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Pharmacogenetics in oncology: Where we stand today?

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ABSTRACT

In a given population, there is considerable variation between individuals with regard to response to as well as toxicity of different drugs. The term "Pharmacogenetics" has largely been used in relation to genes determining drug metabolism, while "Pharmacogenomics" is a broader based term that encompasses all genes in a genome that may determine drug response. In oncology, efficacy and safety of many chemotherapeutic drugs show substantial individual and/or population variability. It can be explained, to a great extent, by gene polymorphism encoding drug-metabolizing enzymes, drug transporters, and drug targets which influence the pharmacokinetics and pharmacodynamics and affect clinical outcomes. Single nucleotide polymorphisms (SNPs) are the most studied genetic variants at present due to ease, accuracy, and reduced the cost of processing as well as due to public availability of online resources for SNPs. Candidate genes for a therapeutic and adverse response can be divided into three categories: Pharmacokinetic, receptor/target, and disease-modifying. Many anticancer drugs are evaluated for their variation in response according to germline variations. This information can be easily incorporated in day-to-day practice to improve efficacy and/or safety of these drugs. In the future, advances gained from pharmacogenetics research will provide information to guide doctors in advising just enough of the right medicine to a person – The practice of "personalized medicine."

Key words: Pharmacogenetics, Pharmacogenomics, Oncology

Introduction

In a given population, there is considerable variation between individuals with regard to response to as well as toxicity of different drugs. Modern medicine aims to utilize various drugs with maximum benefit and minimum or acceptable toxicity. Pharmacogenetics is defined as the study of variability in drug response due to heredity.[1] It studies the variability in candidate genes involved in drug metabolism, transport, or molecular targets/pathways.[2] More recently, the term pharmacogenomics has been introduced. The term "Pharmacogenetics" has largely been used in relation to genes determining drug metabolism, while "Pharmacogenomics" is a broader based term that encompasses all genes in a genome that may determine drug response.[1] Today, the two terms are used interchangeably in most scenarios. In the pre-genomics era, the frequency of genetic variation was thought to be relatively low, and the inherited drug response traits were demonstrated in a relatively small number of drugs and pathways. It was limited to some well-known examples of pharmacogenetics, e.g., prolonged neuromuscular blockade to normal succinylcholine doses, incidences of methemoglobinemia in people with deficiency of enzyme G6PD after intake of few medicines such as primaquine or neurotoxicity following isoniazid therapy. However, after the demonstration of phenotypic polymorphism of cytochrome P450 2D6 (CYP2D6) enzyme, many monogenic pharmacogenetic variations have been identified.[3] So far, the USFDA has recommended pharmacogenomic consideration or package insert labeling for more than 120 drugs with relationships to >50 genes.[2]

Rationale of use of Pharmacogenetics in Oncology

Most anticancer medications have narrow therapeutic indices low overall response rates, rapid and severe systemic toxicity and unpredictable efficacy. Therefore, nowhere is pharmacogenomics research needed more than in cancer treatment to guide clinicians to better predict the differences in drug response, efficacy, resistance and toxicity among chemotherapy and targeted therapy patients, and to optimize the treatment regimens based on these differences.[4]

In oncology, efficacy and safety of many chemotherapeutic drugs show substantial individual and/or population variability. It can be explained, to a great extent, by gene polymorphism encoding drug-metabolizing enzymes, drug transporters and drug targets which influence the pharmacokinetics and pharmacodynamics and affect clinical outcomes.[5,6] There are several known genes which are largely responsible for variations in drug metabolism and response. The most common are the CYP genes, which encode enzymes that influence the metabolism of more than 80% of current prescription drugs.

In addition, the application of pharmacogenomics in oncology is in the discovery of biomarkers that guide selective therapy,

predict toxicities, and target the mechanisms of drug resistance. The American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines recommend treatment regimens based on selective biomarkers for common cancers such as colorectal, lung, breast, melanoma, and certain leukemias. Common biomarkers screened for nonsmall cell lung cancer are epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations. Based on amplification and/or mutation of the receptor, the targeted agents recommended in the guidelines are cetuximab or panitumumab for EGFR amplification positive; erlotinib or afatinib for EGFR mutation positive patients; dabrafenib, vemurafenib, or trametinib for BRAF mutations; crizotinib and ceritinib for ALK-positive patients.[7] Although not all drugs can be personalized, prodrugs, drugs with narrow therapeutic index and drugs that target a key molecule or a critical pathway can be used with better safety and efficacy with the use of pharmacogenomics. Drug safety is an important area in which patients can benefit from pharmacogenetics and pharmacogenomics. With genetic diagnostic tests becoming more common and affordable, it is expected that individual drug dosing will become more accurate and ultimately result in vast improvements in therapeutic response and better drug tolerance.[8]

To date, pharmacogenomics information of 24 biomarkers is included in the drug labels for FDA-approved anticancer drugs. These biomarkers include gene variants, functional deficiencies, expression changes, and chromosomal abnormalities among others.[2]

Pharmacogenomics in Cancer Drug Development

Every year, about 90% of anticancer drugs fail to get FDA-approval due to their intolerable toxicity or inadequate therapeutic efficacy in general unselected population.[9] Pharmacogenomic information can be utilized to preselect a group of individuals who do not have genetic variants for drug resistance and to reduce the doses for patients who carry the genetic variants with a high risk of toxicity. This may lead to smaller sample size for the trial with reduced cost and accelerated drug approval.[10] In addition, genome-wide pharmacogenomics studies may identify novel drug targets or pathways related to the drug or the disease leading to new drug discovery.

Single nucleotide polymorphism

The genetic variants in a person can be found as germline mutations or in tumor genome as somatic mutations. While germline mutations can potentially predict drug efficacy and toxicities, somatic mutations are useful in identifying effective anticancer drug in a given patient. The genetic variants commonly studied in pharmacogenomics include single nucleotide polymorphisms (SNP), nucleotide insertion, deletion, tandem repeat, copy number variation, chromosomal translocation, and gene expression profiling. SNPs are the most studied genetic variants at present due to ease, accuracy and reduced the cost of processing as well as due to public availability of online resources for SNPs. Every individual carries two copies of each gene. Nucleotide sequences in copies of a specific gene may not be identical within a population. These single nucleotide changes are scattered throughout the genome of all species and form the basis for human diversity. SNPs are variations in a DNA sequence that occurs when a single nucleotide in the sequence is different from the norm in at least 1% of the population. SNPs occur in humans every 300–2000 base pairs along the genome.[11] When SNPs occur inside a gene, they create different variants, or alleles, of that gene.

The majority of SNPs are functionally silent, occurring in noncoding or nonregulatory regions of the genome. However, some of the SNPs lead to altered protein structure or expression. These biologically functional SNPs are considered the essence and substrate of human diversity in health, disease as well as metabolism of certain substances including drugs.[11]

Role of Single Nucleotide Polymorphisms in Pharmacogenetics

The role of SNP maps in pharmacogenomics is by two approaches. First is candidate gene approach and the second is linkage-disequilibrium mapping. The candidate gene approach relies on a prior knowledge of disease pathogenesis to identify genes. Various SNPs found in these genes are tested for statistical association with disease in patients enrolled in family, case-control, or cohort studies. Certain gene variations like thiopurine methyltransferase (TPMT) – A drug metabolizing enzyme has been found linked to adverse drug reactions.

Linkage disequilibrium mapping, on the other hand, is a genome-wide approach and relies on nonrandom association between SNPs located nearby each other. Until now, this mapping technique has not been successful for identifying genetic predictors of either disease or drug response in unrelated individuals.[11]

Phenotypic Approach in Pharmacogenetics

Candidate genes for a therapeutic and adverse response can be divided into three categories: Pharmacokinetic, receptor/target, and disease-modifying.[1]

1. Germline variations in certain transporters and enzymes which have an impact on the concentration of drug in the body can lead to variations in adverse drug reactions. For metabolism of one drug, multiple enzymes or transporters might be involved. Some examples of these variations are illustrated in Table 1.
2. Apart from pharmacokinetics, pharmacogenetics also has its influence on drug targets. Many gene products, such as enzymes and transporters, that are direct targets for drugs have an important role in pharmacogenetics. Such examples are illustrated in Table 2.
3. There are some genes which are directly involved with

Table 1: Genetic polymorphism influencing drug pharmacokinetics

Gene	Drug metabolized	Clinical response due to alteration in pK
Thiopurine methyltransferase[12]	Mercaptopurine Thioguanine Azathioprine	• Thiopurine toxicity and efficacy • Risk of second cancers
Uridine diphosphate-glucuronosyl-transferase 1A1[13]	Irinotecan	• Irinotecan toxicity

Table 2: Genetic polymorphism influencing drug response by altering gene targets

Gene target	Drug metabolized	Clinical response due to alteration in target
Dihydropyrimidine dehydrogenase[14]	Fluorouracil Capecitabine Tegafur	• Neurotoxicity
Glutathione transferases (*GSTM1, GSTT1, GSTP1*)[15]	Platinum Compounds	• Decreased response • Increased toxicity
Methylene tetrahydrofolate reductase[16]	Cyclophosphamide	• Cyclophosphamide toxicity

the disease instead of any effect on drugs. In cancer pharmacogenetics, these variations are important and called as somatic mutations. In these cases, tumors exhibit somatically-acquired mutations in addition to the underlying germline variation of the host. For this reason, the action of some of the targeted drugs depends on genetics of tumor apart from genetics of hosts. For example, certain anti-estrogens like tamoxifen are effective in only those breast cancer patients whose tumors express excessive estrogen or progesterone receptors. In lung cancer, the patients whose tumors have activating mutations in the tyrosine kinase domain of EGFR appear to respond better to tyrosine kinase inhibitors like gefitinib and erlotinib than those without the mutations.

Pharmacogenetics in Clinical Practice in Oncology

Many anticancer drugs are evaluated for their variation in response according to germline variations. This information can be easily incorporated in day-to-day practice to improve efficacy and/or safety of these drugs. Some of the notable examples are discussed in next session.

Dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing[14]

Fluoropyrimidines such as 5-fluorouracil (5-FU), capecitabine, and tegafur are mainstay of therapy in many cancers like colorectal cancer and head neck cancer. Dihydropyrimidine dehydrogenase (DPYD) is the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates >80% of administered 5-FU. Inter-individual variety is common for DPYD enzyme which leads to variable response to 5-FU in terms of efficacy, resistance, and toxicity. 5-FU can cause significant toxicity, e.g., myelosuppression, mucositis, neurotoxicity, hand-foot syndrome, and diarrhea in patients who are deficient in DPYD enzyme. A heritability analysis has shown that 5-FU induced cytotoxicity phenotype is a heritable trait with a range of heritability of 0.26–0.65. Of the more than 30 SNPs and insertions/deletions found in/near the DPYD gene, only 3 (one splice-site mutation at intron 14 and 2 SNPs in the coding sequence) are associated with low DPYD activity and higher 5-FU toxicity.[2]

Apart from DPYD, several other genes like ABCB1, methylene tetrahydrofolate reductase, and thymidylate synthetase can influence the response to 5-FU, but the results with these genes are inconsistent until date so currently only DPYD testing is recommended by Clinical Pharmacogenetics Implementation Consortium Guidelines for dosing of fluoropyrimidines. Genetic testing for *DPYD*2A* genotyping to predict the toxicity of 5-FU has positive and negative predictive value of ~50% and ~95%, respectively.

Using DPYD genotype testing, a potentially serious toxicity of fluoropyrimidines can be avoided using either alternative therapy or lower fluoropyrimidine doses, especially in patients without prior exposure to these drugs. However, misinterpretation and misreporting of genetic test can have a negative influence on the therapy in terms of efficacy.

Uridine diphosphate-glucuronosyltransferase 1A1 genotype and irinotecan

Irinotecan is part of many chemotherapeutic regimens for the management of colorectal cancer. The active form of irinotecan is SN38, which is mainly cleared by the hepatic route by glucuronidation using enzyme uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1). This enzyme exhibits wide variations because of variations in gene UGT1A1. Severe hematological and gastrointestinal toxicity are seen among patients with UGT1A1*28 allele. Irinotecan dose reduction is recommended in such patients by a French joint workgroup comprising the Group of Clinical Onco-pharmacology (Unicancer) and the National Pharmacogenetics Network (RNPGx).[13] In such patients, regimens such as FOLFIRI and FOLFIRINOX may be avoided, if possible, for the management of colorectal cancer.

However, in noncaucasian patients particularly Asians, other UGT1A1 deficient variants are also relevant, particularly the *6 and *27 alleles.[17] Hence, there is need of population specific review and guidelines to optimize the treatment using Irinotecan.

Thiopurine methyltransferase genotype and thiopurine dosing[12]

Thiopurines are commonly used not only to treat nonmalignant conditions like inflammatory bowel disease, rheumatoid arthritis, and other immune conditions but are also critical anticancer agents in some hematological malignancies. Azathioprine, mercaptopurine, and thioguanine (TG) are all prodrugs that are inactivated by TPMT. All three agents give rise to the same active TG nucleotide (TGN) metabolites. There is always an inverse relationship between TPMT activity and concentrations of TGN metabolites. The patients who inherit two inactive TPMT alleles (homozygous deficient) experience severe myelosuppression when thiopurines are used in normal doses. Patients with heterozygous TPMT alleles (one active and one inactive) are also found to develop moderate to severe myelosuppression by normal thiopurine dosing.

So far, more than 20 genetic variants in TPMT have been identified and most of them have been shown to reduce TPMT activity. Of these, there are three TPMT SNPs which account for >90% of inactivating alleles, and therefore, in this case, genotyping tests have a high informative value. Genotype-based test is just a guide for starting doses and in most diseases, titration of the dose as per acceptable degree of myelosuppression is necessary. Even though FDA has not suggested any specific guideline for dose reduction, Becquemont *et al*.[18] have suggested 10% of the original dose for homozygous TPMT deficient individuals and 50% reduction for heterozygous patients.

The most important advantage of genotype testing of TPMT gene for thiopurine starting dose is that severe myelosuppression can be avoided without compromising on efficacy. Furthermore, genotype errors should be avoided as these errors can deprive patients of correct and effective treatment.

Glutathione S-transferases gene polymorphism and platinum compounds

Platinum containing drugs are an important part of many chemotherapy regimens. The glutathione S-transferases (GSTs) are responsible for the detoxification of platinum compounds. Two common polymorphisms in GSTP1 have been described which can affect response to platinum compounds.[19] In a study in patients with colorectal cancer, it was found that the majority of patients with GSTP1 T/T genotype needed to discontinue FOLFOX regimen because of neurotoxicity developed due to oxaliplatin.[15] However, the results of this study need to be validated in different populations to recommend genotype testing for GSTP1 as routine test for patients receiving oxaliplatin-containing regimens.

Despite considerable research activity and evidence, pharmacogenetics is rarely utilized in clinical practice. Even with the availability of many examples listed above, clinicians often hesitate to adjust doses based on genetic testing than on indirect clinical measures of renal and liver function. There are multiple reasons for this hesitation which include resistance to abandon the time-tested "trial-and-error" approach, distrust of the genetic tests (which are constantly being refined) or unfamiliarity with the principles of genetics.[3]

Limitations

There are currently no actionable pharmacogenomic data available for the vast majority of chemotherapy drugs as well as targeted therapies. Furthermore, genetic profiling of patients raises issues about confidentiality, privacy, and ownership that must be considered from a public health and a patient's right perspective. This information may be used by insurance companies and employers for moral hazard considerations.[20] The other biggest hurdle for the widespread use of pharmacogenetics testing is the economic impact of routine commercial testing on the health-care system.[21]

Apart from the few examples discussed in this review, there are many other genes (ERCC1, MHTFR, CYP2D6, etc.) which are currently under evaluation to know whether there is any role of pharmacogenetic testing for dosing of anticancer drugs like platinum compounds, cyclophosphamide, tamoxifen, methotrexate, and many more. Until the stronger evidence for pharmacogenetic testing is available for these molecules, there will be hesitation for such testing for personalized treatment in routine practice outside clinical trials.

Future Prospective

Despite all resistance and lack of data at present, there is huge scope for use of pharmacogenetics to personalize drug therapy. As more and more genotype/phenotype studies will be conducted, more and more molecular diagnostic tests which can detect >95% of the important genetic variants will be developed. A major advantage of genetic tests is that they need to be conducted only once in a lifetime. However, this can act as a double-edged sword as a wrong interpretation or reporting can lead to lifetime wrong treatment.

In the future, advances gained from pharmacogenetics research will provide information to guide doctors in advising just enough of the right medicine to a person – The practice of "personalized medicine." However, there are still many economic, ethical, legal and clinical issues needing to be addressed before pharmacogenomics is fully integrated in the care of cancer patients.[22]

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