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# Pharmacogenetics of 5-fluorouracil: anew way to trounce thegastric cancer

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## Abstract

Gastric cancer cases are significantly increasing worldwide. In fast few years varietiesofchemotherapy drug are developed for the treatment of gastric cancer. Among these drugs 5-fluorouracil (5-FU) is broadlyin used.Effectiveness of 5-FU get significantly reduced due to single nucleotide polymorphisms (SNP) in drug metabolizing enzymes (DME). Thus due to the SNP, adverse drug reaction arereported in cancer patient. In order to minimize the side effect, personalized medicine has to be developed according to the individual's genotype, wherepharmacogeneticscan add a boost in chemotherapyregime.The US Food and Drug Administration (FDA) had sanctioned eighty numbers of drugsholding genetic information.In this review, we discussimpact of polymorphisms in four specific drug metabolizing enzyme; Dihydropyrimidine dehydrogenase (DPD),Thymidylate synthase (TYMS),Methylenetetrahydrofolatereductase(MTHFR) andThymidylatephosphorylase(TP)and their effects on 5-fluorouracil.

**Key Words:**gastric cancer, pharmacogenetics, 5-fluorouracil, drug metabolizing enzyme.

## INTRODUCTION

Cancer is a disease which affected different age group and flourished at every corner of the world.

According to Ferlay J etal, globally around 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008 and it has been estimated that most frequently occurring cancer is the lung cancer (1.61 million) which is responsible for high mortality (1.38 million) .In this race of nightmare; gastric cancer also play a central role. It is the disease of digestive system which ismostly spread around the world and one of the fourth most common cancer with one million new cases.Though medical technology is touching the new height but it is not sufficient as survival rate for gastric cancer since last 5 years showed disappointing results. Pharmacogenetics is the new area of research which may lend a hand to solve this scenario. We here by present a case of unusual presentation of renal osteodystrophy in young female who reported as chronic backache with stiffness.

Pharmacogenetics is the branch of pharmacology which deals with the drug metabolizing enzymes and their efficacy leading to the development of personalized medicine.Thus knowing the genetic makeup of an individualand personalized medicine can minimizes the chances of adverse drug reaction and maximizes the therapeutic efficacy to a patient when they are going from regular regime.Single nucleotide polymorphism (SNP) in phase I (Cytochrome P450 2D6) and phase II (UDP-Glucuronosyltransferase1A1, Glutathione S-Transferase P1) drug-metabolizing enzymes hampers the drug efficiency and results into toxicitythroughadverse drug reactions .About 7% of patients in the United Kingdom are found to be affected by adverse drug reactions (ADR) . Very recently it has been discovered that microRNAs act as a mediators in drug toxicity.Different types of oral formulating drugs are present which has been used to treat cancer such as 5-fluorouracil, cyclophosphamide, platinum agents, mercaptopurine, camptothecins, tamoxifen, irinotecannbut in the race of chemotherapy drugs 5-fluorouracil is among the first choice to treat cancer of gastric,colorectal and breast. It is being used for the past 50 years by the different trade name and still it is in trusting list due to its ability to arrest cell cycle with the help of its cytotoxic metabolite.Effectiveness of this chemotherapy drugs varies with age of patient, sex, food intake, comorbidities and impaired liver with renal functions.In the era of genomics number of molecular diagnostic tools are developed such as sequence variation, transcription and personal genome sequencing which adds boost to identify the various ailments specifically and benefited personalized medicine.The specific aim of the personalized medicine is to administer the right drug combination to right person so as to increase the survival rate.After mapping human genome project the task of pharmacogenetics got augmented and its roots flourished at each and every section of treatment.

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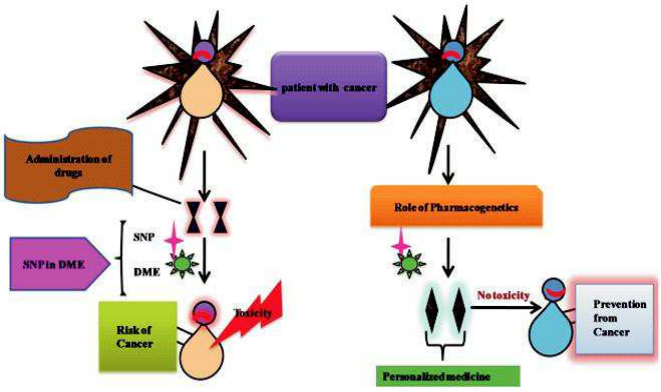


**Figure1 explains the basic rhythm lying behind pharmacogenetics law.**

Figure 1: Steps in pharmacogenetics: Patient when diagnosed with cancer, drug is administered but sometimes due to single nucleotide polymorphisms (SNP) in drug metabolizing enzymes (DME) toxicity results. On the other hand if the role of pharmacogenetics comes in the way of chemotherapy treatment, personalized medicine will be developed as a consequence no toxicity will result and cancer will be prevented.

Pharmacogenetics hold enormous information which is presentintheformofdatabases. PharmGKB (Pharmacogenetics and Pharmacogenomics Knowledge base) is the publically available database which has been developed by NIH Pharmacogenetics Research Network (PGRN). It furnishes specific information to any users who want to query about interaction between drugs, genes and diseases.Further it provides information regarding genetic variation of more than 200 diverse genes which play a vital role in the field of pharmacokinetics (PK) and pharmacodynamics (PD) . In addition Personalized Medicine Coalition Website provides the information regarding the enterprisetakenforpersonalizedmedicine (http://www.personalized medicine coalition. Org) while database regarding the allelic frequency in various ethnic population can be found at FINDbase-PGx.This review will mainly focus onimpact of genetic polymorphism in four specific drugmetabolizingenzyme; Dihydropyrimidinedehydrogenase (DPD), Thymidylatesynthase (TYMS),Methylenetetrahydrofolatereductase(MTHFR) ,Thymidylatephosphorylase(TP)and their effect on 5-fluorouracil, primary drug used in the treatment of gastric cancer

.Table 1 shows different drug metabolizing enzymes which are concerned with metabolism of drugs.

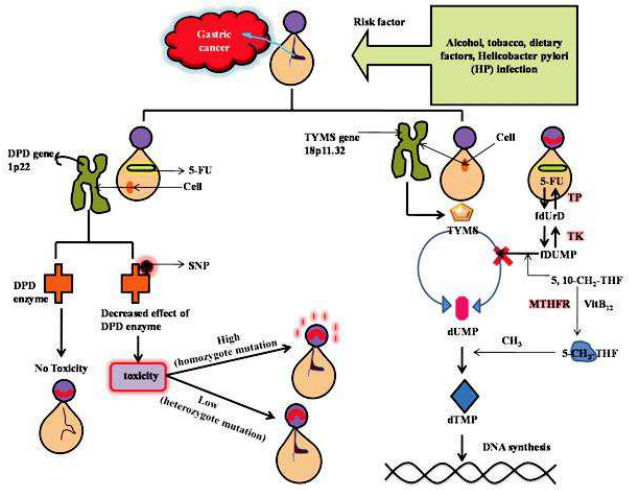


Figure2:Metabolismof5-fluorouracil: Dihydropyrimidinedehydrogenase(DPD) responsible for no toxicity effect from 5-fluorouracil (5-FU) but occurrence of single nucleotide polymorphism (SNP) in DPD impairs its activity and lead to severe toxicities. Thymidylate synthase (TYMS) catalyse the conversion ofdeoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) which is required for DNA synthesis but when 5-FU is administered, it produces its antimetabolitescalledfluorodeoxyuridinemonophosphate(FdUMP) and with 5,10- methylenetetrahydrofolate inhibits the normal functioning of TYMS.

**Dihydropyrimidine dehydrogenase(DPDor DPYD) and5-fluorouracil**

Alcohol, tobacco, dietary factors, Helicobacter pylori (HP) infection are the chief risk factors for gastric cancer.[12] 5-fluorouracil (5FU) is the pyrimidine analog drug which is widely used in chemotherapy regime to those patients who are suffering from gastric cancer but on the dark side, accumulation of 5FU is responsible for making toxic effect to patient as 80% of it,is inactivated by decreased effect of Dihydropyrimidine dehydrogenase (DPD) which is a rate limiting enzyme.[13] Single nucleotide polymorphism (SNP) in DPD gene is the causative agent which lies behind this scene (Figure 2).DPD gene is present in 1p22 human chromosome and comprise of 23 exons.[14]
Recently it has been determined that DPD gene is encompasses of over 20different types of SNP but still, it is unknown whether all polymorphic site cause 5-FU toxicity.[15]

Van Kuilenburg in 2003 has acknowledged 11 mutations in DPD gene comprising single splice-site mutation (IVS14 + 1G-->A), one nonsense mutation (E386X), four missense mutations (M166V, V335L, I560S, D949V) and five polymorphisms (C29R, R21Q, S534N, I543V, V732I) from those cancer patients who are suffering from 5-FU toxicity but it has been identified that IVS14 + 1G-->A(G→ A) is the prevalent mutation which is responsible for toxicity in cancer patient. Heterozygote and homozygote mutations result into decreased effect of DPD,[17] (Figure 2).Recently it is determined that grade IV neutropenia is the consequence of low DPD level.[18] Studies across the worldwide population defined that 3% Caucasians are G→ A while 0% in Asians[2].Table 1 enlisted the pattern of polymorphism in different population.

**Thymidylate synthase (TYMS) and5-fluorouracil**

5-FU enters into cell cycle (G1/S phase) and stops the synthesis of DNA and RNA and induces apoptosis. Other than canceritstoxicity also leads to mucositis, neutropenia, neurological symptoms and demise.[8] The foremost task of the 5-FU is to restrain the function of Thymidylate synthasewhich is the primary enzyme required for DNA replication and folate metabolism.[19] TYMS gene is positioned at chromosome 18p11.32 and consists of 7 exons.[20] The key function of TYMS is to provide deoxythymidine monophosphate (dTMP) an important dNTP for DNA synthesis by catalyzing the conversion of deoxyuridine monophosphate (dUMP) using 5, 10-methylenetetrahydrofolate (5, 10-CH2-THF) which is a methyl donor; consequently when 5-FU is given to cancer patient it released active metabolite called fluorodeoxyuridine monophosphate (FdUMP) which hinder the functional role of TYMS by forming ternary stable complex,[21] thus synthesis of DNA stop (Figure 2) but sometime patient become resistant to 5-FU or raltitrexeddue to over expression of TYMS.[8] The effectiveness of TYMS is chiefly depends on the quantity of tandem repeats present.Different studies are done on diverse population of the world and it has been found that alleles such as TYMS 2R (2R) and TYMS 3R (3R) are common repeats.[22] TYMS with 3R (three repeat sequence) responsible for higher protein translational efficiency than that of 2R (two repeat sequence).[23] Another breakthrough come on the way when it is identified that TYMS 3R allele is having G-C SNP in second repeat of 12thnucleotide known as 3RC mutation.[24] It has been found that TYMS 3RC entitled with low TS expression level,which improved clinical outcome in combination with 5-fluorouraci,[25-26] while patient are less benefited from 5-FU adjuvant chemotherapy and neoadjuvantchemoradiation when3R is homozygous. This fact is true for metastatic colorectal cancer patient where meager survival(12 months vs 16months) and

minimum response rate(9% vs 50%) is found for 5-FU.[8] Furthermore, studies found that levels of plasma folate and homocysteine gets elevated as a consequence of polymorphism in TSER (Thymidylate synthase enhanced region).[19] Mandolaetal in 2003 determined that frequency of 3RC allele in Caucasians, African-Americans and Chinese are 56%, 28% and 37% respectively.[24] This data concluded that Caucasians are at higher risk than that of Chinese and African-Americanswhile another study revealed that Chinese are at higher risk than that of Caucasians or Southwest Asians,[19] thus variation are present in different ethnic population(Table 1). Recently the role of downstream region was explored and it has been found that polymorphism of 6bp deletion/ insertion at 1494 in the 3' untranslated region(TS3'UTR) may affect mRNA expression and steadiness of TYMS than that of 0bp/0bp genotypeand ultimately increasing the risk of gastric cancer as concluded in Chinese population by Zhang Z etal.[19] Different studies has been done around the globe and it has been found that TYMSwith 5-fluorouracil play a significant role in response to chemotherapy drugs butthere is a need of more wider studies.

**Methylenetetrahydrofolatereductase(MTHFR) and 5-fluorouracil**

Methylenetetrahydrofolatereductase (MTHFR) in the presence of vitamin B12catalyses the conversion of 5, 10-methylenetetrahydrofolate(5,10-CH2-THF)to5-methyltetrahydrofolate(5-CH3THF)[2].Methyl group (CH3) isreleased by5-CH3THF to homocysteine which is remethylated to methionine thus homocysteine levelis maintained.MTHFR is the key enzyme which also participates in regulating folatehomeostasis[8]which is the primary constituent of fruits and vegetables and its scarcity may lead to DNA damage.

5, 10-methylenetetrahydrofolate is a coenzymatic substrate which formsstable ternary complex with FdUMP (antimetabolite of 5-FU) and inhibit the normal operation of TYMS (Figure 2).Thus,the efficiency of 5-FU gets accelerated when the echelon of 5, 10-CH2-THF increased due to the decelerate activity of MTHFR.[2] MTHFR gene presenton chromosome 1p36.3 in humans.[27] Number of polymorphism has been recognized and it hampers the normal functioning of MTHFRgene. In recent year 44 single nucleotide polymorphisms has been identified and out of these 37 SNPs are linked with serious deficiency in enzyme activitiesand hyperhomocysteine is the conditions which augment due to this inefficiency .Frequently in MTHFR two SNPswere found C677T and A1298C. Single amino acid substitution (alanine to valine) is associated with MTHFR C677Twhichminimizes enzymatic activity and maximizes thermolability,[2] while mutation in A1298C (glutamine to alanine) responsible for altered function of MTHFR but its effect is lesser than that of C677T, it also end up the specific recognition site for restriction endonuclease; MboII is in such case.[8] The normal functioning of enzyme gets hindered due to homozygous mutation which is about 75% for C677T while that of A1298C is 30%[28]on the other hand individuals who are heterozygous for C677T and A1298C shows similar phenotype like that of C677TT homozygotes so, by following this path allelic frequencies varies with ethnicity; number of studies is already being done and it is resolute that about 24 to 46% Europeans, 26 to 44% East Asians, 57% Mexicans and 11% African Americans are C677T variant[8]while, another report manifest that Caucasians, Italians , Japanese, Blacks from Africa and America shows TT homozygous variation at the rate of 10% ,20% , 10% and 1% whereas for A1298C; 4-12% CC homozygosis were determined in Europeans and North Americans inhabitants while4% in Japanese population.[2] Thus the above frequency demonstrate that Blacks of Africa and America are facing less C677TT variant than that of Caucasians and Japanese which are showing equivalent frequency(Table 1).Huang ZH, et al in 2009 made an important exploration that MTHFR C677T plays a vital role in the molecular prognosis of gastric cancer patient who are going from 5-fluorouracil regime.[29] where in the case of A1298C; higher sensitivity to 5-FU is seen with 1298CC mutated variants as compared with 1298AA a wild type homozygous.[30] Though broad way studies are required as some of the results are controversial.

**Thymidylatephosphorylase (TP) and 5-fluorouracil**

5-FU is the drug of importance because it can use the pyrimidine metabolic pathway of the cell and metabolized by Thymidylatephosphorylase (TP) .Cancer in breast, gastric, colorectal, pancreatic, hepatic, pulmonary, esophageal, urinary bladder, and kidney are the place where expression of TP is mostly established but due to over expression of TP; chemotherapy regime in colorectal cancer, gastric cancer, esophageal cancer, bladder cancer, renal cell carcinoma and non-small cell lung cancer gets held back while some reports doesn't acceptthis notion[31].The chemistry which lie behind its functionality is that TP which is present in cancerous cell catalyses 5-FU to FdUrd(fluorodeoxyuridine)[32]while TK (thymidine kinase ) convert FdUrdinto FdUMP[3]so, efficiency of 5-FU is affected by the expression level of TP which can increase the survival rate of patient. Nakayama et al reported that TP and DPD expression level are having common regulatorypathway hence; expression of TP is correlated with the level of DPD. However more studies are required to evaluate the expression of TP in gastric cancer patient as conflict of result are

**Table 1: Abbreviation**

Enzymes:

DPD:Dihydropyrimidine dehydrogenase, UGT1A1: UDP glucuronosyltransferases, CYP2D6: Cytochrome P450 2D6, TPMT:Thiopurinemethyltransferase,MTHFR:Methylenetetrahydrofolatereductase,TYMS:Thymidylate synthase, GSTP1: Gluthathione S-transferase,TP:Thymidylatephosphorylase

Drugs:

5-FU:5-fluorouracil,6–MP:Mercaptopurine MT:Methotrexate,CP:Cyclophosphamide,O:Oxaliplatin

Populations:

C: Caucasians, A: Asians, IS:Indian Subcontinent, SEA:South East Asian, AF: African,EuA: European Americans, E: Europeans,EA: East Asians, M: Mexicans, AA:AfricanAmericans,NA:North Americans, J: Japanese, T: Taiwanese, AE:Australian European, Ch:Chinese.

Others:

NTR: Number of tandem repeats, VA: Variable alleles, #: CC homozygousseen in many published report.

**CONCLUSION**

Mankind is gifted by the diverse genetic variation i.e. each individual of us is having different genetic content, due to this disparity; role of pharmacogenetics comes into play. The eventual objective of the study is to throwlight on drug metabolizing enzymes and their outcome on commonly used 5-fluorouracil drug. There are about 80 numbers of drugs which presently hold genetic information and are sanctioned by Food and Drug

**Table 1: Display different drug metabolizing enzymes which are involved in cancer drugs metabolism and frequency of polymorphismsin differentpopulation.**

| Enzyme | Drugs | Cancer | Gene encoding | mutation | Population |
|---|---|---|---|---|---|
| **DPD** | 5-FU | Gastric, Colorectal ,breast | *DPD* | IVS14 + 1G-->A | C :3%; A :0%(2) |
| **UGT1A1** | Irinotecan | Colorectal | *UGT1* | *UGT1A1*28* | IS:19-24%, A:12-27%,C:5-15%, SEA: 1.2-5% |
| **CYP2D6** | Tamoxifen | Breast | *CYP2D6* | *CYP2D6*(VA) | C: 5-10% *CYP2D6*4* (33); EuA: 50% *CYP* |
| **TPMT** | 6-MP | Colon | *TPMT* | *TPMT*3A*, *TPMT*2*all, *TPMT*3C* | C:4.4%,0.4%,0.2%(all) (35); SEA: 2.3-1%, AF: |
| **MTHFR** | 5-FU and MT | Gastric, colorectal | *MTHFR* | C677T, A1298C | C677T? E: 24-46%, EA: 26 -44%, M: 57%, AA: 11% (8). |
| **TYMS** | 5-FU | Gastric, colorectal | *TYMS* | NTR(2R,3R, 3RC) | C:16% 2R/2R,51-55% 2R/3R,29-32% 3R/3R(36-37);Ch:2% |
| **GSTP1** | CP and O | colorectal | *GSTP1* | *GSTP1 I105V* | AA:19%,EuA:7%, T:3%,AE:9%(38-39) |
| **TP** | 5-FU | Gastric, colorectal, | *TP* | Over expression | J-significant over expression among 111 patient(31) |

Administration (FDA) . Strength, peace, joy, inspiration, hopes, courage is the empowering way through which a person can surmount the cancer psychologically but physiologically 5-fluorouracil (5-FU) is the chief and standard chemotherapy drug which is regularly used in the treatment of gastric or other cancer. Recently 5-FU dependent function with DPD, TYMS, MTHFR and TP is correlated (summarized inFigure 2) and it has been determined that mutation plays a significant role in its efficacy.Research is going on for further genes which are involved in regulating 5-FU metabolic pathwaythereby;more number of genes should be studied in a broader way instead of concentrating only in single gene. Moreover, polymorphic status of these genes can be studied in various populations which will open the window in the prognosis of gastric cancer. Anothereffective approach is widely in used where 5-FU is administeredincombination with other drugs likeCisplatinthat increases the success rate. However, before prescribing, it is very much necessary that drug response by an individual should be known and accordingly right dose of drug must be given. Nanoparticles can be used in the treatment of gastric cancer as recently it is determined that using of 5-FU nanoparticles in mouse model inhibit hepatic cancer growth .Cost effectiveness, trained manpower and planned clinical trials isthe need of time so thatpharmacogenetics can reach every doorstep and optimizethe therapy. Future is near when, before administering 5-FU or other drugs doctors' mayrecommend the patient for genotype screening along with other general tests and accordingly he/she may administrate personalized drugs.Thus clinical application of pharmacogenetics can play a decisive role in the treatment of gastric cancer.

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