Role of pharmacogenomics in the therapy of cancer.

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Abstract

Although, the field of pharmacy is accepting many challenges for better patient care, the therapy for cancer (chemotherapy) has been remained as a challenge, because of the adverse reactions associated with the drugs. Clinicians and healthcare professionals need to understand how to use genetic biomarkers to personalize cancer therapy using pharmacogenomic studies. In this era of evaluating medicine pharmacogenomics plays a key role in cancer therapy, which involves the study of genetic basis for individual differences in response and adverse effects. most of the patients while undergoing chemotherapy will have "wait and watch " period before the effectiveness of the therapy is assessed, during this period some patients may experience adverse effects which may be life threatening ,while some patients may not. This difference of drug effectiveness is completely based on the patient's genetics. If physicians could predict the higher risk group of patients based on the pharmacogenetic studies, it will result in better prescribing pattern of chemotherapy agents. The genomic studies play an important role in chemotherapy than in any therapy because of the reason that, the tumour's gene determines the effectiveness of the drug and the germ line genomes influences the patient's sensitivity towards toxicity associated with chemotherapy. This review highlights the pharmacogenomic associates that are needed to consider for better prescribing pattern in cancer therapy.

Key words:

Pharmacogenomics, cancer therapy, chemotherapeutic agents, germ line genomes.

Introduction

Pharmacogenomics is the study of genetic variations among individuals which determines the drug response and toxicity with application of genome wide genotyping and sequencing technologies. The main aim of this study is to identify genetic markers, which facilitates the decision making by physician in drug selection, treatment duration, dose on patient's genetic basis, which further results in decreased toxicity and increased efficacy. In the recent era of genetics, there has been advancement in gene sequencing technologies, clinical trial designs; statistical genetics analysis methods have shown promise in discovery of variants associated with chemotherapy. Beyond these advancements, there have been remained some challenges in pharmacogenomic studies used in chemotherapy because of the reason; there are two genomes (tumour and germ line) to be considered. Variation in tumour genome is due to somatic mutations that are acquired while, the variation in germ line genomes are inherited genetic differences. These variations are ought to be studied to assess the heterogeneous responses seen with chemotherapy.

Another difficulty associated with pharmacogenomics in chemotherapy is performing studies in human beings, as the chemotherapeutic drugs are toxic in nature to be given to normal individuals. The solution for this is use of large clinical studies to discover markers and to confirm the findings in a validation cohort. Despite of these challenges, pharmacogenomics has led to discovery of genetic markers associated with chemotherapy which is a milestone in therapy of cancer.

Role of germ line DNA Variants in chemotherapy

There is well- studied clinical evidence between germ line genetic variations and drug toxicity. This implicates the need for physician's knowledge about germ line genetic information of the patient. Germ line mutations mostly affect pharmacokinetics of the drug resulting in the chemotherapy related adverse reactions. In this concern, pharmacogenomic markers helps to identify the high risk group of patients, developing serious adverse drug reactions.

One of the examples for this is, several pains in musculoskeletal system have been reported in half of the women receiving aromatase inhibitors. The reason for this is four SNPs (single nucleotide polymorphisms) mapping to the T-cell leukaemia 1A (TCL1A), which are responsible for musculoskeletal adverse reactions in patients receiving aromatase inhibitors. Further studies showed that TCLIA is induced by higher expression of estrogen in cells with variant alleles of these four SNP's. This showed an evidence for estrogen dependent TCLIA SNP-dependent regulation of cytokine receptors, cytokines, and Necrosis factor transcriptional activity. This outlines a strong biological basis for the genetic association which is central in pharmacogenomic studies.

In addition germ line mutations may show effect on drug efficacy. Recent studies showed that a germ line mutation in the proapoptotic gene BIM has resulted in resistance to tyrosine kinase inhibitors that are widely used in chronic myeloid

leukaemia (CML). Identification of this mutation resulted in better biological insight into various strategies to overcome the resistance that are in preclinical testing currently.

Role of somatic mutations in chemotherapy

A somatic mutation helps in understanding the underlying biology of cancer by keen study of genetic variations that caused tumerogenisis providing molecular drug targets. Tumour sequencing helps in site specific cancer treatment. Many drugs have been developed for specific molecular targets; one of the examples is crizotinib in anaphylactic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC). DNA sequencing in tumour cells is identified to decrease toxicity associated with chemotherapy. Another instance for this is, genomic markers like TCLIA plays a key role in decreasing adverse reactions like musculoskeletal pain in women taking aromatase inhibitors.

Strategies for development of pharmacogenomic evidence

Pharmacogenomic studies have uncovered an abundant bio-markers including both somatic and germ line mutations. The TPMT, a predictive marker may help in enhancing treatment response by reducing toxicity while maintaining anti-cancer activity. Despite of the benefits implementation of pharmacogenomics is has been slow, due to contradictory professional guide lines and differing thresholds for evidence. Whereas, randomized controlled trials have been evolved as a standard for treatment response and genetic testing for markers like ALK.

Randomization in experiments helps in control of biases by balancing factors that are suspected to affect outcomes among study groups. However, due to time, cost and the large sample size, clinical trials are not always feasible for providing evidence. whereas observational studies may give incorrect results due to more number of biases but still observational studies have proved their efficacy over clinical trials offering some advantages like large number of subjects at an affordable cost, ability to perform studies on meaningful genomic subgroups, longer follow up times, and also provides time to examine drugs and their interactions with the genome that are used off-label.in concern of all these , rigorously designed high-quality observational studies can play important role in decision making in cancer pharmacogenomics.

Polymorphisms in drug-metabolizing enzymes

Thiopurine methyltransferase and 6-Mercaptopurine (6-MP)

6-MP is used in leukaemia for its antimetabolite action .the mechanism of action is through inhibition of formation of important nucleotides that are necessary in DNA and RNA synthesis. Generally, thiopurine methyltrasferase (TPMT) catalyses the s-methylation of 6-MP and forms inactive metabolites. Whereas, genetic variations in TPMT shows effects on bioavailability and toxicity of 6-MP. According to a survey, 1 in 300 individual inherit TPMT autosomal recessive trait and show toxicity for 6-MP. If a patient shows polymorphism of TPMT are at high risk of severe haematological toxicities when administered with 6-MP due to decrease in metabolism rate. The molecular level studies show three allies designated as TPMT*2, TPMT*3A, TPMT*3C are also the causes of about 95% of observed cases. Each of the alleles encodes TPMT proteins that degrade faster than normal proteins leading to deficiency in enzyme. This difference is common among ethnic groups.

A recent study showed that that 71% of patients suffering from bone marrow intolerance to 6-MP were TMPT deficient phenotypically and the number of hospital administrations are more among these patients and in some cases platelet transfusions are also recommended to cope with the situation. In this concern genetic based, Molecular diagnosis of TMPT deficiency can assist in in determining safe starting dose of 6-MP.

UDP- glucuronosyl Transferase 1A1

UDP-glucuronosyl Transferase 1A1 is an important enzyme that is responsible for glucuronoidation of toxic SN-38 to less toxic SN-38G.polymorphism in this enzyme UGT1A1 enzyme affects the metabolism of irinotican which is a very important drug in chemotherapy. The pharmacogenetic studies on irinotican have been shown to be effected by polymorphism of UGT1A1. The dose limiting toxicities like diarrhoea and myelosupression are avoiding the optimal use of irinotican. The genetic variations in the enzyme are due to polymorphisms in UGT1A1 promoter region that contains several repeating TA elements. If seven TA repeats are present instead of wild type six TAs results in reduced UGT1A1 expression and also UGT1A1*28 has been shown effect on glucuronoidation of SN-38,which results in increased toxicity. This study provides an evidence of pharmacogenomic studies in the predictions of drug toxicity.

Polymorphism in drug transporters MDRI

P-glycoprotein (PGP), an important protein in transport of a wide range of hydrophobic drugs, including chemotherapeutic agents. PGP was found to be over expressed in cancer patients who are multi drug resistant. Generally, PGP is encoded by MRI gene (ABCB1) which is an ATP binding cassette transporter. This membrane transporter is found in normal cell tissues like colon, proximal tubules of kidney, brush bordered cells of small intestine etc. in addition it's expression varies among individuals. Grouping the genetic variations in MDR1 may help in the prediction of chemotherapeutic adverse reactions depending on racial background.

Application of pharmacogenomics to chemotherapy

Of all the fields, application of pharmacogenomics to chemotherapy is most promising. For an instance, selective genostratification is done to achieve better results .selection of population based on genes helps in better application of

pharmacogenomics to clinical trials which helps in providing proof of the concept. However, pharmacogenomic studies result in reduction of sample size and also the time taken to perform trails. On the other hand application of pharmacogenomic to identify genetic markers helps in early detection of cancer and also facilitates quick therapy selection. Application of pharmacogenomic techniques like genotyping, expression profiling, and proteomics helps in examination of candidate's genetic expression in mRNA or protein level.

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