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Pharmacogenetics and Cancer Treatment: Progress and Prospects

Munindra Ruwali

Abstract

The response of cancer patients to chemotherapy follows a very heterogeneous pattern. Pharmacogenetics is the study of inherited differences in interindividual drug disposition and effects, with the goal of selecting the optimal drug therapy and dosage for each patient. Pharmacogenetics for cancer treatment is very significant, as cancer therapies exhibit severe systemic toxicity and unpredictable efficacy. There is presence of genetic polymorphisms in the genes which code for the metabolic enzymes and cellular targets for the majority of chemotherapy agents, but to predict the outcome of chemotherapy in patients is not currently possible for most treatments. A greater understanding of the genetic determinants of drug response can revolutionize the use of many medications. By identifying the patients at risk for severe toxicity, or those likely to benefit from a particular treatment, individualized cancer therapy can be achieved for most cancer patients. The prediction of cancer treatment outcome based on gene polymorphisms is becoming possible for many classes of chemotherapy agents, and the most clinically significant examples of chemotherapy agents are discussed in the chapter. However, further studies are needed in well characterized and larger cancer populations with proper validation of pharmacogenetic markers in experimental settings before application in clinical routine diagnostics.

Keywords: cancer, pharmacogenetics, polymorphism, chemotherapy, genetic variations

1. Introduction

The treatment of cancer has witnessed major advances which have resulted from the recent revolution in medical interventions. It is commonly observed in clinical settings that the same doses of medication cause considerable variations in efficacy and toxicity across human populations [1, 2]. These variations can lead to unpredictable life-threatening or even lethal adverse effects in cases receiving the medications [3, 4]. Genetic factors are important determinants for drug efficacy and toxicity since the interindividual variability in drug response cannot be explained only by physiological, life style, age, comedication, etc. factors (**Figure 1**). Pharmacogenetics is the study of how genetic inheritance influences response to drugs. The term "pharmacogenetics" was coined in the 1950s, with the discovery that there is an inherited basis for differences in the disposition and effects of drugs and xenobiotics [5]. The studies found that antimalarial drugs and certain foods (soy beans) cause hemolytic reactions in patients with glucose-6-phosphate

dehydrogenase (G6PD) deficiency. The term pharmacogenomics and pharmaco-genetics are often used interchangeably. Pharmacogenetics was first used in the literature in 1997 and ever since the developments in this field have been greatly facilitated by rapid progress in molecular technology, in particular, high throughput DNA sequencing, microarrays and genotyping [6].
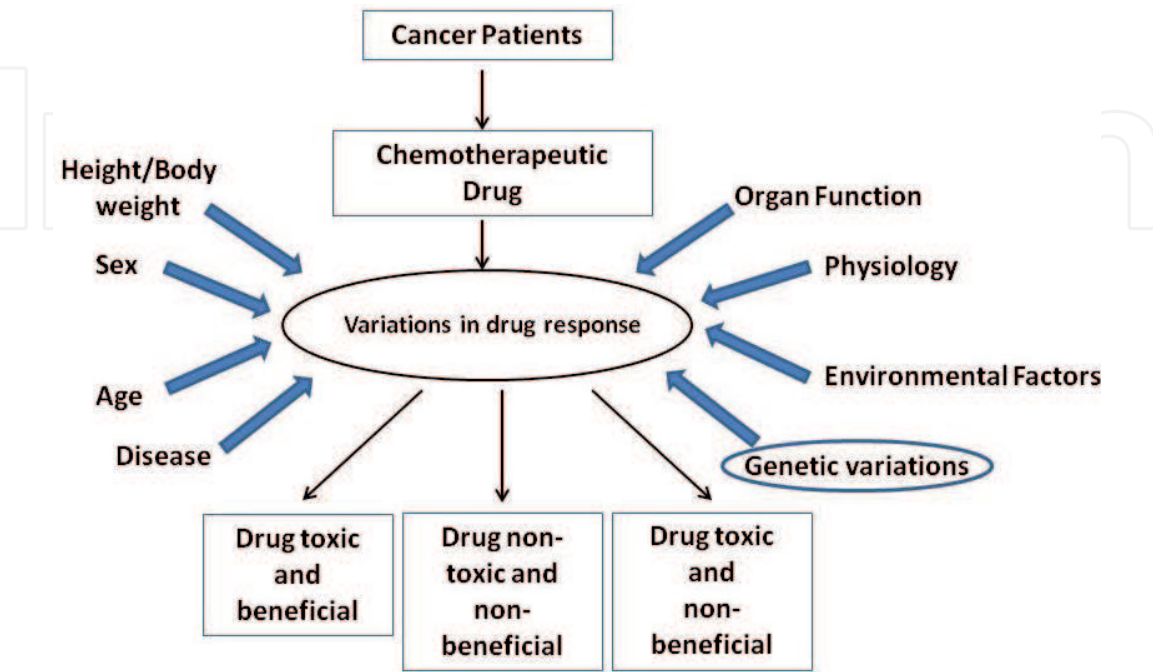

Figure 1.
Inter-individual variations in drug response.

Gene	Significant polymorphisms	Target drug	Action	Clinical relevance
TPMT	TPMT*2, *3A,*3B,*3C	6-Mercaptopurine (6-MP)	Increased levels of 6-MP	Myelotoxicity
DPD	DPD*2A	5-FU	Increased levels of 5-FU	Neurologic, hematological toxicities
UGT1A1	UGT1A1*28	Irinotecan	Increased levels of SN-38	Severe diarrhea, neutropenia
GST	Deletion, Ile105Val	Platinum agents	Increased DNA damage	Drug toxicity increased
XRCC1	Arg194Trp, Arg280His, Arg399Gln	Platinum agents	Increased DNA damage	Drug toxicity increased
ERCC1	K751Q	Platinum agents	Increased DNA damage	Drug toxicity increased

TPMT: thiopurine S-methyltransferase, DPD: dihydropyrimidine dehydrogenase, UGT1A1: UDP glucuronosyltransferase family 1 member A1, GST: glutathione S-transferase, XRCC1: X-ray repair cross complementing 1, ERCC1: excision repair 1, endonuclease non-catalytic subunit.

Table 1.
Pharmacogenetic biomarkers and their clinical impact.

Cancer	Biomarkers	Drugs
Breast	HER2	Trastuzumab, lapatinib
	ESR1	Exemestane, letrozole
Colorectal	KRAS	Cetuximab, panitumumab
	EGFR	Cetuximab, panitumumab
	DPD	5-Fluorouracil, capecitabine
	UGT1A1	Irinotecan
Lung	ALK	Crizotinib, ceritinib
	EGFR	Erlotinib, gefitinib
Gastrointestinal stromal tumor	c-Kit	Imatinib
Melanoma	BRAF	Vemurafenib, dabrafenib, trametinib
Pancreatic	EGFR	Erlotinib
Head and neck	EGFR	Cetuximab
Acute promyelocytic leukemia	PML-RARα	Arsenic trioxide, tretinoin
Cutaneous T-cell lymphoma	CD-25/IL2RA	Denileukin diftitox

HER2: human epidermal growth factor receptor 2, ESR1: estrogen receptor 1, KRAS: Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, EGFR: epidermal growth factor receptor, DPD: dihydropyrimidine dehydrogenase, UGT1A1: UDP glucuronosyltransferase family 1 member A1, ALK: anaplastic lymphoma receptor tyrosine kinase, c-Kit: stem cell growth factor receptor, BRAF: B-Raf proto-oncogene, PML-RARα: promyelocytic leukemia/retinoic acid receptor alpha, CD-25/IL2RA: cluster of differentiation 25/interleukin 2 receptor subunit alpha.

Table 2.
Cancer pharmacogenetic biomarkers in FDA drug labelling.

Cancer pharmacogenetics has started getting a lot of attention due to the potential for individualisation of cancer therapy, minimizing toxicity, while maximizing efficacy. Cancer pharmacogenetics allows identification of patients at risk for severe toxicity, or those likely to benefit from a particular treatment and thus helps us move toward the ultimate goal of individualized cancer therapy. There are significant differences between cancer and other disease pharmacogenomics. In cancer, both germline genome of the patient and the somatic genome of the tumor are involved. The former is responsible for the inter-individual inherited genetic differences while the latter is due to accumulation of acquired somatic mutations resulting in inconsistent responses. Cancer pharmacogenomics also faces the problem of conducting human studies, availability of healthy volunteers for receiving cancer drugs and multigenic control of drug response. **Table 1** lists some of the major biomarkers which are associated with cancer treatment toxicities while **Table 2** lists some of the biomarkers associated with cancer treatments mentioned in US FDA-approved drug labels.

2. Candidate genes

The prediction of cancer treatment outcome based on gene polymorphisms is becoming a reality for many classes of chemotherapy agents, and the most clinically significant examples are discussed below.

2.1 Thiopurines

Thiopurines are a family of drugs that includes 6-mercaptopurine (6-MTP) which is a daily component of maintenance therapy for childhood acute

lymphoblastic leukemia treatment [7], thioguanine and azathioprine. There are three major metabolic pathways for 6-MTP namely activation of 6-MTP into 6-TGN (activating and cytotoxic route for thiopurines) by hypoxanthine guanine phosphoribosyl transferase (HGPRT), inactivation of 6-MTP into thiouric acid via oxidation catalyzed by xanthine oxidase and inactivation of 6-MTP via S-methylation of the thiol moiety in the liver and red blood cells by thiopurine methyltransferase (TPMT). This methylation shunts the active drug away from TGN formation. Thiopurines are inactive prodrugs that require metabolism to thioguanine nucleotides (TGN) to exert cytotoxicity by incorporation of TGN into DNA. This activation is catalyzed by methylation by thiopurine methyltransferase (TPMT) of the thiopurine agents azathioprine, mercaptopurine, and thioguanine [7, 8], thereby shunting drug away from TGN formation. Genetic variants present in TPMT may alter the treatment response in cases receiving chemotherapeutic drugs. TPMT exhibits huge variations in enzyme activity with a major portion of population (90%) exhibiting high activity while about 10% have intermediate activity, and 0.3% have low or no detectable enzyme activity [9, 10]. Out of several genetic variants, TPMT*2 (238G>C), *3A (460G>A and 719A>G), *3B (460G>A), and *3C (719A>G) account for about 95% of intermediate or low enzyme activity cases [7, 11–14]. Caucasians have more prevalence of TPMT polymorphisms and a trimodal distribution of TPMT enzyme activity while southeast Asians have less prevalence and a unimodal distribution [15–17].

Several studies have shown that TPMT-deficient patients are at very high risk of developing severe hematopoietic toxicity if treated with conventional doses of thiopurines [18, 19]. Studies have also been carried out to show that patients who are heterozygous at the TPMT locus are at intermediate risk of dose-limiting toxicity [20, 21]. In one of our studies, a poor treatment response was observed in head and neck cancer patients receiving chemotherapy with cisplatin and 5-FU which might be due to the higher intracellular concentration of cisplatin due to lower or intermediate TPMT enzyme activity [22]. Liu et al. [23] examined primary erythrocyte TPMT activity in children with leukemia in a genome-wide association study and found that TPMT was the only gene that reached genome-wide significance. In another study of 67 patients treated with azathioprine for rheumatic disease, 6 patients (9%) were heterozygous for mutant TPMT alleles, and therapy was discontinued in 5 of 6 patients because of low leukocyte count within 1 month of starting treatment [20].

2.2 5-Fluorouracil (5-FU)

5-Fluorouracil (5-FU) is a uracil analog that is widely used to treat solid tumors, such as colorectal and breast cancer and requires activation to 5-fluoro-2-deoxyuridine monophosphate (5-FdUMP). At least 85% of 5-FU is inactivated by dihydropyrimidine dehydrogenase (DPD) to dihydrofluorouracil in the liver. [24] 5-FdUMP acts by inhibiting the tumor cell replication via inhibition of thymidylate synthase (TS), an enzyme that is required for de novo pyrimidine synthesis. DPD inactivates 5-FU in the liver and has huge differences in activity among individuals leading to excessive amounts of 5-FdUMP in patients with low activity which causes gastrointestinal, hematopoietic, and neurological toxicities [25–32].

The DPD gene has several reported polymorphisms associated with reduced DPD activity [32, 33]. In general, 3–5% of individuals are heterozygous carriers of mutations that inactivate DPD, and 0.1% of individuals are homozygous for mutations that inactivate DPD [27, 34–36]. DPD*2A allele is caused by a G>A transition at a GT splice donor site flanking exon 14 of the DPD gene (IVS14+1G>A). A decreased DPD activity has been found to be associated with severe or fatal

toxicity from standard doses of 5-FU [37]. Another mutation at codon 534 leads to a 1601G>A nucleotide change. In one of our study, head and neck cancer patients exhibited a poor treatment response which had IVS14+1G>A genetic variant. [22] Similarly, it was also reported that IVS14+1G>A was associated with increased toxicity and poor treatment response in patients of invasive ductal carcinoma and head and neck cancer. Zhao et al. [38] found that DPD variant c.85T>C (rs1801265, DPYD*9A) was associated with treatment outcome in acute lymphoblastic leukemia.

2.3 Irinotecan

Irinotecan, a topoisomerase I inhibitor, is used to treat various solid tumors, and requires activation by carboxylesterase to its active metabolite, SN-38. The toxicities associated with Irinotecan, namely diarrhea and leucopenia, are due to increased levels of SN-38. UDP-glucuronosyltransferase 1A1 (UGT1A1) present in liver metabolizes SN-38 by glucuronidation to produce the more polar and inactive SN-38 glucuronide, which is removed in the bile and urine [39]. In chemotherapy, a decreased rate of glucuronidation has been shown to be an important factor in prediction of toxicity. The rate of glucuronidation is reduced as a consequence of reduced transcription rate due to abnormal dinucleotide repeat sequences (5–8 repeats) within the TATA box of the UGT1A1 gene promoter [40]. An inverse relationship exists between the number of TA repeats and the UGT1A1 transcription rate. The variant allele UGT1A1*28 results from the presence of seven repeats, instead of the wild-type number of six. The UGT1A1*28 allele is associated with reduced UGT1A1 expression, and leads to reduced SN-38 glucuronidation [41].

(TA)n TAA promoter polymorphisms are more frequent in Caucasians than in Asians which have more missense polymorphisms in the exons [42]. Studies have shown that the UGT1A1*28 allele leads to significantly increased amounts of the active metabolite SN-38, and consequently an increased chance of developing side effects such as diarrhea and leukopenia during irinotecan therapy. [41, 43]. In one study of 20 patients with solid tumors treated by irinotecan, severe toxicity was observed in UGT1A1*28 heterozygotes and homozygotes [41]. In another retrospective study of 118 cancer patients treated with irinotecan, a significant proportion of the 26 patients suffered from severe diarrhea or neutropenia. Upon examination, all 26 were UGT1A1*28 homozygotes or heterozygotes (15 and 31%, respectively), whereas only 3% UGT1A1*28 homozygotes and 11% UGT1A1*28 homozygotes were found among 92 patients without toxicity [43]. Font et al. [44] reported that 34% of non-small cell lung carcinoma (34%) patients with the common genotype achieved disease control (partial response or stable disease) compared with 13 of 24 patients (54%) with the variant genotypes.

2.4 Platinum agents

Platinum agents like cisplatin, carboplatin and oxaliplatin act by inhibiting cell replication as a result of formation of DNA adducts. However, sometimes the effect of platinum agents is compromised as a result of decreased drug accumulation, detoxification, reduced or no DNA adduct formation and an increased activity of DNA repair system. One of the factors that can influence response to platinum chemotherapy agents is polymorphisms in glutathione (GSH)-dependent enzymes. Glutathione-S-transferases (GSTs) catalyze the conjugation of GSH to platinum agents, forming less toxic and more water-soluble conjugates. There are five subclasses of the GST family (GSTA1, GSTP1, GSTM1, GSTT1, and GSTZ1) [61] that influence cytotoxicity to a variety of chemotherapeutic agents [45].

Several genetic variants exist in the GSTs which may lead to complete absence (GSTM1 and GSTT1) or partially deficient enzyme (GSTP1) activity. Ethnic differences are reported in the distribution of null or variant allele frequencies of GSTM1, GSTT1 and GSTP1. Studies from our laboratory have shown association of polymorphism in drug metabolizing cytochrome P450s (CYPs) and GSTs with head and neck cancer [46]. Studies also revealed significant increase in head and neck cancer risk in cases with null genotypes of GSTM1 or GSTT1, though inconsistent reports are also available. Likewise, no consistent data is available on the association of GSTP1 polymorphism with head and neck cancer risk [47]. Further, site specificity is also reported in the expression of GSTs in the squamous mucosa of head and neck which may lead to the differences in the susceptibility when analyzed according to the tumor location. An association between the GSTM1 and GSTT1 null genotype for non-laryngeal upper aero-digestive tract (UADT) or oral cancer risk was reported in smokers or tobacco chewers. In contrast, no site specific differences in the distribution of GST variant forms have also been observed in few studies [48].

The null genotypes for GSTM1 or GSTT1 were associated with a reduction in risk of relapse in several tumor types treated with chemotherapy such as acute lymphoblastic leukemia, acute myeloblastic leukemia, breast cancer, ovarian cancer, and lung cancer. In addition to null phenotypes, single nucleotide polymorphisms (SNPs) also affect response to chemotherapy and survival of patients as seen in breast cancer patients with an I105V SNP in the GSTP1 gene. Women with the low-activity VV genotype had better survival upon cyclophosphamide-based chemotherapy [49]. Dasgupta et al. [50] compared the role of the I105V genotype in multiple myeloma treated with standard or high dose chemotherapy and found that the patients with the 105VV homozygote allele had an improved progression free survival. The substitution of isoleucine with valine at position 105 reduces enzyme activity against alkylating agents. Stoehlmacher et al. [51] showed that SNP in GSTP1 was associated with overall survival in 107 patients with metastatic colorectal cancer who received 5-FU/oxaliplatin combination chemotherapy. In this study, 10 patients (9%) were homozygous for valine, 45 patients (42%) were heterozygous, and 52 (49%) were homozygous for isoleucine. Interestingly, GSTM1 and GSTT1 mutations that abolish enzyme activity had no predictive power for patient outcome.

Anticancer agents act by causing DNA damage in tumor cells which is subsequently repaired by the DNA repair machinery of the cell. Thus, more the active DNA repair system, less will be the treatment outcome. XRCC1 is a prominent gene involved in DNA repair via the base excision repair pathway which repairs single strand breaks through interaction of XRCC1 with PARP-1, PNK, Polb, and Lig3a [52]. XRCC1 has several genetic variants out of which the prominent ones are Arg194Trp on exon 6, Arg280His on exon 9, and Arg399Gln on exon 10 [53]. A study conducted by Quintela-Fandino et al. [54] in head and neck cancer cases found that XRCC1 Gln/Gln was responsible for 61.5% of cases with complete response. The role of XRCC1-Gln399Gln genotype was also investigated by Duell et al. [55]. It was reported that the allele results in high rate of sister chromatid exchange after exposure to ionizing radiation in human lymphocytes. There are also reports which suggest the role of XRCC1 G28152A Arg399Gln polymorphism in development of lower grade of fibrosis as a result of radiotherapy in 60 nasopharyngeal cancer patients [56]. Mahimkar et al. [57] studied clinical outcome in advanced oral cancer patients treated with postoperative radiotherapy and did not observe a significant association between polymorphisms of XRCC1 and clinical outcome. Zhai et al. [58] observed that Codon399 Gln/Gln allele was associated with a higher tumor regression ratio after radiotherapy for primary nasopharyngeal

neoplasm and metastatic lymph nodes. Ghazali et al. [59] conducted a systematic review and found that risk of severe acute mucositis was associated with the G allele of XRCC1 (1196A>G) in head and neck cancer patients treated with radiotherapy alone or chemotherapy.

Excision-repair cross-complementing 1 (ERCC1) gene encodes a helicase which is required for the nucleotide excision repair pathway. Several polymorphisms in ERCC1 which result in differing DNA repair capacities have been identified. Lowered mRNA production was observed as a result of a silent C118T SNP in ovarian carcinoma cell lines [60]. The TT genotype resulted in a reduction in codon usage by half with a reduction in ERCC1 mRNA production and therefore be associated with reduced DNA repair capacity [61]. Platinum is a standard chemotherapy for advanced non-small cell lung cancer (NSCLC), and platinum-induced DNA lesions are repaired by ERCC1. Studies have shown that patients homozygous for the ERCC1 118C allele demonstrated a significantly better survival. In colorectal carcinoma patients treated with 5-fluorouracil and oxaliplatin, the K751Q SNP of the ERCC2 (Xeroderma pigmentosum group D gene, XPD) determined in peripheral blood lymphocytes was of prognostic relevance. The patients having KK homozygotes responded more frequently to chemotherapy and lived significantly longer than did heterozygotes or QQ homozygotes [62]. Time to progression was significantly higher in cisplatinum-treated patients with non-small cell lung cancer harboring the K751Q ERCC2 genotype than those harboring the K751K genotype. However, contradictory results on the association of ERCC2/XPD variant alleles with decreasing overall survival of non-small cell lung cancer patients after cisplatinum-based therapy were also reported [63]. A nonsynonymous SNP, altering a lysine to glutamine at codon 751 of the XPD protein, was significantly associated with treatment outcome in patients with metastatic colorectal cancer [62].

3. Pharmacogenetics: challenges and next generation approaches

The current pharmacogenetics approaches face many stumbling blocks. Candidate gene-based approaches do not provide a reliable prediction of tumor drug response and normal tissue toxicity because of a lack of understanding of the precise role of all participating factors. Genome wide association study provide a more robust platform for pharmacogenetic analysis as has been demonstrated by Watters et al. [64]. A number of other issues plague SNP genotyping in the clinical settings such as quality control which is due phenotypic heterogeneity, a long duration involved in validation of pharmacogenetic markers in experimental settings, the combined effects of many low-risk polymorphisms, selection of the most appropriate panel of SNPs, analyzing the correlation between genotype, gene expression, and enzyme activity, criteria for risk assessment and thresholds, consideration of ethnic variations as the distribution and frequency of SNPs vary among different ethnic groups which makes it difficult to extrapolate the findings of one group on another [65]. Newer targeted therapies are also gaining popularity. Trastuzumab (herceptin), a humanized recombinant monoclonal antibody (IgG) targets Human Epidermal Growth Factor Receptor 2 (HER2), Gefitinib (Iressa) inhibits the tyrosine kinase activity of the Epidermal Growth Factor Receptor, Bevacizumab (Avastin) is an anti-angiogenesis agent, the addition of which to standard chemotherapy regimens has shown improved response rates and survival rates in the treatment of metastatic colorectal cancer [66]. Likewise, Cetuximab (Erbitux), a monoclonal antibody, targeting EGFR has also shown promising results in colorectal cancer and head and neck cancers.

Future developments in some key areas will play a critical role in deciding the overall influence of pharmacogenetics data on therapeutic decisions. Improvements are needed in genome-wide technologies such as development of gene expression arrays, high throughput technologies, SNP chips, genome-wide scans which could potentially identify previously unidentified, functionally important candidate genes and SNPs. Mouse models could be used for genome-wide scans in offspring from phenotypically distinct mice from resistant and susceptible strains. Knockout and transgenic techniques could also be used for establishing the key elements that contribute to drug response and disposition. Candidate gene approach could be enhanced by knowledge gained from genome wide techniques and by incorporating a metabolic pathway approach. The cost of SNP/genomic technology should reduce which needs to be counterbalanced by the huge costs incurred due to adverse drug reactions/toxicities. For inclusion of a genetic test into clinical practice, it must provide reliable, predictive, and actionable information that would have otherwise been unknown [67]. Before clinical implementation, strong evidence from randomized controlled clinical trials is needed.

The future of pharmacogenetics should focus on specimen collection of both germline and tumor DNA from early and later phase clinical trials with prospectively collected efficacy and toxicity data which will be vital in the discovery and validation of pharmacogenomic associations. At next steps, genes that have undergone replication and validation should be assessed for clinical implementation. A large retrospective case-control validation and replication studies and Phase II biomarker-driven clinical trials may allow for a more efficient and rapid method of translation from bench to bedside.

4. Conclusions

The major problems of cancer chemotherapy are the development of drug resistance and the severe side effects. Since many chemotherapeutic agents have modest tumor specificity, normal tissues are also damaged. This prevents the application of sufficient high doses of drugs to eradicate the less sensitive tumor cell populations. Thereby, tumors develop drug resistance that leads to treatment failure and fatal consequences for patients. Genetic variations in genes have explained a great deal of interindividual variation in response and toxicity of anticancer drugs. Cancer treatment utilizes multiple therapeutic agents with a wide variety of toxicities, often with narrow therapeutic indices. Pharmacogenetics has the potential to revolutionize cancer therapy. Though there has been substantial success in situations where single genes play a large role in overall drug response, the future of cancer treatment lies in whole-genome approaches. Reduction of the toxicogenetic and toxicogenomic side effects has been one of the major goals in the search for new anticancer drugs and therapy protocols. SNP genotyping should be introduced into clinical settings to facilitate clinical decision making regarding treatment strategies to avoid adverse drug reactions while achieving the best drug response. Few of the studies discussed do provide a stronger scientific basis for the use of genomic information for the individualization of cancer therapy based on a patient's genetic profile.

Conflict of interest

The author declares no conflict of interest.

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