

Role of Pharmacogenetics in Gastrointestinal Cancer

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1. Introduction

Worldwide, gastrointestinal (GI) system tumors are the leading group of cancers in terms of incidence and cause of cancer deaths (Parkin, 2005). They are usually diagnosed at an advanced stage which is rarely curable, and even if detected early the rate of recurrence is quite high. Therefore despite improvements in the diagnosis and treatment of GI cancers, 5-year survival rates remain disappointing. Effective new treatments are urgently needed, and existing therapies need to be individualized to determine patients who are likely to respond to a given chemotherapy, as well as to identify patients at risk of developing severe toxicity. This approach will enable clinicians to optimize and personalize cancer treatment. Pharmacogenetics is, perhaps, the most promising method to provide this (Yalcin, 2009). Metabolism of chemotherapy agents varies depending on patient age, gender, diet, concomitant drug use, comorbidities, and hepatic and renal functions and moreover GI functions may be impaired due to surgery, chemotherapy and the disease or existing comorbidities in GI cancer patients.

Pharmacogenetics focuses on the influence of genetic structure on cancer treatment because enzymes that metabolize the drug, proteins that transport the drug and its metabolites, and drug receptors are determined by a patient's genetic profile (Vesell, 1989). However, it is not only the genetics of the patient, but also the genetic alterations of the tumor that are critical (Yong, 2006, Vesell, 1989). Pharmacogenetics may help to decide the most sensitive and least toxic therapy in order to increase survival, reduce treatment related cost and improve patient's quality of life. In this chapter, the most common drugs, combinations thereof, and biological agents used for the treatment of GI tumors are reviewed for their relevant pharmacogenetic aspects.

2. 5-Fluorouracil (5-FU)

The uracil analogue 5-FU has been used in the treatment of GI cancers for over 50 years (Meta-Analysis Group in Cancer, 1998). 5-FU acts in several ways, but principally as a thymidylate synthase (TYMS) inhibitor. Inhibition of this enzyme blocks synthesis of the pyrimidine, thymidine which is a nucleotide required for DNA replication. TYMS methylates deoxyuridine monophosphate (dUMP) into deoxythymidine monophosphate (dTMP). Administration of 5-FU causes a depletion in dTMP, so that rapidly dividing cancer cells undergo cell death.

5-FU itself is a prodrug, which must be activated by entering the pyrimidine synthesis pathway. Although 5-FU can enter the pathway at 3 different points, the key entry point is the conversion of UMP to UDP, which is catalyzed by pyrimidine monophosphate kinase. 5-FU is given intravenously, because oral bioavailability is limited due to high concentrations of dihydropyrimidine dehydrogenase (DPYD) in the gut mucosa. DPYD is an enzyme present in the liver, intestinal mucosa and various other tissues. DPYD catabolizes 5-FU to 5,6-dihydro-5-fluorouracil (DHFU). Capecitabine is an oral analogue of 5-FU which can be used instead of intravenous 5-FU. Capecitabine is converted to 5-FU via a 3 step activation process. The first two steps occur in the liver and the last step is carried out by the enzyme thymidine phosphorylase (TYMP), which is over expressed in a large number of tumors (approximately 3 times more compared to normal tissue). Only a fraction of the administered 5-FU reaches its target cell and is transformed to active metabolites that is converted to 5-fluoro-2'-deoxyuridine-5'-monophosphate (5-FdUMP) within the cell to inhibit TYMS. Eighty-five percent of 5-FU is catabolized to its inactive metabolites via DPYD. Inherited deficiency of DPYD leads to greatly increased drug sensitivity and toxicity (Figure 1) (Daher et al, 1990).

5-Fluorouracil (5-FU)

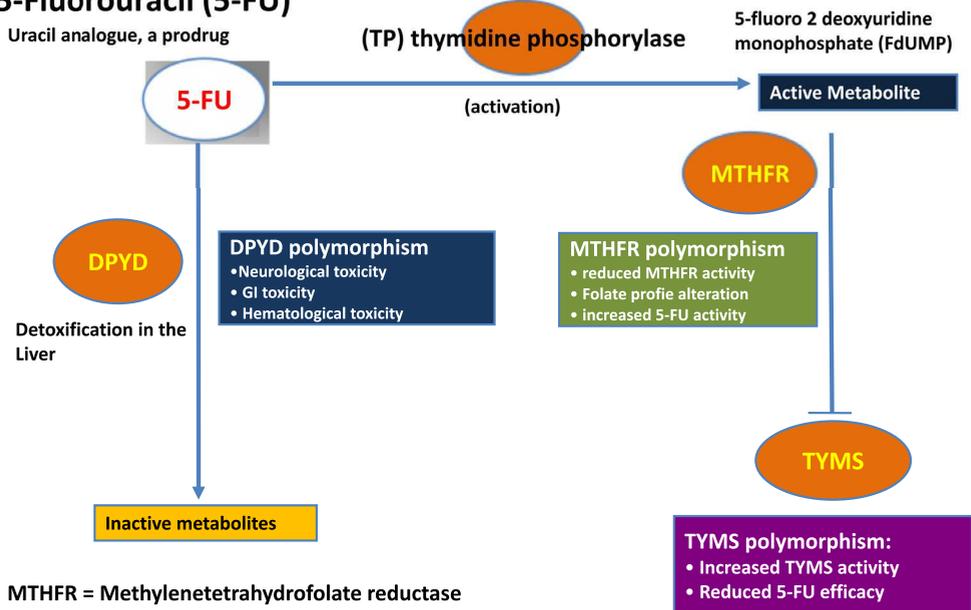


Fig. 1. 5-Fluorouracil metabolism

2.1 Dihydropyrimidine Dehydrogenase (DPYD)

5-FU is primarily degraded by the enzyme DPYD. When DPYD enzyme deficiency is present, blood levels of 5-FU and its active metabolites increase. DPYD enzyme deficiency

can result in fatal myelotoxicity, mucositis, neuro and cardiac toxicity such as myocardial infarction, sudden death, unstable angina, hypertension and pulmonary edema (Diasio, 2001, Fleming et al, 1993, Milano et al, 1999). Although technically difficult, determination of DPYD enzyme activity in mononuclear cells may be useful (Lu, Zhang, Diasio, 1993). The gene encoding the DPYD enzyme is located at 1p22 and consists of 23-exons (Wei et al, 1998). The reasons for DPYD deficiency are base substitutions, splicing abnormalities, and frame-shift mutations. More than 40 different DPYD polymorphisms have been reported so far (Ridge et al, 1998). Severe 5-FU toxicity is associated with 17 of these mutations. Homozygote and heterozygote DPYD dysfunction is estimated to be 0.1% and 3% to 5%, respectively in the general population. DPYD*2A is the most common DPYD polymorphism associated with 5-FU toxicity. Partial loss of the enzyme due to heterogeneous G>A transition at the 5' slicing donor consensus sequence in intron 14 leading to exon 14 skipping is associated with increased 5-FU toxicity due to inactive enzyme formation. The heterozygote form is characterized by severe toxicity while the homozygote form is characterized by mental deficiency. DPYD deficiency was demonstrated in 61% of patients with severe 5-FU toxicity. DPYD*2A polymorphism was identified in 50% of patients with grade 4 neutropenia. P456L (1358C>T) mutation is a novel DPYD variant associated with 5-FU related cardiotoxicity in pancreatic cancer patients (Shahrokni et al, 2009). However, multiple other factors and genes are thought to be involved in 5-FU toxicity because DPYD enzyme activity is normal in most patients with severe 5-FU toxicity (Mattison, Soong, Diasio, 2002, Ridge et al, 1998). Genetic variations of other enzymes particularly TYMS and TYMP involved in 5-FU metabolism are also important.

2.2 Thymidylate Synthase (TYMS)

TYMS is a target of 5-FU. It plays a significant role in folate metabolism. TYMS enables conversion of deoxyuridylate to deoxythymidylate (Miller and McLeod 2007, Johnston et al, 1995). Increased TYMS enzyme expression in tumors has been shown to be associated with resistance to 5-FU and capecitabine (Kidd et al, 2005). In particular, intratumoral TYMS levels in metastatic lesions are indicative of 5-FU resistance. This is a result of differences between TYMS expressions of primary and metastatic lesions (Pullarkat et al, 2001, Marsh et al, 2001, Salonga et al, 2000). The 5' untranslated region of the TYMS (5'-UTR) gene contains a 28-base pair tandem repeat sequence in the promoter region (TSER) which usually hosts double (allele *2) and triple (allele *3) repeats. The *3 allele is associated with a two to four fold increased expression of TYMS compared to *2. In patients with stage III colon cancer treated with adjuvant therapy, the outcome is poor in the presence of a TSER3 polymorphism. While the response rate is 50% in those with *2/*2, it is 8% in those with *3/*3 (Marsh et al, 2001). TYMS polymorphisms also affect survival. Median survival of cases with *2/*2 is 16 months vs. 12 months in cases of *3/*3. (Salonga et al, 2000). TYMS polymorphisms are also relevant in predicting response to neoadjuvant 5-FU treatment in rectal cancer. Cases of *3/*3 are associated with a poor response to the treatment (Salonga et al, 2000, Villafranca et al, 2001).

2.3 Thymidylate Phosphorylase (TYMP)

TYMP mRNA levels in patients not responding to 5-FU were 2.6-fold higher than in responding patients in pretreatment biopsies of patients with colorectal cancer (Metzger et

al, 1998). Survival was significantly increased in patients with both TYMS and TYMP under nonresponse cutoff values, and low intratumoral expression of TYMS and TYMP was associated with a response to 5-FU and improved survival (Metzger et al, 1998, Meropol et al, 2006).

2.4 Methylenetetrahydrofolate reductase (MTHFR)

MTHFR generates active folate which is necessary for normal hematopoiesis. Reduced MTHFR activity has been associated with increased sensitivity to 5-FU. Low activity MTHFR variants 677T and 1298C predispose to severe myelotoxicity in patients treated with 5-FU (Robien et al, 2005).

3. Gemcitabine

Chemotherapy has proved of only limited effectiveness in pancreatic cancer. Gemcitabine is a deoxycytidine nucleoside analogue used in the treatment of advanced-stage pancreatic cancer (Burriss et al, 1997). It has also proved to be of benefit in the adjuvant treatment of resected pancreatic cancer. Treatment with gemcitabine produces clinical benefit and symptom improvement in 20% to 30% of patients and 1-year survival rate of patients raised from 2% to 18% by gemcitabine. Gemcitabine undergoes metabolic activation by kinases to form a cytotoxic trinucleotide in the cell. Metabolic inactivation of gemcitabine by deamination is catalyzed by cytidine deaminase (CDA) or after phosphorylation by deoxycytidylate deaminase (DCTD) (Plunkett et al, 1995, Gandhi et al, 1990). Gemcitabine is a hydrophilic molecule and therefore does not cross the cell membrane by diffusion. To achieve gemcitabine cytotoxicity functional nucleoside transporters, namely human equilibrative nucleoside (hENT1) and human concentrative nucleoside transporters are needed. Nucleoside-transporter-deficient cells are highly resistant to gemcitabine (Spratlin et al, 2004, Mackey et al, 1998). "SLC29A1" is the most abundant of the nucleoside transporters. Intratumoral SLC29A1 protein expression, was related to prolonged survival in patients with pancreatic carcinoma treated with gemcitabine. Analysis of SLC29A1 mRNA expression revealed a significant correlation with longer survival in these patients following treatment (Sebastiani V et al, 2006, Giovannetti E, 2006).

Deoxycytidine kinase (DCK) deficiency is one of the most common forms of acquired resistance to gemcitabine in vitro (Sebastiani V et al, 2006, Bergman AM, et al, 2002). A correlation has been described between higher levels of DCK activity and increased gemcitabine sensitivity in patients with advanced pancreatic cancer treated with gemcitabine, whereas low tumoral DCK protein expression is associated with a worse overall survival (OS) and progression-free survival (PFS) (Sebastiani V et al, 2002, Kocabas NA et al, 2009). Ribonucleotide reductase (RR) is a target enzyme for gemcitabine (Goan YG et al, 1999). The pharmacology and pharmacogenetics of ribonucleotide reductase subunit M1 (RRM1) is of particular interest due to its potential role in gemcitabine chemosensitivity and synergy with other chemotherapeutic agents, particularly cisplatin (Sebastiani V, et al, Mini E et al, 2006, Ueno H et al, 2007). In genetically modified lung cancer cell lines, RRM1 expression correlated inversely with gemcitabine sensitivity (Bepler G et al, 2006). Deactivating enzymes of gemcitabine include 5', 3'-nucleotidase, cytosolic (NT5C), deoxycytidylate deaminase (DCTD), and cytidine deaminase (CDA). Upregulation of CDA may play a role in gemcitabine resistance, while impaired activity may result in increased

toxicity but not efficacy (Bepler G et al, 2006, Mathijssen RH et al, 2001). In addition to impaired tumor-specific mRNAs'/proteins' expression, a variety of genetic polymorphisms can have an impact on gemcitabine efficacy and toxicity. Tumor-specific expression of ENT1, RRM1 or ERCC1, and some DNA repair genetic polymorphisms appear to be indicators of prognosis in patients receiving gemcitabine chemotherapy. The expression level or genetic polymorphism of CDA seems to be a good predictor of adverse side effects caused by gemcitabine. SNP, CDA 208A4G, or CDA expression level may be used as biomarkers for prediction of gemcitabine-related severe toxicity: germline homozygosity for CDA 208A in a Japanese patient with pancreatic cancer treated with gemcitabine and cisplatin resulted in severe hematologic and nonhematologic toxicity (Yonemori K et al, 2005). This is an important finding since considerable numbers of homozygote carriers of CDA 208A exist in Japanese and some African populations (Ueno H et al, 2007, Yonemori K et al, 2005).

4. Irinotecan (CPT-11)

Irinotecan is a camptothecin analogue which acts as a topoisomerase I inhibitor (Mathijssen RH et al, 2001). It is used alone or in combination with 5-FU, and folinic acid, in the treatment of colorectal cancer, gastric cancer, and in combination with 5-FU, folinic acid and oxaliplatin in advanced pancreatic cancer. Irinotecan may cause unpredictable severe toxicity such as diarrhea and neutropenia which may lead to either discontinuation or significant dose reduction of the drug. Irinotecan is activated to its cytotoxic metabolite SN-38 that inhibits the nuclear topoisomerase 1 enzyme, which is critical for DNA replication. Activation, transportation, and deactivation of irinotecan are complex and involve several enzymes, including carboxylesterase (CE), "CYP3A4", and uridine diphosphate glucuronosyltransferase (UGT1A1). Irinotecan is converted to its active metabolite, SN38, by the CE present in the gastrointestinal tract (Figure 2) (Charasson et al, 2004, Khanna et al, 2000). This enzyme has many allelic variants and genotypes. SN38 is primarily inactivated in the liver by UGT1A1 via glucuronidation. Mild hereditary deficiency of UGT1A1 leads to Gilberts syndrome which is characterized by intermittent hyperbilirubinemia (Innocenti et al, 2004, Iyer et al, 2002). Since patients with Gilbert's syndrome experienced severe toxicity in early phase studies, the association of irinotecan toxicity and the UGT1A1 polymorphism has been under thorough investigation (Wasserman et al, 1997). UGT1A1 inactivates SN38 via a phase II reaction. The wild type UGT1A1 is designated as UGT1A1*1. More than 50 genetic variations of UGT1A1 have been identified up to now (Tukey et al, 2002). Each of these leads to different degrees of functional variations. Among them UGT1A1*6, UGT1A1*28, UGT1A1*36 and UGT1A1*37 are functionally important polymorphisms. The UGT1A1*28 polymorphism is associated with reduced UGT1A1 expression and, as a result, decreased glucuronidation of SN38. This, in turn, increases blood levels of active metabolites resulting in increased toxicity (Khanna et al, 2000, Innocenti 2004, Iyer 2002, Hoskins et al, 2007). The pharmacokinetics of irinotecan is poorly associated with body surface area. Since SN38 undergoes glucuronidation to a lesser extent in patients with Gilbert and Crigler Najjar syndromes, irinotecan toxicity increases in these patients, because of reduced or deficient expression levels of UGT1A1. Gilbert syndrome results from the UGT1A1*28 homozygote transition of a promoter polymorphism caused by seven TA repetitions. In the presence of the UGT1A1*28 polymorphism, transcription is decreased by 70% and toxicity is increased. Patients with the 7/7 genotype (homozygous for seven TA repetitions) exhibit a

9.3-fold increase in risk of grade 4 neutropenia, and irinotecan is associated with severe side effects in this population (Iyer et al, 2002, Hoskins et al, 2007; McLeod et al, 2003). In an early study the UGT1A1*28 allele increased the risk of leukopenia and/or diarrhea, however most of the later studies found only increased risk of hematological toxicity such as neutropenia (Ando et al, 2000). In fact, in a meta-analysis of 10 studies assessing the irinotecan induced toxicity in UGT1A1*28 patients, irinotecan dose, and overall toxicity, risk of experiencing irinotecan induced hematologic toxicity for homozygous UGT1A1*28 patients was found to be a function of the dose of irinotecan administered, and genotyping was recommended at only high doses (> 200 mg/m²) of irinotecan (Hoskins et al, 2007). Genotyping has limited benefit at intermediate doses, such as 180mg/m² used in the FOLFIRI (folinic acid/5-FU/irinotecan) regimen. Unless administered concomitantly with another myelotoxic agent, UGT1A1*28 testing is not recommended at doses < 150 mg/m².

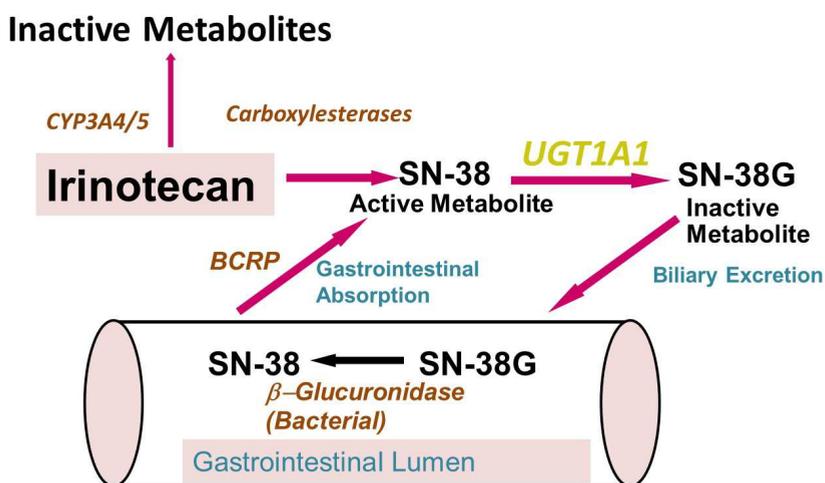


Fig. 2. Irinotecan Metabolism

Transport proteins that excrete irinotecan and metabolites have also been investigated for their potential association with irinotecan response and toxicity. P-glycoprotein represents one of these proteins, and it is encoded by the ATP binding B1 (ABCB1 or MDR1) gene. However, the pharmacogenetic results regarding ABCB1 and irinotecan are conflicting to date. Genetic variation in ABCB1 was associated with early toxicity and lower response to treatment. Specifically, carriers of the ABCB1 1236T-2677T-3435T haplotype responded to treatment less frequently with shorter survival (Glimelius et al, 2011).

5. Platinum compounds (Cisplatin and Oxaliplatin)

Cisplatin and oxaliplatin are commonly used in gastrointestinal cancers (Vermorken et al, 1984, Raymond et al, 1998, Levi et al, 2000) Platinum analogues block DNA replication by forming different DNA adducts, through intra-strand and inter-strand crosslinks. Platin resistance occurs due to detoxification or efficient repair of DNA by the nucleotide excision repair system. DNA repair enzymes "ERCC1" and "ERCC2" –also known as "XPD" and

glutathione S transferase π (GSTP) enzymes—are involved in the activity of these agents (Levi et al, 2000). GST π is a phase II metabolic enzyme that inactivates platinum derivatives by adding a glutathione to its electrophile group. High expression of the genes that code for these enzymes is inversely correlated with therapeutic response in colorectal and gastric cancer (Ruzzo et al, 2007). Preclinical models of oxaliplatin resistance have also been studied in colorectal cancer cell lines. In these cell lines a total of 6 target genes were identified: AKT1, CDK5, RGS11, GARP, TRIP, and UGCGL1. Three of these genes (AKT1, CDK5 and TRIP) were shown to be involved in NF- κ B pathway regulation. It was suggested that low levels of TRIP and high levels of AKT1 and CDK5 could contribute to NF- κ B activation and consequently cell antiapoptotic activity and oxaliplatin acquired resistance. These findings show that the NF- κ B pathway plays a pivotal role in mechanisms of acquired oxaliplatin resistance (Martinez-Cardus et al, 2009).

6. Combination chemotherapy

6.1 Folfox (Oxaliplatin/5-FU/folinic acid)

Many chemotherapy combinations are used in the treatment of gastrointestinal cancers. However, strong evidence of pharmacogenetics is available only in a minority of the reference studies (Stoehlmacher et al, 2004; Goldberg et al, 2006). The N9741 trial is a randomized phase III trial designed to compare the efficacy of FOLFOX (folinic acid/5-FU/oxaliplatin), IROX (irinotecan/oxaliplatin), and IFL (irinotecan/bolus 5-FU/folinic acid) in patients with metastatic colorectal cancer (Goldberg et al, 2006). The pharmacogenetic evaluation of this study revealed that both the objective response rate and incidence of grade ≥ 3 side effects, particularly diarrhea, were lower in black patients. The low response rate in black patients was especially marked in the FOLFOX arm. Overall, the rate of response was 41% and 30% in white and black patients, respectively ($P = .015$). The rate of severe toxicity was 48% in whites and 34% in black patients in the FOLFOX arm ($P = .047$). Despite the lack of significant median survival difference between these two patient groups in the FOLFOX arm, median survival was lower in black patients in both the IFL and IROX groups. In all arms, black patients experienced less toxicity, particularly less diarrhea, compared to white patients. The UGT1A1 7/7 polymorphism was identified at a rate of 21% and 9% in black and white patients, respectively, in this study. However, the role of the UGT1A1 polymorphism with respect to response and toxicity could not be demonstrated. Significant differences were also detected between white and black patients in the prevalence of other pharmacogenetic variances such as CYP3A, MDR (multidrug resistance), ERCC1, ERCC2, and GSTP. These genes are important in the metabolism and detoxification of irinotecan and oxaliplatin (Grothey et al, 2005). Of note, the type of GSTP polymorphism was shown to be associated with early development of oxaliplatin neuropathy in patients receiving FOLFOX.

The polymorphism that causes a single nucleotide change of C to T, at codon 118, converts a codon of common usage (AAC) to a less used codon (AAT), both coding for asparagine. This change results in decreased ERCC1 gene expression, which impairs repair activity. A small study showed that the ERCC1 codon 118 polymorphism predicted response to oxaliplatin/5-FU chemotherapy in patients with advanced colorectal cancer (Viguier et al, 2005). In this retrospective study including 91 patients, response rate was 61.9%, 42.3%, and 21.4% in T/T, C/T, and C/C groups, respectively ($P = 0.018$). However, the results of the

studies regarding the ERCC1 codon 118 polymorphism are somewhat contradictory, likely due to a variety of factors such as ethnicity, environment (smoking or diet), the number of patients enrolled and/or linkage to other polymorphisms (Ryu, 2006). A SNP in codon 751 of the ERCC2 gene which leads to glutamine instead of lysine, was associated with a reduced response rate (Park et al, 2001, Stoecklacher et al, 2004). Additionally, patients with the GSTP1 105 Val/Val genotype had a better progression free survival (PFS) and overall survival (OS) than patients carrying the GSTP1 105 Ile allele (Stoecklacher et al, 2004). In a more recent study analyzing the pharmacogenetic factors in patients with advanced colorectal cancer treated with FOLFOX chemotherapy PFS was related only to genes involved in oxaliplatin pharmacodynamics, with a tendency for a better outcome in patients bearing the GSTP1 105 Val/Val genotype or the XPD 751Lys allele (Etienne-Grimaldi et al, 2010). Lymphocytic activity of GSTP1 has been shown to be significantly reduced in GSTP1 105 Val/Val patients compared with GSTP1 105 Ile/Ile patients (Dusinská et al, 2001). However, the functional impact of XPD 751 Lys→Gln at the protein level is not clearly established.

6.2 Cisplatin/5-fluorouracil

Combination of cisplatin and 5-FU (CF) constitutes the backbone of chemotherapy regimens commonly used for upper gastrointestinal system tumors including gastric and hepatobiliary cancer (Kilickap et al, 2011). In gastric cancer TYMS and ERCC gene expression has been studied individually as the predictors of chemoresistance (Lenz et al, 1996, Metzger et al, 1998). In another study although TYMS and ERCC1 expression associated with poor prognosis, it did not reach statistical significance ($P = 0.076$) (Metzger et al, 1998). Kim *et al*, developed a three gene predictor of clinical outcome for metastatic gastric cancer patients treated with cisplatin and 5-FU (Kim et al, 2010). The combined expression of MYC, epidermal growth factor receptor (EGFR) and fibroblast growth factor receptor 2 (FGFR2) was found to be an independent predictor of decreased OS of CF treated metastatic gastric cancer patients (Kim et al, 2010). The findings of the study showed that over expression of these 3 genes was associated with chemoresistance and the results were consistent with the experimental studies showing that inhibitors of EGFR act synergistically with cisplatin and 5-FU, while an FGFR2 inhibitor acts synergistically with 5-FU and MYC over expression is associated with cisplatin resistance (Kim et al, 2010). Taken together, combined expression of MYC, EGFR and FGFR2 is predictive of poor survival in patients with metastatic gastric cancer treated with CF chemotherapy.

The xCT gene, which codes for part of the plasma membrane cysteine/glutamate transporter, contributes to tumor cell protection against immune defense mechanisms (Huang et al, 2010). The plasma membrane xc-cysteine/glutamate transporter mediates cellular uptake of cysteine in exchange for intracellular glutamate and is highly expressed by pancreatic cancer cells. In advanced pancreatic cancer Huang *et al*, looked at the prognostic significance of SNPs in the xCT gene in patients treated with a combination of gemcitabine and platinum (Huang et al, 2010). The xCT gene, encodes the cysteine-specific xCT protein subunit of xc-, which is important in regulating intracellular glutathione levels, critical for cancer cell protection against oxidative stress, tumor growth and resistance to chemotherapeutic agents. A statistically significant correlation was noted between the 3' UTR xCT SNP rs7674870 and OS: Median survival time (MST) was 10.9 and 13.6 months,

respectively, for the TT and TC/CC genotypes ($P = 0.027$). In another study Pacetti *et al*, investigated polymorphisms in genes involved in activity and resistance to drugs, mainly DNA repair gene polymorphisms, in an effort to link them to treatment response. The substitution of glutamine for lysine in position 751 of the XPD gene (Figure 2) led to increased overall survival from 262 days to 446 days (Pacetti *et al*, 2010). These studies suggest that genetic polymorphisms in xCT gene may serve as a predictor of treatment outcome in advanced pancreatic cancer.

7. Biologic agents

7.1 Overview

Biologic agents used in GI cancers alone or in combination with chemotherapy include bevacizumab (Avastin, Roche), cetuximab (Erbix, KGaA), panitumumab (Vectibix, Amgen), and erlotinib (Tarceva, Roche), sunitinib (Sutent, Pfizer), imatinib (Gleevec, Novartis). These drugs do not act only through different mechanisms of action but also demonstrate differences in their pharmacokinetics and pharmacodynamics. Meanwhile, data on their pharmacogenetics are only now emerging.

7.2 Bevacizumab

Bevacizumab is a humanized monoclonal antibody (MoAB) that binds the vascular endothelial growth factor (VEGF). Increased VEGF expression is involved in tumoral angiogenesis and associated with poor prognosis. Bevacizumab prevents receptor binding of VEGF, and inhibits VEGF signaling pathways, thus stops angiogenesis and tumor growth. The therapeutic benefit of bevacizumab has been shown in the treatment of patients with advanced-stage colorectal cancer. Thus far, however, adequate pharmacogenetic data have not been produced to predict toxicity, response, or resistance.

7.3 EGFR monoclonal antibodies (Cetuximab and Panitumumab)

Cetuximab and panitumumab are MoAB used as single agents or in combination with chemotherapy for the treatment of advanced colorectal cancer. Cetuximab is a MoAB that binds to the EGFR and blocks EGF signaling pathway and tumor growth. Panitumumab is the anti-EGFR MoAB similar to cetuximab, binds EGFR and inhibits downstream of EGF signaling. Panitumumab is a fully human MoAB in contrast to cetuximab which is chimeric. The pioneering studies of BOND trials, showed that cetuximab may provide benefit in patients with chemotherapy refractory advanced colorectal cancer (Saltz *et al*, 2007). In the BOND 2 trial metastatic colorectal cancer patients progressing after irinotecan-based chemotherapy were randomized to receive irinotecan plus bevacizumab plus cetuximab (CBI) or bevacizumab and cetuximab (CB) (Lenz *et al*, 2007). In this trial, germline polymorphisms of the genes involved in angiogenesis (VEGF, interleukin-8 [IL-8], transforming growth factor [TGF]- β), the EGFR pathway (EGFR, cyclooxygenase-2, E-cadherin), DNA repair (ERCC1, ERCC2, XRCC1, XPD), and drug metabolism pathway (GSTP, UGT1A1) were investigated. Genomic DNA was extracted for genotyping from 65 patients (31: CBI arm and 34: CB arm). Thirty five patients had tissue samples available for the gene expression assay (18: CBI arm and 17: CB arm). High intratumoral gene expression levels of EGFR, VEGFR2 and NRP1 were associated with longer OS in patients receiving

combined monoclonal antibodies with or without irinotecan. The FCGR3A V158F, cyclinD1 A870G and EGFR R497K polymorphisms were associated with clinical outcome in patients receiving the cetuximab and bevacizumab combination independent of KRAS mutation status (Lenz et al, 2007, Zhang et al, 2007). Patients with high intratumoral EGFR gene expression levels had a median survival time of 21.8 (range, 9.6-28.2) months, compared to patients with low EGFR gene expression levels, whose median survival was 10.2 (range, 8.3-13.6) months ($P = 0.033$). In the RP analysis, the EGFR gene expression level was found to be the best single determinant of survival (Zhang et al, 2007)

Initially anti-EGFR antibodies were tested in patients with metastatic colorectal cancer which showed elevated EGFR expression, as determined by immunohistochemistry. However, response to EGFR MoAB was not found to be correlated to EGFR expression. Retrospective data suggested that the severity of skin rash might be positively correlated with tumor response to anti-EGFR MoAB, but only in patients with tumors expressing wild type K-RAS. In the NCIC CTG CO17 study a rash of grade 2 or higher was strongly associated with improved survival in patients treated with cetuximab (Jonker et al, 2007). A correlation between K-RAS mutation and resistance to the EGFR antibodies cetuximab and panitumumab has been demonstrated. K-RAS mutations account for approximately 30% to 40% of patients with mCRC. (Van Cutsem et al, 2008, Amado et al, 2008, Bokemeyer et al, 2008). Patients with a K-RAS mutation in codons 12, 13 and 61 in their tumor tissue have lower rates of response to cetuximab and panitumumab and shorter PFS time. The benefit of anti-EGFR MoAB monotherapy is limited to only the patients with K-RAS wild type CRC except patients with the codon 13 D13G K-RAS mutation benefit from the therapy similar to the wild type tumors (De Roock et al, 2010). Therefore, K-RAS mutation analysis is required before prescribing EGFR MoAB therapies.

The B-type Raf kinase BRAF V600E mutation was detected in 11 of 79 patients who had wild type K-RAS (Di Nicolantonio et al, 2008). This BRAF mutation is associated with resistance to cetuximab and panitumumab with significantly shorter PFS and OS compared to wild type patients (Di Nicolantonio et al, Di Fiore et al, 2008). Mutations of genes other than K-RAS and BRAF, such as the phosphatase and tensin homologue (PTEN), and phosphatidylinositol 3-kinase (PI3K) were also associated with shorter survival of MCRC patients receiving EGFR antagonists (Karapedis et al, 2008). Thus, these mutations may serve as additional biomarkers to predict resistance of EGFR antagonists.

7.4 Erlotinib

Erlotinib belongs to a group of drugs called EGFR tyrosine kinase inhibitors. EGF has receptors on cancer cell surfaces. Stimulation of this receptor activates the tyrosine kinase enzyme inside the cell. The drugs that inhibit this enzyme, and stop the growth factor receptor are known as tyrosine kinase inhibitors (TKIs). Erlotinib is a small-molecule TKI targeting EGFR (Hidalgo et al, 2001; Li et al, 2007). Erlotinib, similarly to other EGFR-directed therapies, is associated with toxicity involving skin rash and diarrhea. The molecular basis of these side effects is under investigation. Basal layers of both the epidermis and the GI mucosa express EGFR, and EGFR signaling has been implicated in the physiological regulation of these tissues. Inhibition of this physiological pathway is implicated in toxicity. Erlotinib is metabolized predominantly by CYP3A4, so inhibitors of this enzyme would be expected to increase systemic availability and inducers would be

expected to decrease it (Moore et al, 2007a). Potent inducers of CYP3A4 may reduce the efficacy of erlotinib, whereas potent inhibitors of CYP3A4 may lead to increased toxicity (Hidalgo et al, 2001, Li et al, 2007, Rudin et al, 2008). For example, concomitant use of ketacanazole, a CYP3A4 and ABCB1 inhibitor, increases the AUC of erlotinib by 66% which will result in increased erlotinib toxicity. Meanwhile pre- or co-treatment with rifampicin, a CYP3A4 inducer, increases erlotinib clearance by three-fold and reduces AUC by 66%, which will result in the loss of clinical activity. Therefore concomitant use of inhibitors and inducers of CYP3A4 should be avoided.

Besides CYP genes the inhibition of glucuronidation may also cause interactions between erlotinib and substrates of UGT1A1. Patients with low expression of UGT1A1 or genetic glucuronidation disorders may have hyperbilirubinemia (Rudin et al, 2008). In advanced pancreatic cancer, erlotinib in combination with gemcitabine showed statistically superior overall survival compared with gemcitabine alone (6.4 months vs. 5.9 months, respectively) (Moore MJ et al, 2007). In this study, patients responded equally well to treatment with erlotinib regardless of whether their tumors expressed abnormal levels of EGFR. In a subgroup of analyses in this study the mutation status of the K-RAS and EGFR gene copy number (GCN) were evaluated as predictive markers in 26% of patients who had tumor samples available for analysis. The K-RAS mutation status was evaluated by direct sequencing of exon 2, and EGFR GCN was determined by fluorescence in situ hybridization (FISH) analysis. The results were correlated with survival, which was the primary endpoint of the trial. K-RAS mutations were identified in 78.6% of the patients and EGFR amplification or high polysomy (FISH-positive results) was identified in 46.7% of the patients. The hazard ratio of death between gemcitabine/erlotinib and gemcitabine/placebo was 0.66 (95% confidence interval [CI], 0.28-1.57) for patients with wild type K-RAS and 1.07 (95% CI, 0.68-1.66) for patients with mutant K-RAS (P value for interaction = .38), and the hazard ratio was 0.6 (95% CI, 0.34-1.07) for FISH-negative patients and 0.90 (95% CI, 0.49-1.65) for FISH-positive patients (P value for interaction = .32). Although survival was longer in patients with wild type K-RAS in comparison to K-RAS mutated patients, in this molecular subset analysis of patients from NCIC CTG PA.3, EGFR GCN and K-RAS mutation status were not identified as markers predictive of a survival benefit from the combination of erlotinib with gemcitabine for the first-line treatment of advanced pancreatic carcinoma (da Cunha Santos et al, 2010, Moore MJ et al, 2007b).

In the AViTA study, patients with advanced stage pancreatic cancer were treated with gemcitabine plus erlotinib with or without bevacizumab. In this study, although no molecular pharmacogenetic marker has been identified yet, survival was positively correlated with severity of erlotinib induced skin rash (Verslype C et al, 2009). Therefore, reassessment of erlotinib treatment is recommended in patients who do not develop rash within the first 4 to 8 weeks of treatment.

7.5 Imatinib

Imatinib mesylate is approved for the treatment of advanced and also resected high risk patients with cKIT or platelet derived growth factor receptor alpha (PDGFRA) activating mutation positive gastrointestinal stromal tumors (GIST). Sensitivity of imatinib in GIST correlates to exon mutations of cKIT and PDGFRA. The outcome of patients with cKIT exon 11 mutations are more favorable compared to exon 9 mutations and to wild type tumors.

Approximately 80% of GISTs harbor an activating mutation in the cKIT gene and another 5% to 7% have a PDGFRA gene mutation (Heinrich MC et al, 2008). These mutations are not only important in tumorigenesis, but also predict treatment response to imatinib, and provide prognostic information. If the tumors have a c-KIT exon 11 mutation the response rate is 69% to 86%, but only 17% to 48% in patients with tumors harboring a c-KIT exon 9 mutation (Heinrich MC et al, 2008). These patients respond better to the dose of 800 mg imatinib compared to the standard 400 mg dose. Most of PDGFRA gene mutations are associated with imatinib response, with the most notable exception of D842V. In wild type GIST without any c-KIT and PDGFRA mutations, the response rate to imatinib is only 0% to 45% (Heinrich MC et al, 2008). Median time to progression (TTP) is 25, 17, and 13 months for patients with tumor mutations in c-KIT exon 11, c-KIT exon 9, and neither c-KIT nor PDGFRA genes, respectively (Heinrich et al, 2008). Median OS is 60, 38, and 49 months, respectively. Although patients may experience prolonged disease control while on imatinib, most patients will develop imatinib resistance within 2-3 years on therapy. Lowered plasma levels of imatinib over time is often responsible for disease progression. This phenomenon is called as "acquired pharmacokinetic drug resistance". This may be because of an altered expression pattern or activity of drug transporters such as efflux transporters (ATP-binding cassette transporters, such as ABCB1 and ABCG2) and uptake transporters [solute carriers such as organic cation transporter 1 (OCT1) and organic anion transporting polypeptide 1A2 (OATP1A2)]. ABCB1 and ABCC1 expression was shown in GIST, whereas ABCB1, ABCG2, and OCT1 were found in mononuclear cells in CML patients. Despite increasing accumulation of preclinical data, clinical studies on imatinib pharmacogenetics are still insufficient and the results are somewhat contradictory.

7.6 Sunitinib

Sunitinib is an oral, multitargeted TKI. It inhibits VEGF receptors (VEGFRs) 1, 2, and 3, PDGFR α and β KIT, Fms-like tyrosine kinase 3 receptor (FLT3), and the receptor encoded by the RET proto-oncogene. Among the GI tumors sunitinib is approved for first-line treatment of metastatic pancreatic neuroendocrine tumours (PNET) and in imatinib-resistant metastatic GIST. In a multicenter study including patients with GIST, metastatic renal cell cancer or other cancers, genetic markers in the pharmacokinetic and pharmacodynamic pathways of sunitinib that predispose to development of toxicity were investigated (van Erp et al, 2009). The study was performed in 219 patients treated with single-agent sunitinib. A total of 31 SNPs in 12 candidate genes were analyzed for a possible association with toxicity. The risk for leukopenia was increased when the G allele in CYP1A1 2455A/G (odds ratio (OR), 6.24; $P = .029$) or the T allele in FLT3 738T/C (OR, 2.8; $P = .008$) were present or CAG in the NR1I3 (5719C/T, 7738A/C, 7837T/G) haplotype (OR, 1.74; $P = .041$) was absent. Any toxicity higher than grade 2 prevalence was increased when the T allele of VEGFR2 1191C/T (OR, 2.39; $P = .046$) or a copy of TT in the ABCG2 (-15622C/T, 1143C/T) haplotype (OR, 2.63; $P = .016$) were present. The risk for mucosal inflammation was increased in the presence of the G allele in CYP1A1 2455A/G (OR, 4.03; $P = .021$) and the prevalence of hand-foot syndrome was increased when a copy of TTT in the ABCB1 (3435C/T, 1236C/T, 2677G/T) haplotype (OR, 2.56; $P = .035$) was present. This study suggested that polymorphisms in specific genes encoding for metabolizing enzymes, efflux transporters, and drug targets are associated with sunitinib-related toxicity. The response of patients with advanced GIST to sunitinib is related to the type of primary

mutation. Patients with original (pre-imatinib) exon 9 mutant or wild type tumor had a significantly longer duration of response compared to patients with exon 11 mutations. The median time to progression was 14.3 months for patients with original exon 9 mutations, 13.8 months for patients with wild type cKIT and PDGFRA, and 5.1 months for patients whose original mutation was in exon 11 (Heinrich MC et al, 2008).

8. Conclusion

Despite progress in the development of new chemotherapy agents and targeted therapies, and the improved outcome in patients with GI cancers, there is still need for development of more efficacious treatments. Meanwhile, individualization of management of cancer patients is also crucial because only a portion of patients respond to a given treatment, usually with a low complete response rate. Therefore oncologists are seeking ways to predict whether a selected chemotherapy will be effective and tolerable in patients prior to treatment. Coupled with the complexity and diversity of each individual patient and the disease, each case should be handled uniquely and treatment should be tailor made. At this point pharmacogenetic plays a pivotal role. Recent progress in our understanding of carcinogenesis and molecular biology led to development of sophisticated pharmacogenetic assays to facilitate the delivery of more effective, less toxic chemotherapy regimens by individualizing treatments for patients with relatively resistant tumors of the GI tract. Based on the results of pharmacogenetic studies of clinical trials new tests are on the horizon and, data from these tests will enable cancer physicians to treat their patients better and save more lives. In this chapter recent pharmacogenetic studies relevant to the treatment of patients with GI cancer are reviewed. Genetic polymorphisms and tumor gene expression patterns are discussed. Many of the trials reviewed herein are expected to result in approval of new pharmacogenetic tests.

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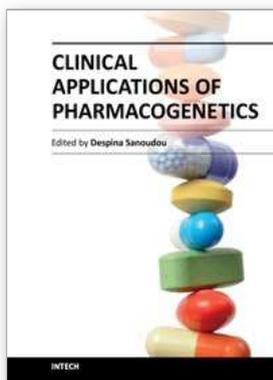
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The rapidly evolving field of Pharmacogenetics aims at identifying the genetic factors implicated in the inter-individual variation of drug response. These factors could enable patient sub-classification based on their treatment needs thus expediting drug development and promoting personalized, safer and more effective treatments. This book presents Pharmacogenetic examples from a broad spectrum of different drugs, for different diseases, which are representative of different stages of evaluation or application. It has been designed so as to serve both the unfamiliar reader through explanations of basic Pharmacogenetic concepts, the clinician with presentation of the latest developments and international guidelines, and the research scientist with examples of Pharmacogenetic applications, discussions on the limitations and an outlook on the new scientific trends in this field.

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