risk of relapse or resistance in acute lymphocytic leukemia (ALL) patients after treatment with mercaptopurine/methotrexate combination compared with non-TT genotypes [38]. It is possible that the apical villi of intestinal epithelial cells expresses ABCB1 at higher level in patients with TT genotype for the 2677G>T/A SNP [52] which result in increased drug efflux in the intestinal lumen and decreased systemic drug exposure.

With regard to drug toxicity, results from almost all studies indicated lower systemic drug exposure of anticancer drugs and subsequently less toxicity in individuals carrying T allele compared with wild-type and other variant alleles. The T allele was significantly associated with a threefold decrease in the risk of neutropenia in patients with renal cell carcinoma after treatment with sunitinib compared with other variants [30]. Increase in the clearance of sunitinib and its active metabolite was shown in renal cell, neuroendocrine tumors of the pancreas, and gastrointestinal stromal tumor of patients carrying 2677TT SNP [49]. This is supported by results of a study [32] showing that NSCLC patients with at least one variant allele were significantly associated with lower incidence of grade 4 neutropenia after treatment with irinotecan/cisplatin combination compared with wild-type. The 2677TT polymorphism is probably associated with higher drug efflux activity as evidenced by the lower area under the plasma concentration–time curve (AUC) and higher clearance of SN-38G [32]. Results of one study [40], on the other hand, showed significant association between slower development rate of neuropathy in prostate cancer patients with wild-type genotype after docetaxel/thalidomide treatment compared with those with at least one variant allele. Improved efficacy together with increased toxicity was involved with either increased or decreased drug exposure depending on the ABCB1 genotypes. The observation of the decrease in efficacy while toxicity is increased was observed in patients with variants alleles of 2677G>T/A [40]. It is likely that the variant alleles were associated with increased drug efflux activity in tumor tissues where ABCB1 is already overexpressed [40]. In endothelial and hematopoietic cells where ABCB1 is expressed at low level, these polymorphisms may affect drug penetration by altering gene expression which results in higher intracellular drug concentration and subsequently increased toxicity [40].

3435C>T SNP: The 3435C>T polymorphism is a synonymous SNP without amino acid change. This mutation is a wobble mutation that translates to isoleucine [51]. The correlation between homozygous T allele for 3435C>T SNP and low P-gp expression in the intestine compared with homozygous wild-type has been reported [56]. One possible explanation is that the 3435C>T polymorphism affects mRNA stability, protein expression, and protein conformation to substrate specificity [46]. No association of this SNP and clinical outcomes in ovarian cancer patients was found after treatment with paclitaxel [19]. This may suggest the influence of other functional nonsynonymous polymorphisms such as 2677G>T/A [46]. Linkage analysis in individual DNA samples showed a linkage between the G2677T/A and C3435T [19]. Similarly, the function of P-gp which is influenced by 1236C>T and 3435C>T polymorphisms signifies the importance of linkage disequilibrium [16]. Therefore, using the most frequent haplotype (1236C>T, 2677G>T, and 3435C>T) rather than a single SNP 3435C>T, may be a more useful approach for phenotype prediction [51].

Two studies [21, 24] reported that patients with de novo AML and advanced NSCLC carrying wild-type (CC) genotype had a significantly higher response rate following treatment with idarubicin/cytarabine and platinum-based therapy compared with CT and TT genotypes (84% vs. 59 vs. 60% and 24.5% vs. 19.0% vs. 12.5%, respectively). A significant association between TT genotype and poor tumor response was found in patients with breast cancer after anthracycline treatment compared with those with CT or CC genotype (33.3 vs. 71.4% vs. 70.6%) [20]. It is possible that the P-gp activity in patients with CC genotype was lower (7.5%) than that with CT or TT genotype (10.7% and 19.9%, respectively) [21]. This resulted in an increase in intracellular accumulation of chemotherapeutic agents. Nevertheless,

one study [17] found significant improvement in patients with advanced breast cancer who carried TT genotype after anthracycline treatment compared with CT genotype. The TT genotype was associated with lower MDR1 expression in the intestine compared with the CC genotype [56]. This results in a reduction in drug efflux into intestinal lumen and, therefore, increased plasma drug concentration.

Five studies [21, 37–39, 44] showed that patients with de novo AML, ALL, and gastric cancer who carried at least one T allele were significantly associated with short survival time after treatment with idarubicin/cytarabine, vincristine, 6-mercaptopurine/methotrexate, 5-fluorouracil, and taxane/irinotecan compared with wild-type genotype. Four studies [31, 41, 45, 57], on the other hand, reported significant association between T allele and long survival time in patients with breast cancer, advanced multiple myeloma, acute lymphoblastic leukemia, and advanced breast cancer with wild-type genotype after treatment with tamoxifen, bortezomib/doxorubicin, doxorubicin, and docetaxel/doxorubicin. Similar to that reported with G2677T/A and C1236T polymorphisms, one study [45] showed no significant difference in the survival time of patients with advanced breast cancer after docetaxel/doxorubicin treatment. Strong association was shown between the risk of relapse after doxorubicin treatment in ALL patients with 3435C>T but not with 2677G>A/T or 1236C>T polymorphism [31]. Despite the linkage disequilibrium between 1236C>T, 2677G>A/T and 3435C>T, only the 3435C>T polymorphism affects mRNA stability, protein expression, protein conformation to substrate specificity, and thereby alters P-gp activity [46].

Carriers of variant T-allele were shown to be associated with increased risk of B cell-lymphocytic leukemia (B-CLL) and low P-gp activity in the leukemic blasts compared with wild-type (CC) genotype (CC, CT and TT = highest, intermediate, and lowest P-gp activity, respectively) [34]. One possible explanation is an increased intestinal uptake and decreased renal elimination of carcinogens that are transported by P-gp due to lower P-gp expression in gastrointestinal and renal epithelia. Therefore, the MDR1 C3435T polymorphism may constitute one of the links between environmental and genetic factors in the pathogenesis of B-CLL [34]. On the other hand, lower P-gp activity and longer survival time (EFS) were reported in leukemic blasts in patients with wild-type compared with CT/TT genotypes (7.5% vs. 10.7% or 19.9%, respectively) [21]. As such, one interpretation of these findings is that lower P-gp activity in leukemic blasts leads to the increase in intracellular accumulation of chemotherapeutic agents. Interestingly, despite the assumed linkage disequilibrium between 1236C>T, 2677G4A>T and 3435C>T, only 3435C>T affects P-gp expression at mRNA levels [58]. Therefore, this SNP appears to be the main determinant of variation in ABCB1 mRNA expression in the liver [58].

For drug toxicity, three studies [31, 32, 45] reported significant association between TT genotype and increased toxicity (neutropenia, bone marrow toxicity, and diarrhea) in patients with advanced NSCLC, ALL, and advanced breast cancer after treatment with irinotecan/cisplatin, doxorubicin, and docetaxel/doxorubicin compared with wild-type genotype or those carrying at least one C allele. Hoffmeyer et al. [56] reported that the TT genotype of C3435T was associated with a reduction in P-gp expression and a decrease in cellular elimination and, thus, an increase in plasma drug concentrations and toxicity. However, one study [30] reported significant association between TT genotype and a tenfold decrease in the risk of neutropenia in renal cell carcinoma patients after sunitinib treatment compared with the CC/CT genotype.

ABCB1 diplotype and haplotype

Several studies investigated the impact of ABCB1 haplotypes on treatment outcomes of cancer patients to clearly define whether the association between gene polymorphisms and treatment outcomes was due to each single variant or the combination of the three major polymorphisms1236C>T, 2677G>T, and 3435C>T. The 3435T/2677T/1236T haplotype was shown significantly associated with lower response rates in breast cancer patients after anthracycline treatment compared with other haplotypes [20]. This was supported by the results of another study [18] in advanced colorectal cancer patients after irinotecan/5-FU treatment. Two studies [18, 40] demonstrated that patients with prostate or advanced colorectal cancer who carried 2677T-3435T or 1236T/2677T/3435T haplotype were significantly associated with shorter OS compared with 2677G/3435C or 1236C/2677G/3435C haplotype after treatment with docetaxel/thalidomide, and irinotecan/5-FU therapy. In another study [6], on the other hand, osteosarcoma patients carrying 1236T/2677T/3435T haplotype were significant associated with longer OS after cisplatin/adriamycin/methotrexate/vincristine/cyclophosphamide combination therapy compared with CGC haplotype. Three studies [30, 31, 40] reported significant association between 2677TT/3435TT or2677TT/1236TT haplotypes and the risk of neutropenia in patients with prostate cancer, renal cell carcinoma, and ALL after treatment with docetaxel/thalidomide, sunitinib, or doxorubicin compared with 2677GG-3435CC or 2677GG/1236CC haplotype. In one study, in particular [30], the 1236T/2677T/3435T haplotype was found to be significantly associated with a tenfold decrease in the risk of neutropenia in renal cell carcinoma patients after sunitinib treatment compared with other haplotypes. Two studies [29, 32] reported significant association between the 2677TT/3435TT or 2677TT/3435TT/1236TT haplotype and lower AUC of the active metabolite of irinotecan and

irinotecan in patients with advanced NSCLC, pancreatic, lung, ovarian and mesothelioma cancers, and cholangiocarcinoma compared with those with absence of this haplotype. Moreover, significantly higher P-gp efflux activity was shown in patients carrying 2677TT/3435TT haplotype compared with others [32].

ABCG2 gene

ABCG2, also known as breast cancer resistance protein or BCRP, is located on chromosome 4q22, forming dimers in the cell membrane, which then acts as the active transporter [59]. The protein is predominantly expressed in placenta and moderately expressed in the liver, small intestine, colon, ovary, kidney, and heart [60]. Two frequently occurring nonsynonymous SNPs in this gene are C421A (rs2231142, and Q141K) which encodes Gln141Lys and G34A (rs2231137, and V12M) which encodes Val12Met [23, 32]. These two SNPs alter P-gp transporter function by changing membrane localization and ATPase activity [60]. The ABCG2 mediates multidrug resistance to cancer cells against several chemotherapeutics such as SN-38 (an active metabolite of irinotecan), mitoxantrone, and topotecan [61].

421C>ASNP: Two studies [23, 27] reported that patients with breast cancer and chronic myelogenous leukemia who carried at least one C allele (CC/CA) were significantly associated with poor response to anthracycline-based chemotherapy and imatinib compared with AA genotype. In another study [59], the CA/AA genotype was significantly associated with short OS in primary lung cancer patients after treatment with etoposide, gemcitabine, and platinum-based drugs compared with CC genotype. The AA genotype was significantly associated with a threefold decrease in the risk of neutropenia in patients with renal cell carcinoma after sunitinib treatment compared with CC genotype [30]. On the other hand, the higher risk of developing breast cancer was reported in individuals with AA compared with CC genotype [23].

34G>ASNP: The GG genotype was shown to be significantly associated with poor response to imatinib therapy in chronic myelogenous leukemia patients compared with AA/AG genotype [27]. Breast cancer patients who carried AA genotype had longer OS after anthracycline-based therapy compared with GG/GA genotype [23]. Association between the AA/GA genotype and skin rash development was reported in NSCLC patients after gefitinib treatment compared with GG genotype [62]. Individuals with AA genotype were associated with a risk of breast cancer compared with G allele [23]. It appears that patients with AA, compared with wild-type genotype, were significantly associated with better response to anticancer therapy, longer overall survival time, increased risk of skin rash development, and increased risk of breast cancer development.

ABCC gene

ABCC or multidrug resistance-associated protein (MRP) is also known as ATP-binding cassette, subfamily C [57].

ABCC1: ABCC1 is highly expressed in the adrenal gland, bladder, choroid plexus, colon, erythrocytes, bone marrow, kidneys, lungs, placenta, spleen, stomach, testes, helper T cells, as well as muscle cells [63]. ABCC1 is overexpressed in lung, breast, prostate, and ovarian cancer, gastrointestinal carcinoma, melanoma, and leukemia [64]. It confers resistance against various anticancer drugs by reducing intracellular accumulation by co-export of drug with a reduction in glutathione level [65]. MRP1 mediates transport of certain xenobiotic substrates such as vincristine and VP-16 (etoposide) [65]. Two studies [1, 57] reported higher response rate after taxane/platinum therapy and short PFS after bortezomib/oxorubicin therapy in variance genotype of G2168A polymorphism compared with wild-type genotype.

ABCC2: ABCC2 is located on chromosome 10q24 and is expressed in liver, kidney, and small intestine [32]. It plays an important role in biliary excretion of organic anions and antitumor agents including irinotecan and cisplatin. The most common SNPs of this gene are 24C>T (promoter), 1249G>A (exon 10), and 3972C>T (exon 28) [32]. Carriers of the ABCC2–24C>T-T allele were shown to be associated with higher tumor response rate and longer survival time (PFS and OS) in patients with advanced gastric cancer and NSCLC after platinum/5-FU and irinotecan/cisplatin treatment compared with those carrying CC genotype [10, 32]. However, significant association between T allele and poor response was reported in all SCLC patients with shorter survival time (PFS and OS) compared with CC genotype [9]. The 3972C>T-CT genotype was significantly associated with higher tumor response rate and longer PFS in patients with advanced NSCLC patients after irinotecan/cisplatin treatment compared with CC/CT genotype [32].

ABCC3: ABCC3 mediates the efflux of organic anions, including metabolites conjugated with glucuronate, sulfate or glutathione such as etoposide–glucuronide [59]. Two studies [6, 25] showed that osteosarcoma patients who were carriers of the rs4148416-T allele were significantly associated with higher probability of poor response (95% CI OR 1.20–13.85) and shorter OS (95% CI HR 2.73–20.2) after the combination treatment of cisplatin, adriamycin, methotrexate, vincristine, and cyclophosphamide compared with CC genotype.

ABCC4: The TC genotype of T1393C polymorphism was significantly associated with longer EFS and lower methotrexate plasma levels in patients with acute lymphoblastic leukemia after 6-mercaptopurine/methotrexate treatment compared with TT genotype. The second polymorphism, A934C-AC genotype, was significantly associated with

longer EFS and increase in the frequency of grade 3 or 4 thrombocytopenia compared with TT genotype [66].

Association between SLC transporter gene polymorphisms and clinical outcomes

The carriers of the SLC19A1 rs1051266-GG and SLCO1B1 rs2306283-GG/AA genotypes were associated with the more rapid response rate in patients with metastatic colorectal cancer after irinotecan treatment compared with GA/AA and GG genotypes [4]. The GG genotype of SLC22A1-rs683369 polymorphism was significantly associated with higher rate of loss of response or treatment failure in patients with chronic myelogenous leukemia after imatinib treatment compared with CC/GC genotypes [27]. Three studies [67–69] reported the association between shorter survival time and the rs2257212 SNP in the SLC15A2, G80A SNP in the SLC19A1, and rs324148SNP in the SLC29A1 gene. Association between longer survival time and SLC19A1-IVS4(2117) C>T, SLC22A4-rs460089, SLC29A1-rs9394992, and SLCO1B1-rs2306283 polymorphisms was shown in four studies [4, 69–71] in patients with metastatic colorectal cancer, de novo AML, advanced NSCLC, and chronic myeloid leukemia (CML) after treatment with irinotecan, Ara-C, pemetrexed/bevacizumab, and imatinib. Significant association between the GG genotype of the SLC19A1-RFC polymorphism and lower plasma methotrexate concentrations was reported in ALL patients compared with other variant groups [72]. The AA genotype in SLC19A1-G80A SNP was significantly associated with higher plasma levels of methotrexate compared with GG/GA genotype [67].

Three studies [43, 70, 73] reported association between the risk of leucopenia and SLC19A1-IVS2G>A, SLC22A16-T1226C, SLC23A2-rs4987219, and rs1110277 SNPs in patients with breast cancer, advanced NSCLC, and esophageal squamous cell carcinoma after treatment with doxorubicin/cyclophosphamide, pemetrexed/bevacizumab, and 5-FU/cisplatin combination therapy.

Association between cytochrome P450 gene polymorphisms and clinical outcomes

Patients carrying CYP3A5*3, CYP19A1-rs4646 SNP, CYP1B1*3, CYP2C9*2, and CYP2C9*3 genotypes were significantly associated with poor response to chemotherapeutic drugs [27, 74–76]. Cancer patients carrying CYP1A1*2A, CYP3A4*1B, CYP19A1-rs4646, CYP1B1*3, CYP2B6*2 and *8, CYP2D6*10 (intermediate metabolizers) and CYP2D6*3, CYP2D6*4, CYP2D6*6 and CYP2D6*41 (poor metabolizers) were significantly associated with shorter survival time [43, 74, 75, 77–80]. Patients with gastric cancer with rs60823196 and rs138978736 SNPs in the CYP2A6 gene were significantly associated with higher risk of developing severe diarrhea after treatment with S-1/oxaliplatin compared with wild-type [81]. Two studies [7, 82] reported increased risk of neuropathy in patients with breast cancer carrying CYP2C8*3 after treatment with paclitaxel compared with wild-type genotype.

Four studies reported significant association between CYP2C9*3 polymorphism and tumor response and/or pharmacokinetics of anticancer drugs [77–80]. The reduction (19.7%) in the incidence of adenoma was shown after treatment with high dose compared with low dose celecoxib in patients with this polymorphism compared with wild type. The frequency of this SNP was higher in patients with head and neck squamous cell carcinoma (HNSCC) compared with healthy subjects. With regard to pharmacokinetic change, a 27% reduction in elimination rate and significantly higher AUC of indisulam was found compared with those carrying homozygous extensive metabolizers (*1/*1) following 600 mg/m^2 dose or more [76, 83–85]. Two studies [8, 76] reported that patients with CYP2C9*2 SNP were significantly associated with neoadjuvant chemotherapy resistance. In addition, the frequency of this SNP was found to be higher in HNSCC patients compared with healthy subjects.

The extensive metabolizers of CYP2D6 were significantly associated with a slight reduction in the AUC of TP3076 with a corresponding slight decrease in the AUC of TP3011 (active metabolite) and the risk of recurrence in Her2-neu-positive breast cancer patients who received adjuvant tamoxifen therapy [86, 87]. One study [88] demonstrated that intermediate metabolizers (CYP2D6*10 and *41) and poor metabolizers (**3*, **4*, and **6*) were significantly associated with increased risk of tamoxifen-induced hot flushes in patients with breast cancer compared with extensive metabolizers.

Discussion and conclusion

This systematic review provides current status of the information on the relationship between clinical treatment outcomes (efficacy and toxicity) and polymorphisms of genes encoding proteins involved in the pharmacokinetic processes of chemotherapeutic drugs, i.e., drug transporters and Phase I drug metabolizing enzymes CYP. Various studies reported conflicting results for the polymorphisms of the major genes and association with treatment outcomes in patients with various types of cancer. Nevertheless, among the investigated gene polymorphisms, it appears that the 1236C>T, 3435C>T and 2677 G>T/A SNP of the ABCB1 gene are the most promising determinants of clinical outcomes. Although, both of 1236C>T and 3435C>T polymorphism are synonymous SNPs [16, 51], several studies have demonstrated that not all synonymous SNPs are silent. They can

induce modifications in protein expression, conformation, or function of P-gp [46, 47]. Moreover, linkage analysis showed a linkage between the G2677T/A and C3435T [19]. Therefore, using the haplotype (1236C>T, 2677G>T, and 3435C>T) analysis rather than a single SNP may be a more useful approach for phenotype prediction. Strong evidence on the association between gene expression and P-gp activity was well demonstrated; the 3435C>T polymorphism was associated with lower P-gp activity as compared to wild-type [34]. In another study, however, 3435C>T SNP was reported to be associated with higher P-gp activity as compared to wild type [21]. Evidences of genetic polymorphisms of CYP and clinical treatment outcomes were reported. Some patients with CYP variants have been shown to experience unsatisfactory treatment response (efficacy and toxicity) with anticancer drugs [27, 43, 74–80], suggesting that variants are associated with either reduction or absence of CYP activity [89].

Controversial results reported in various studies may be due to several factors including difference in populations studied, sample size, tumor sites and stages, chemotherapeutic drug regimens, and evaluation parameters for efficacy and/or toxicity. Patients' ethnicity is an important factor which at least in part explains the discrepancies in various reports. For instance, lowest P-gp activity was reported in one study [34] in Caucasian patients who carried homozygous T allele for 3435C>T SNP compared with the CT and CC genotypes. On the other hand, lower P-gp activity was reported in Korean patients with leukemic blasts carrying wild-type genotype compared with CT/TT genotypes (7.5%, 10.7% and 19.9%, respectively) [21]. The possible explanation for such discrepancy could be differentiated in MDR1 processing, including transcriptional initiation, and RNA maturation [21]. Apart from the ethnic factor, study design and sample size also contributed significantly to results conclusion and interpretation. The number of patients included in various studies was as low as 15 or as high as 6640. Inadequate sample size significantly impacted statistical analysis and, thus resulted conclusion and interpretation. This is the limitation of most clinical studies particularly in cancer patients where the number of patients with each type of cancer who received treatment with each drugs is usually small. Difference in gene variants investigated in different studies also limited results interpretation and conclusion on the association between treatment outcome and gene polymorphisms. Furthermore, various studies applied different parameters for efficacy evaluation. In some studies [1, 4, 7, 17, 19, 20, 23, 24, 26, 27, 76, 90–94], only tumor response was used as an efficacy criterion, while others [9, 10, 18, 21, 22, 25, 32, 71, 72, 74, 75] used both tumor response and survival time as efficacy criteria. Even when tumor response was used for efficacy assessment, various definitions were applied. Some studies [22, 25] applied tumor response the extent of tumor necrosis, while others applied Response Evaluation Criteria in Solid Tumors (RECIST) and WHO criteria [1, 7, 9, 17, 18, 23, 24, 74, 91, 92, 94], percentage of tumor lesions [4, 20, 76], reduction of BCR/ABL fusion gene transcripts by quantitative PCR [26, 27, 71], percentage of blast cells in the bone marrow aspirates and biopsy including absolute neutrophil and platelets count [21], Becker's criteria [32], Sokal score [90], percentage of prostate-specific antigen [93], and reduction of serum PSA from baselines [75]. Furthermore, several survival parameters were used in various studies including overall survival (OS) [6, 9, 10, 18, 22, 23, 25, 30, 33, 37, 40, 43, 45, 59, 69, 75, 79, 95, 96], progression-free survival (PFS) [2, 4, 9, 30, 32, 36, 37, 39, 43, 57, 59, 68, 74, 75, 97–99], event-free survival (EFS) [6, 21, 38, 44, 66, 67, 71, 78, 96, 100], disease-free survival (DFS) [25, 69, 77, 80] or recurrence therapeutic [35, 72, 101] and toxic effects of chemotherapeutic drugs [7, 28–32, 36, 40, 43–45, 62, 66, 73, 81–83, 92, 97, 102–106]. Direct comparison of treatment efficacy among various studies was, therefore, difficult.

Polymorphisms of P-gp were generally associated with reduced drug efficacy (due to decreased drug accumulation in cancer cells) as well as reduced toxicity (reduced plasma drug concentrations as a consequence of accelerated drug elimination) [40]. This may be explained by the fact that the SNPs of P-gp may be evident only in cancer cells which overexpress P-gp. In addition, the association of P-gp and drug resistance may not necessarily be mediated through direct pumping of the active drug/metabolite out of tumor cells, but also through its functions as a transporter of signals to the cell cycle and programmed cell death [20]. Nevertheless, no such correlation was, on the other hand, observed in other studies [107]. Unfortunately, correlation with activity of P-gp was not investigated in almost all studies and, therefore, definitive conclusion cannot be drawn. Only two studies reported association between 3455 SNP and lower P-gp activity as compared to wild-type [34], while other study showed this SNP associated with higher P-gp activity when compared with wild type [21]. Apart from polymorphisms of genes involved in the transport of chemotherapeutic drugs, other factors could also influence treatment efficacy and safety. These include polymorphisms of protein targets of drug action and environmental factors.

The systematic review points to the possibility of individualized therapy of cancer chemotherapy based potential genetic determinants, i.e., polymorphisms in drug transporter and metabolism genes. Thorough understanding the role of pharmacogenetics could help establishing an individualized chemotherapy and patients benefit more from chemotherapy to prolong their lives. Further studies should be focused on these promising genetic markers and their association with clinical outcomes using standardized protocols.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest in this work.

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