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Pharmacogenomics Influencing Drug-Gene Interactions Leading Towards Personalized Medicine

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Introduction

Recent times have pointed out that the genetic polymorphism in oncogenes influences the chemotherapeutic responses in cancer treatments. We are aware of the fact that every year thousands of deaths are caused by fatal drug reactions; a few potential causes that can be mentioned include- the fact that there are the severity of the disease being treated, drug interactions, nutritional status, renal and liver functions being affected, and also the inherited differences in drug metabolism and genetic polymorphism [1,2]. This may be due to the difference in DNA sequence among individuals, groups, or populations. Genetic polymorphisms may be the result of chance processes, or may have been induced by external agents (such as, xenobiotics / drugs, viruses, environmental exposures or radiation). Sequence variations (mutations) in the genes encoding enzymes and other proteins result from stochastic genetic processes and may accumulate in the population, depending on selective pressures [3]. One of the major causes of interindividual variation of drug effects is due to genetic variation of drug metabolism. Persidis [4] has very appropriately defined: that "pharmacogenomics approach is a redefinition of what a disease is at the molecular level". This is the reason why the progress in SNP mapping and characterization is also very important, as it will help pinpoint the genomic variations much sooner and enable the clinically relevant correlations to be made more effectively [5-7].

Pirmohamed and Park [8] have reported that clinical observations of inherited differences in drug effects were first documented as early as 1950s [9-12], giving rise to the field of pharmacogenetics, and later pharmacogenomics.

We have studied genetic polymorphisms in several drug metabolizing genes [13-19], and how this information can be used by clinicians for determining drug doses or alternate chemotherapeutics. In the context of chemotherapeutic drugs, we have demonstrated that polymorphisms in genes encoding drug metabolizing enzymes influence and affect the clinical outcome [13,16,17,19]. It was essential to examine the addition factors or parameters such as patients' demographics such as age, sex, hormones, and behavioral factors such as cigarette smoking, alcohol consumption, and nutritional status as these also have been found to influence the expression of phase I and II biotransformation genes [13-19]. This data was used to correlate the allele's verses drug toxicity. The principle behind this is due to the fact that responsible enzymes, commonly referred to as xenobiotic metabolizing enzymes (XMEs) or drug metabolizing enzymes (DMEs), may convert an inactive substance into one which is pharmacologically active. They may however, produce a toxic or even carcinogenic metabolite. Variations in genes coding for drug metabolizing enzymes and drug transporters have not only been shown to be associated with differences in pharmacokinetics and pharmacodynamics of drugs, but also with susceptibility to the neoplasm [20,21]. This emphasizes the importance of genetic polymorphisms, not only in the treatment, but also in the progression of the diseases. Such studies give us the idea that –one drug cannot be a magic wand for all people suffering from similar diagnosis. Thus discovery of Biomarker SNPs has been gained importance.

We may find that the terms Pharmacogenomics and pharmacogenetics are synonymous for all practical purposes; pharmacogenomics uses genome-wide approaches to elucidate the inherited basis of differences between persons in the response to drugs [22]. Confirming that genetic polymorphisms in disease-modifying or treatment-modifying genes can influence drug response.

In a review by Evans and McLeod [22], it was mentioned that there are more than 30 families of drug-metabolizing enzymes in humans, and essentially all have genetic variants, many of which translate into functional changes in the proteins encoded. So far about 25 genetic variations in drug targets which have a profound effect on drug efficacy are described by various authors [22]. These monogenic traits were discussed by these authors giving instructive examples of a multigenic effect involving the CYP3A family of P-450 enzymes. Hence, it is evident that genetic variation in cellular ion transporters can also have an indirect role in predisposing patients to toxic effects of drugs. For example, patients with variant alleles for sodium or potassium transporters may have substantial morbidity or mortality resulting from drug-induced syndrome [23].

This article outlines a wide spectrum of genes that interact with drug metabolizing enzymes with respect to various chemo-treatments (regimens) of cancer patients by studying and determining their genotypes from the biopsy samples- from our research such as breast cancer, head and neck cancer, hematological malignancies and lung cancer and correlates the mechanism by which these genetic variation influence treatment response [13-19, 24-26]. Further during these investigations we have listed several biomarkers which are very important to determine before treatment.

We have described the SNPs of these genes influencing the targeted pathways of chemotherapeutic agents. As it is a matter of great concern that poor responders to chemotherapeutics leads to poor quality of life (QOL) of the patients, and increases their burden of suffering [24]. In our attempt to answer this question on "why one drug does not suit all" we have gathered relevant information on Pharmacogenomics, and this review is all about knowing the SNP changes or genotyping the tumor samples which will be a great advantage for better diagnosis and for selecting the right therapeutic agent depending on the patient's tumor profile. Epigenetic changes also contribute to speeding up the tumorigenesis process [27], and there is very little information in this area. Environment and

environmental agents play a critical role in promoting carcinogenesis and influencing drug response [28]. It is an attempt to bring out these aspects in this article by refereeing to the Pharmacogenomics research conducted by us for the last seven years. It is now understood that genetic polymorphisms in disease-modifying or treatment-modifying genes can influence drug response and has been documented by several other authors [29-39].

Keywords: Cancer; Pharmacogenomics; Pharmacogenetics; Microarray; Genomics; Polymorphism; Molecular therapeutics; SNP; biomarkers; adverse drug reactions; drug safety.

Pharmacogenetics / Pharmacogenomics

It is a fact that pharmacogenetics is becoming an increasingly important field in the study of cancer chemotherapy, since genetic factors could alter drug metabolizing activity and could predict drug toxicity and efficiency. As early as 1892, Sir William Osler made an observation that "If it were not for the great variability among individuals, medicine might as well be a science and not an art." Advances in genetic technologies improve our understanding of disease etiology and those factors influencing response to treatment [5]. Although there has been relatively little progress to date in using genetics to improve the treatment of common diseases, nevertheless there are some encouraging signs of progress in basic research. The efficacy and safety of chemotherapeutic drugs exhibit substantial individual and/or population variability whose explanation can be found by analyzing genetic factors in pharmacokinetics and pharmacodynamics [29-32,37,38].

Our research, was to understand genes involved in pharmacogenomics, which seeks to identify the factors that influence responses to therapeutic agents, in cancer patients compared to healthy age matched volunteers using methods such as PCR, RFLP/SSCP and SNP analysis by Sanger's sequencing [13-19,40] to identify SNP biomarkers. Genotyping methods are improving so rapidly that it will soon be simple to test for thousands of single-nucleotide polymorphisms in one assay. It may now be possible to collect a single blood sample from a patient, submit a small aliquot for analysis of a panel of genotypes. We have also applied in vitro and bioinformatics techniques to study drug-gene interactions and protein phylogeny and interactions [41-48].

Statistical analysis determined the significance of the results. The role of genes like CYPs, TS, MTHFR, SULT1A1, and DPD in cancers as seen in our studies, represents a test for ADR when the drug is administered and the proportion of people with a negative test who will not have an ADR, respectively [13-19,40]. These are among some of the first reports from India analyzing the association of polymorphisms in several drug metabolizing genes, showing the drug-gene interactions which are associated with various cancers.

Our findings suggest that using these genotyping technologies to understand the genetic changes that influence the tumor growth at molecular biologic level supervene earlier than histologic changes, and that molecular interventions are an early diagnosis in the process of cancer therapy or cancer progression. This must be seriously considered in long-term survivors of cancer patients, to improve their overall quality of life and to reduce the side effects of drug overdoses.

A patient's genotype needs to be determined only once for any given gene, because except for rare somatic mutations, it does not change. In our opinion, genotyping results will be of greatest clinical value if they are reported and interpreted according to the patient's diagnosis and recommended treatment options. The potential for Pharmacogenomics is enormous as it yields a powerful set of molecular diagnostic methods that will become routine tools with which clinicians will select medications and drug doses for individual patients, setting the trends for personalized medicine.

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