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Pharmacogenetics-Guided Dosing for Fluoropyrimidines in Cancer Chemotherapy

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Cancer is a Global Public Health Problem

Cancer is a leading cause of mortality worldwide. It is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells with accumulated genetic alterations that promote cancerous initiation, development, growth, and metastasis [1,2]. According to estimates from the International Agency for Research on Cancer (IARC), there were 12.7 million new cancer cases in 2008 worldwide, of which 5.6 million occurred in developed countries and 7.1 million in developing countries [3]. The corresponding estimates for total cancer deaths in 2008 were 7.6 million (about 21,000 cancer deaths a day), 2.8 million in developed countries and 4.8 million in developing countries [3,4]. Worldwide, almost 32.5 million people diagnosed with cancer within the five years previously were alive at the end of 2012. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths. Lung cancer is the leading cancer site in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths. By 2030, the global burden is expected to grow to 21.4 million new cancer cases and 13.2 million cancer deaths simply due to the growth and aging of the population, as well as reduction in childhood mortality and deaths from infectious diseases in developing countries [3]. A total of 574,743 cancer-related deaths were recorded in 2010 in the United States (US), and cancer is the second leading cause of death after heart diseases. One in 4 deaths in the US is due to cancer. A total of 1,665,540 new cancer cases and 585,720 cancer deaths are estimated to occur in the US in 2014 [5]. This means that more than 4,500 new cancer will be diagnosed each day and about 1,600 Americans will die each day in 2014. During the most recent five years for which there are data (2006-2010), cancer incidence rates in the US declined slightly in men (by 0.6% per year) and were stable in women, while cancer death rates decreased by 1.8% per year in men and by 1.4% per year in women. In the UK, more than 331,000 people were diagnosed with cancer in 2011 (i.e. 910 people every day). In the UK, there were around 159, 000 deaths from cancer in 2011, with lung, bowel, breast and prostate cancers together accounting for almost half of all cancer deaths.

Cancer Chemotherapy Often Fails due to Drug Resistance and Severe Organ Toxicities

Cancer is treated with surgery, radiation, chemotherapy, hormone therapy, immune therapy, and targeted therapy [6-8]. Cancer chemotherapy attempts to eradicate or functionally disable tumor cells by the use of synthetic and/or natural compounds while preserving normal cells. Chemotherapeutic agents can eliminate tumor cells by direct cytotoxicity, activating host immune response, inhibiting the proliferation processes of tumor cells and inducing apoptosis. However, they are characterized by significant interindividual variations in pharmacokinetics (i.e. clearance and half-life) and pharmacodynamics (i.e. therapeutic responses and drug toxicities) [6,9-13]. This will make cancer chemotherapy unsuccessful and the outcomes are unpredictable in patients. Such variability is partially due to genetic factors arising from both tumor and noncancerous cells that lead to alterations in drug metabolism and transport, and/or drug targets (e.g. receptors or signaling transduction proteins) [14]. Chemotherapeutic agents typically have a narrow margin of safety, in that the ratio of the dose associated with antitumor efficacy and the dose associated with toxicity is small. These drugs are usually prescribed at a maximum tolerated dose in order to achieve maximum cancer cell death; as such toxicity often is unavoidable, since there are frequently only subtle differences in the genome of cancer and normal host cells.

Cancer chemotherapy drugs have a high rate of failure because they usually kill only specific types of cancer cells within a tumor or the cancer cells mutate and become resistant to the chemotherapy. In addition to tumor resistance, severe organ toxicities are also an important reason for chemotherapy failure when most anticancer drugs cannot selectively kill tumor cells only.

Pharmacogenes in Fluoropyrimidine Pathways: Genotype-Phenotype Relationships

Fluoropyrimidines are antimetabolites widely used in the treatment of solid tumors including colorectal, breast, lung, and gastric cancer [15]. Three fluoropyrimidines including 5-fluorouracil (5-FU), capecitabine, and tegafur are commonly used in cancer chemotherapy. Capecitabine, an orally administered prodrug of 5-FU, is converted by carboxylesterase into 5′-deoxy-5-fluorocytidine (5′-dFCR) and then by cytidine deaminase to 5′-deoxy-5-fluorouridine (5′-dFUR) in the liver [15]. 5′-dFUR is then converted to 5-FU by thymidine or uridine phosphorylase. Tegafur is also a prodrug of 5-FU, which is converted by hepatic (CYP2A6) to an unstable intermediate, 5-hydroxytegafur, which spontaneously breaks down to generate 5-FU [15].

5-FU is widely prescribed for chemotherapy of solid tumors such as colorectal and breast cancer; and is commonly administered either via bolus intravenous injection with leucovorin or via continuous infusion [16]. It is an analogue of uracil serving as a prodrug that is converted to 5-fluoro-2-deoxyuridine monophosphate (5-FdUMP),

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a metabolite that inhibits thymidylate synthase (TYMS). TYMS is an enzyme required for de novo pyrimidine synthesis and its inhibition slows cancer-cell replication [17]. 5-FU may also act through the incorporation of its cytotoxic metabolites into the DNA and RNA. The conversion of 5-FU to 5-FdUMP is mediated by thymidylate phosphorylase (TYMP) to 5-fluorodeoxyuridine and then by thymidine kinase to 5-FdUMP or indirectly by 5-fluorouridine monophosphate (5-FUMP), or 5-fluroridine (5-FUR) to 5-fluorouridine diphosphate (5-FUDP) and then by ribonucleotide reductase to give rise to 5-fluorodeoxyuridine diphosphate and 5-FdUMP [16]. 5-FdUMP covalently binds to TYMS and prevents the binding and conversion of dUMP to dTMP, necessary for pyrimidine and DNA synthesis, and simultaneously inhibits conversion of 5,10-methylene tetrahydrofolate to dihydrofolate, a key component of the folate pathway [16]. The inhibition of TYMS leads to an imbalance of deoxyuridine triphosphate (dUTP) and deoxythymidine triphosphate (dTTP) and a rise in the misincorporation of dUTP into DNA, resulting in cellular apoptosis.

In the liver, more than 80% of 5-FU is converted to inactive dihydrofluorouracil (DHFU) by polymorphic dihydropyrimidine dehydrogenase (DPYD) [15,16]. DHFU is converted by dihydropyrimidinease (DPYS) to fluoro-β-ureidopropionate (FUPA) and subsequently to fluoro-β-alanine (FBAL) by β-ureidopropionase (UPB1) [16]. Deficiency in enzymes of this inactivating pathway can lead to severe and even life-threatening toxicities. On the other hand, 5-FU may serve as the substrate of several drug transporters but the data are conflicting. Transport of 5-FU by solute carrier family 22 member A7 (SLC22A7, an organic anion transporter) has been observed in vitro [18] and tumor resistance to 5-FU therapy has been implicated with breast cancer resistance protein (BCRP/ABCG2), ATP-binding cassette transporter C3 (ABCC3), ABCC4, and ABCC5.

DPYD is expressed in many cell types throughout the body, with liver and peripheral blood being the major sites. The gene consists of 23 exons spanning 950 kb, resulting in 4,399 nucleotides encoding a 1,025-amino acid protein. The activity of DPYD varies considerably among individuals. Patients with low DPYD activity cannot efficiently inactivate 5-FU and form excessive amounts of active metabolites leading to hematopoietic, neurological and gastrointestinal toxicities [15,16]. The most common DPYD variant associated with fluoropyrimidine toxicity is *DPYD*2A* that carries a G>A SNP (rs3918290) in the splice site of intron 14, leading to skipping of exon 14 and synthesis of a truncated protein, which is degraded by the ubiquitin-proteasome system. The *DPYD*13* variant carries an SNP of rs55886062 1679T>G that results in Ile560Asn or Ile560Ser substitutions. Approximately 3-5% of the Caucasian population carry heterozygous mutations that inactivate DPYD, and 0.1% are homozygous for inactivating mutations. Severe toxicity occurs after 5-FU therapy in patients with reduced DPYD activity (<100 pmol/min/mg of protein in peripheral mononuclear cells). Currently, 17 mutations associated with reduced DPYD activity have been reported.

Genetic polymorphisms of *TYMS* also may affect the clinical outcomes of 5-FU chemotherapy in patients [15,16]. A lower TYMS activity is associated with a better antitumor response to 5-FU treatment. *TYMS* expression is regulated by a polymorphism that is characterized by a variable number of tandem repeats (two or three repeats) in the enhancer/promoter region of the *TYMS* gene. The common variant of *TYMS* is a 28 bp repeat in the 5′-untranslated region (5′-UTR), a 6 bp deletion in the 3′-UTR and a G>C SNP within the third repeat of this region. A higher number of repeats increases expression levels of TYMS; as such, patients who have a homozygous genotype with three tandem repeats have higher TYMS activity and a lower probability of responding to 5-FU therapy compared to patients with two tandem repeats.

Many clinical studies in cancer patients have shown that polymorphisms of *MTHFR* may affect the clinical response to fluoropyrimidine therapy, but the results are inconsistent [19-25]. The most commonly studied SNPs are 677C>T and 1298C>A. 677C>T has been associated with poorer response or shorter survival, better response, but had no effect on response or survival in other studies [20-23]. Similarly, 1298C>A has been associated with shorter survival but had no effect in other studies, and the TA haplotype of both variants was associated with worse response or had no effect [20-23]. It appears that it is difficult in establishing an association between *MTHFR* polymorphisms and clinical outcomes of fluoropyrimidine-based chemotherapy.

Pharmacogenetics-Guided Dosing for Fluoropyrimidine Therapy

Approximately 3-5% of Caucasians have partial DPYD deficiency and 0.2% have complete DPYD deficiency. The Clinical Pharmacogenetics Implementation Consortium (CPIC) Dosing Guidelines for fluoropyrimidines (i.e. 5-fluorouracil, capecitabine or tegafur) recommends an alternative drug for patients who are homozygous for *DPYD* non-functional variants (**2A* rs3918290, **13* rs55886062 leading to Ile560Asn or Ile560Ser, and rs67376798 leading to Asp949Val; about 0.2% of patients) since these patients are typically DPYD deficient [26]. A 50% reduction in starting dose of fluoropyrimidines is recommended for heterozygous patients (3-5% of patients) with an intermediate activity of DPYD (30-70% that of the normal population) followed by an increase in dose in patients experiencing no or clinically tolerable toxicity to maintain efficacy, a decrease in dose in patients who do not tolerate the starting dose to minimize toxicities or pharmacokinetics-guided dose adjustment.

Conclusions and Future Perspectives

Overall, the clinical impact of DPYD and TYMS polymorphisms on 5-FU toxicity has been established, and genotyping test of DPYD and TYMS could be useful in selecting patients who are more likely to tolerate and to respond better to 5-FU therapy. However, much of the data is contradictory and complicated by combination treatment regimens and other factors and thus so far no good pharmacogenetic biomarkers have been identified and validated for routine clinical application for predicting clinical outcome of fluoropyrimidine therapy. The low frequency of the functionally important variants and lack of diagnostic tools for prospective genotyping and phenotyping testing also hinder the use. Given that cancer patients are often treated with 5-FU plus other anticancer drugs such as oxaliplatin and irinotecan, other factors related with patients and drug administration must be taken into account when predicting fluoropyrimidine drug response based on genotype-phenotype relationships.

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