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Pharmacogenetics and Pharmacogenomics of Colorectal Cancer: Moving Towards Personalized Medicine

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1. Introduction

Colorectal cancer (CRC) remains one of the most deadly diseases in the western world, and starts to become a concern in developed countries (Labianca et al., 2010). However, significant steps have been made recently in CRC therapy. Until the 80's, 5-fluorouracil (5-FU) was the only available drug to treat patients, with limited efficacy. Today, 4 cytotoxic agents (5-FU associated with folinic acid, capecitabine, oxaliplatin, irinotecan) and three monoclonal antibodies (cetuximab, panitumumab, bevacizumab) are available, mostly as part of combinations (Koutras et al., 2011). In particular, the rise of targeted therapies in digestive oncology has fueled a new hope by significantly stretching the therapeutic options available so far. Despite these improvements, treatment of metastatic CRC (mCRC) remains a challenging task, and it is acknowledged now that although improving response rates, the introduction of the latest targeted therapies only marginally impacts on either progression free survival (PFS) or overall survival (OS) of mCRC patients. Because of the cost of these new therapies, identifying biomarkers likely to sort patients on their ability to benefit or not, from these new drugs is paradigmatic of the current trend to move towards a more personalized medicine in oncology. Because genetic variability is one of the main factor regulating efficacy and toxicity of most anticancer agents, addressing the issues of pharmacogenomics and pharmacogenetics (PGx) in CRC patient becomes critical, far beyond the only use of costly targeted therapies. Although often used interchangeably, the term "pharmacogenetics" refers historically to inherited changes in genes coding for drug metabolizing enzymes or membrane transporters, thus impacting on the pharmacokinetic (PK) profile and exposure levels eventually, whereas "pharmacogenomics" is a broader definition encompassing genetic changes at the tumor level potentially affecting drug response (Amstutz et al., 2011). Whether they are somatic or found in the germline, all these mutations can potentially have deleterious impacts on the clinical outcome of patients with CRC cancer. At the tumor level, genetic changes affecting the expression of pharmacological

targets or downstream signaling pathways can lead to treatment failure, as highlighted by the now canonical KRAS mutational status in patients undergoing anti-EGFR therapies. Constitutive mutations are mostly associated with increased toxic risk, as largely publicized by the dihydropyrimidine dehydrogenase (DPD) deficiency syndrome, a condition that puts 5-FU patients at risk of life-threatening toxicities. Of note, when not directly life-threatening, inherited genetic mutations affecting drug disposition in the body and pharmacokinetics can ultimately lead to treatment failure too, because the induced-toxicities often require discontinuation of the treatments until the patient recovers. For all these reasons, developing pharmacogenetic and pharmacogenomic testing in routine clinical practice is now seen as a major issue in oncology.

2. Pharmacogenomics: A matter of life & death at the tumor level

2.1 Cytotoxics: Why should we not forget that they are targeted therapies too

Standard care of colorectal cancer includes the use of a variety of cytotoxic agents, used either alone or more frequently as part of combinations (e.g., the canonical Folfiri and Folfox4 regimen). Each of these drugs have their own specific target (e.g., thymidylate synthase for 5-FU, DNA for oxaliplatin, topoisomerase I for irinotecan) and in this respect, numerous studies have focused on the deregulations affecting these targets, either at the genetic or the molecular level, as an attempt to predict treatment efficacy. Indeed, variations in the expression level of the targeted protein, polymorphisms inducing conformation changes, or increase in the repair systems/salvage pathways have been identified as major causes for treatment failure in mCRC patients.

2.1.1 5-FU & Oral 5-FU: The older, the better

5-FU remains the pivotal drug for treating CRC. Initially used alone, it soon turned to be systematically associated with folinic acid so as to enhance its effect as an antimetabolite, before being introduced as the backbone of several polychemotherapies including irinotecan (a.k.a. Folfiri regimen) or oxaliplatin (a.k.a. Folfox regimen). 5-FU's main target is thymidylate synthase (TS), an enzyme essential to the DNA synthesis and cell replication. Several genetic polymorphisms can affect both *TYMS*, the gene coding for TS, and the folate cycle necessary for the synthesis of methylene tetrahydrofolate, the cofactor required for a complete inhibition of the target through the formation of a stable ternary complex between the enzyme, the cofactor, and fluorodeoxyuridine monophosphate (FdUMP). TS overexpression in tumors is generally associated with resistance to 5-FU treatment, both in vitro and at the bedside (Popat et al., 2004, Lenz et al., 2004). Conversely, another pivotal study has demonstrated that higher TS expression was predictive of higher response with adjuvant fluoropyrimidine (Edler et al., 2002). However, other clinical reports failed in demonstrating such relationship (Locker et al., 2006, Lurje et al., 2009), thus preventing substantial step to be undertaken for implementing screening for TS expression in tumors in routine clinical practice. Variations in TS expression are, at least in part, related to mutations affecting the *TYMS* gene promoter. For instance, the TSER*3 genotype has been associated with increased mRNA production, thus potentially leading to lower response rates in mCRC patients treated with 5-FU (Uetake et al., 1999). Beside the issue of over-expressing TS tumors likely to resist to 5-FU, constitutive polymorphisms in the 5′ and 3′UTRs of the *TYMS* gene responsible for downregulation of TS, have been associated with increased toxicities in patients treated with 5-FU or oral capecitabine (Larguiller et al., 2006). However,

as for TS expression level in tumors, the actual clinical relevance of these polymorphisms is far from being consensual. Lower response rates have been reported in colorectal cancer patients with the TS 5'-UTR 3R genotypes (ie, TSER*3), as compared to individuals harboring the homozygous TS 5'-UTR 2R/2R genotype (Salgado et al., 2007). Of note, other groups (Stoehlmacher et al., 2004, Kostopoulos et al., 2009) failed in observing any significant difference in the clinical outcome according to the TS 5'-UTR genotypes, whereas conversely, other authors (Jakobsen et al., 2005; Dotor et al., 2006) found longer survival in carriers of TS 5'-UTR 3R genotypes as compared with those carrying the TS 5'-UTR 2R/2R genotypes. Such conflicting results for predicting outcome from *TYMS* genomic status is not surprising. Several factors such as genetic and epigenetic regulations may interfere with the genotype-to-phenotype relationships (Pullmann et al., 2006). For instance, the loss of heterozygosity in tumours at the TS locus may cause the heterozygous TS 5'-UTR 2R/3R risk genotype to acquire either the 2R/loss or the 3R/loss genotype. Consequently, individuals theoretically at risk of treatment failure on the basis of their TS 5'-UTR 2R/3R genomic status may harbor actually the favorable 2R/loss genotype in cancer cells and exhibit higher response eventually when treated with 5-FU (Ruzzo et al., 2007). In addition to target TS, other non-synonymous SNPs (677C>T: MTHFR*4 and 1298A>C:MTHFR*6 allelic variants) affecting methylene tetrahydrofolate reductase (MTHFR), one of the key-enzyme involved in the synthesis of reduced folate cofactor, could lead to lack of efficacy when down-regulated (Etienne-Grimaldi et al., 2007, Zintsaras et al., 2009, Braun et al., 2009). However, as for *TYMS*, the actual impact of *MTHFR* genetic polymorphisms on the clinical outcome with 5-FU or 5-FU-derivatives remains to be fully elucidated because inconsistent data have been generated so far (Sharma et al., 2008, Ruzzo et al., 2007). All these contradictory findings with *TYMS* and the associated *MTHFR* genomic status are better understood when one keeps in mind that TS is not the main locus of action of 5-FU. Incorporation into RNA and DNA can be alternative mechanisms of actions for the cytotoxic effects of 5-FU, depending on the way the drug will be metabolized within tumor cells (Ciccolini et al., 2000a). In this respect, the expression levels of activating/deactivating enzymes at the tumor level (eg, orotate phosphoribosyl transferase, thymidine kinase, thymidine phosphorylase, dihydropyrimidine dehydrogenase) have been associated with clinical outcome in patients treated with 5-FU-containing regimen, although once again the data collected so far proved to be rather conflicting (Ciccolini et al., 2004; Soong et al., 2008). For instance, thymidine kinase is implicated both in the activation of 5-FU to active metabolite FdUMP with subsequent theoretical better TS inhibition if highly expressed, and in the *de novo* salvage pathway likely to help cancer cells to survive to 5-FU-induced thymineless stress (Fanciullino et al., 2007). Similarly, thymidine phosphorylase (TP) is involved in the tumoral activation of both 5-FU and capecitabine, but could promote neoangiogenesis too, thus rendering the clinical impact of TP levels in tumors hardly predictable (Ciccolini et al., 2004). Furthermore, deregulation of downstream proteins involved in the transmission of apoptosis in cells exposed to thymineless stress can affect 5-FU or capecitabine antiproliferative efficacy, despite proper inhibition of target TS. Because 5-FU exerts its cytotoxic effects partly through a p53/Fas-dependent apoptotic pathway involving Bax translocation and mitochondrial permeabilization, deregulations affecting each of these steps can interfere with the actual upstream *TYMS* status or the extent of TS inhibition (Borralho et al., 2007). For instance, down-expression of Apo-1 Fas CD95 receptor has been associated with resistance to 5-FU or capecitabine in non-clinical colorectal models, including after that a near-total inhibition of TS activity was achieved (Ciccolini et al., 2000b; 2001).

However, subsequent clinical studies failed in demonstrating the role Fas expression could play as a predictive marker in patients with colorectal cancer (Backus et al., 2001; Bezulier et al., 2003).

2.1.2 Oxaliplatin: A metal precious to the patients

In clinical practice, oxaliplatin is given in mCRC patients in association with 5-FU/folinic acid, a combination known as the Folfox regimen. It can be further combined now with the latest monoclonal antibodies targeting VEGF or EGFR-1. Oxaliplatin is a third-generation platinum derivative that targets complementary DNA strands, thus inducing cell death eventually. However, the nucleotide excision repair (NER) system is designed to remove the oxaliplatin-induced DNA-adducts, and several factors (XPD (a.k.a. ERCC2), XPC and XPA) are implicated in the repair process of DNA helixes once adducts have been formed. In addition, XPG and ERCC1 are implicated in the cleavage of the damaged DNA strand and participate to the repairing pattern of cells exposed to oxaliplatin. Any changes in those repair mechanisms can lead to increase of sensitivity or loss of efficacy in patients. Several genotypes at the tumor level have been associated with clinical outcome in oxaliplatin-regimen. In particular, it has been demonstrated that polymorphisms affecting *ERCC1* and *XPD* genes are related to patient survival. For instance, ERCC1-118 T/T, or XPD-751 A/C and C/C genotypes have been associated with reduced disease-free survival in patients treated with oxaliplatin (Ruzzo et al., 2007). In another study, the Lys751Gln polymorphism of the *XPD* gene has been identified as a predictive marker in mCRC patients undergoing FolFox treatment (Le Morvan et al., 2007). Beside the NER, basepair excision repair is also involved in the chemosentivity to oxaliplatin. *XRCC1* gene is affected by several polymorphisms, and expression of the wild-type allele has been associated with better clinical outcome in patients with mCRC (Suh et al., 2006, Stoehlmacher et al., 2001), although subsequent studies failed in confirming the relevance of establishing *XRCC1* genotype as a predictive biomarker with oxaliplatin (Ruzzo et al., 2007). Along with the issue of efficacy, mutations affecting Glutathione-S Transferase (GST), the enzyme responsible for the cell detoxification of oxaliplatin, could have an impact on the clinical outcome with oxaliplatin. Overexpression of tumoral GSTP1 has been found in CRC patients, thus leading to lack of efficacy (Glasgow et al., 2005). However, the exact role the genetic status *GSTP1* plays in patients treated with oxaliplatin remains controversial. For instance, the GSTP1 ile105val genotype has been associated with improved survival in patients treated with Folfox regimen (Stoehlmacher et al., 2002), although the same genotype was predictive of reduced survival in another study (Sun et al., 2005) . In addition, the GSTP1-105 G allele, could explain higher incidence of severe neurotoxicities, the most common side-effect of oxaliplatin, observed in some patients (Ruzzo et al., 2007). Another polymorphism affecting the *AGXT* gene coding for the enzyme responsible for the metabolism of oxalate, which peaks during oxaliplatin infusion, could explain higher risk of neurotoxicity in patients (Gamelin et al., 2007).

2.1.3 Irinotecan: Twist again 'till double-strand DNA breakage

Irinotecan (CPT-11) is a topoisomerase-I (Topo-1) inhibitor usually combined with 5-FU/folinic acid regimen, an association known as the FolFiri regimen. Topo-1 relieves torsional strain in DNA, thus allowing DNA replication, recombination, and repair. Irinotecan prevents religation of the DNA strand by binding to topoisomerase I-DNA

complex, thus causing double-strand DNA breakage and cell death eventually. Expression levels of target topo-I has been associated with clinical outcome in multivariate analysis performed from large studies including several hundreds of patients undergoing irinotecan-based therapy (Braun et al., 2008; Kostopoulos et al., 2009). However, the lack of randomized, prospective trial prevents, for the time being, the evaluation of Topo-1 level in tumours to be proposed in routine clinical setting as a predictive biomarker for irinotecan efficacy, and little is known about the genetic or epigenetic events affecting the Topo-1 gene likely to modify expression levels of the target protein. However, in the Focus trial, Topo-1 expression level was found to be related to efficacy, although it remains unclear whether the expression level is to be considered as a predictive or a prognostic marker (Braun et al., 2008). In addition, as for oxaliplatin, deregulations affecting DNA-repairing enzymes like *XRCC1*, ERCC1 and *GSTP1* have been found to be predictive of the clinical outcome in irinotecan-treated patients. Polymorphism affecting the *XRCC1* gene (eg, the GGCC-G haplotype) was associated with improved response rates in patients given irinotecan, much probably in relation with loss of ability to repair DNA damage (Hoskins et al., 2008). Conversely, better response and, in some cases, improved PFS was observed in patients undergoing FolFiri regimen with tumors overexpressing GSTP1 and ERCC1 (Vallbohmer et al., 2006). This finding may be confusing because higher expression in DNA-repair enzymes is normally associated with resistance to DNA-targeting agents. Here, high ERCC1 levels could be indicative of a higher DNA damage, thus making the tumor cells more sensitive to Topo-I inhibition by irinotecan. In the same study, EGFR expression was found to be associated too with better response, although to date, no molecular mechanisms underlying this observation have been found.

2.2 Biotherapies: Where are my keys?

Treatment of colorectal cancer has taken benefit from the rise of the biotherapies in clinical oncology, because both anti-VEGF and anti-EGFR monoclonal antibodies can be used now in association with cytotoxics agents. However, the efficacy of most targeted therapies is generally contingent upon a number of biomarkers at the tumor level to be checked.

2.2.1 Anti-EGFR monoclonal antibodies: Why hitting the target is not enough

Cetuximab and panitumumab are two anti-Her1 monoclonal antibodies indicated for treating metastatic colorectal cancer. Initially proposed alone, both drugs showed better efficacy and improved survival when combined with standard Folfox4 or Folfiri regimen. Although cetuximab is a chimeric IgG1 and panitumumab a 100% human IgG2, these both antibodies target the extracellular domain of EGFR-1, thus blocking the downstream signaling pathway normally leading to cell proliferation and differenciation, neoangiogenesis and invasion patterns associated with colorectal cancer. Cetuximab and panitumumab prescription is contingent upon the completion of pharmacogenomics testing. Expression level of target EGFR is the first condition, although in clinical practice, the relevance of this test is more and more debated and controversial at the bedside. However, several studies have demonstrated how patients with elevated *EGFR* gene copy number are more likely to respond to cetuximab or panitumumab therapy (Moroni et al., 2005; Sartore-Bianchi et al., 2007, Heinemann et al., 2009). More interestingly and consensual, determination of the mutational status of KRAS soon turned to be the paradigm of implementing pharmacogenomic testing prior to initiating treatment with a targeted

therapy. The EGFR/KRAS/Raf pathway is implicated in signal transduction from receptors to the nucleus, thus promoting cell proliferation and differentiation. KRAS transmits signal after binding to guanosine triphosphate (GTP), and becomes inactive when GTP is converted to GDP. Mutations affecting *KRAS* will maintain the protein continuously activated in a switch-on position, even if the upstream receptor is inhibited by a monoclonal antibody. It was demonstrated in the mid-2000's that specific *KRAS* mutations (eg, codons 12/13) was associated with lack of response in cetuximab-treated patients (Lievre et al., 2006). Subsequent studies all confirmed the predictive value of wild-type (WT) *KRAS* for the response with anti-EGFR biotherapies, either cetuximab or panitumumab, regardless of their use as monotherapy or combined with cytotoxics (Heinemann et al., 2009, Asghar et al., 2010). However, WT *KRAS* is a mandatory but no sufficient condition to guarantee an optimal efficacy with anti-EGFR therapies. Mutations affecting *BRaf*, an effector of KRAS, has been associated with treatment failure, although it remains unclear whether *BRaf* mutational status should be used as a prognostic or a predictive marker (Di Nicolantonio et al., 2008). Similarly, correlation was found in cetuximab-treated patients between *EGFR* gene amplification, WT *KRAS* status, PTEN expression, and response. Of note, loss of PTEN expression was systematically associated with treatment failure, thus suggesting that PTEN could be a novel predictive biomarker for anti-EGFR therapies (Frattini et al., 2007). Along with PTEN, several other parameters like epiregulin and amphiregulin expression have been recently identified as putative biomarkers (Jacobs et al., 2009; Laurent-Puig et al., 2009; Di Fiore et al., 2010), although larger prospective studies will be necessary to validate their clinical relevance to predict clinical outcome with EGFR-inhibitors.

2.2.2 Anti-VEGF therapy: Desesperatly seeking biomarkers

Bevacizumab is the only *stricto-sensu* antiangiogenic therapy approved for treating mCRC patients in association with cytotoxics. This humanized monoclonal antibody targets circulating VEGF-A. To date, no predictive biomarkers have been identified with bevacizumab. Overexpression of VEGF is usually associated with poor survival in mCRC patients, but VEGF level is generally considered as a prognostic, rather than a predictive, biomarker. Even in a prognostic setting, the actual role *VEGF* polymorphism plays remains unclear. For instance, in some studies, the -460CC genotype was found to have a favorable impact on OS in gastric cancer patients (Kim et al., 2007), but deleterious in breast cancer patients (Lu et al., 2005). Beside, some studies in breast cancer patients have found a relationship between *VEGF* polymorphisms (eg, -2578A/A and -1154A/A genotypes) and better survival in patients treated with the paclitaxel + bevacizumab regimen (Schneider et al., 2008). Similar relationship between *VEGF-A* polymorphism and both toxicity and DFS has been evidenced more recently (Etienne-Grimaldi et al., 2010). A similar trend has been found with digestive cancers (Formica et al., 2010). Additionally, circulating PDGF could be implicated in resistance to anti-angiogenic drugs (Crawford et al., 2009), as well as SDF1 and FGF2 factors (Batchelor et al., 2007). Finally, plasma cytokines and vascular factors could be associated with clinical outcome in patients undergoing bevacizumab-based therapy (Kopetz et al., 2010). However in a recent study, Loupakis et al. have investigated the molecular and genetic markers likely to predict efficacy in mCRC patients treated with the Folfoxiri plus bevacizumab quadruple combination. Among the various bevacizumab-related biomarkers they monitored in plasma (ie VEGF, PIGF, sVEGFR2, TSP-1 plasma level) and the screening of several polymorphims affecting *VEGF* (eg., -2578C/A, -1498C/T, -1154G/A, 936C/T) and *VEGFR-2* (-604A/G, 1192C/T, 1719T/A), little relevant association

with PFS was found (Loupakis et al., 2011). This latter study illustrates the difficulty in identifying relevant biomarkers for response in heavily treated mCRC patients receiving several drugs in a row, the observed efficacy being the resulting combination of the numerous parameters affecting each drug.

3. Pharmacogenetics: When genetics help finding the right exposure

3.1 Cytotoxics: Improving the efficacy/toxicity balance

Beside those affecting tumors, several constitutive genetic mutations can impact on the disposition of anticancer drugs, especially when they concern genes coding for detoxifying enzymes in the liver. Although for years, such polymorphisms were mostly associated with increased risk of developing severe and sometimes deadly toxicities upon drug intake, they may impact as well on treatment efficacy eventually. Indeed, when they are not directly life-threatening, drug-induced toxicities and their management often require treatment discontinuation, delays in subsequent radiotherapy courses if scheduled, with a subsequent loss of chance and poor clinical outcome eventually.

3.1.1 5-FU & Oral 5-FU

Fluoropyrimidines pharmacokinetics is primarily dependent upon an intense liver first pass effect mediated by dihydropyrimidine dehydrogenase (DPD), the enzyme that converts uracil into dihydrouracil. It is generally estimated that about 90-95% of an administered 5-FU dose will be metabolized in the liver before being distributed throughout the body. DPD exhibits a similar pivotal role in the disposition of oral fluoropyrimidines like capecitabine or UFT, all generating 5-FU eventually. *DPYD* gene is highly polymorphic because several dozen of mutations have been described thus far (Van Kuilenburg, 2004). Mutational inactivation of the *DPYD* gene has been characterized as an autosomal recessive disease in Caucasians' population, with probably a higher impact in black American (Mercier C et al., 2006). Genetic and epigenetic regulations, such as promoter hypermethylation or variations in transcriptional factor expression, could play as well a critical role in *DPYD* dysregulations (Etienne MC et al., 1994, Zhang et al., 2006), although this issue remains debated today. Admittedly, three relevant mutations (canonical IV14+1G>A (*DPYD**2A), plus 2846A>T, and 1679T>G) should be screened at bedside to anticipate 5-FU-related side effects (Morel et al., 2006). Numerous clinical reports have demonstrated the deleterious effect of DPD genetic polymorphism in patients undergoing 5-FU based regimen. Regardless of the upstream genetic events leading to the loss of enzymatic activity, impaired DPD has been systematically associated with increased risk of developing severe/lethal toxicities upon 5-FU exposure. In a proof-of-concept study, DPD deficiency was retrospectively identified as the culprit for 70% of the severe toxicities and 80% of the toxic-death cases monitored over a two-year observation period, and when performed, drug monitoring confirmed strong overexposure to 5-FU in DPD-deficient individuals (Ciccolini et al., 2006). However, some reports failed in providing data for this pivotal role *DPYD* genetic polymorphism could play in the incidence of severe toxicities with 5-FU. In a gene-candidate study, Schwab et al. have investigated the role several polymorphisms, including the *DPYD**2A allelic variant, could play in the tolerance to 5-FU. Surprisingly, this genotype was found to be only marginally associated with toxicities, but it has to be underlined that in this study, no complementary functional investigations were undertaken to evaluate globally the DPD status in those

patients (Schwab et al., 2008). In addition to 5-FU, several reports have suggested that *DPYD* genetic polymorphism could be an issue with capecitabine too. The very first toxic-death case has been first observed in the late-2000' in a patient treated with capecitabine who was found to be profoundly DPD deficient after post-mortem investigations (Mercier et al., 2007a). Several other clinical reports have demonstrated how *DPYD* genetic polymorphism could put deficient patients at risk of experiencing severe toxicities if given capecitabine (Mercier et al., 2007b). Lastly, another genetic polymorphism could be a rising concern with capecitabine. Deregulations affecting cytidine deaminase (CDA), one of the three enzymes responsible for the conversion of prodrug capecitabine to 5-FU, could lead to severe toxicities. As for DPD, the gene coding for CDA is highly polymorphic with either loss (poor metabolizer) or gain (ultra-metabolizer, UM) of enzymatic activity. The first life-threatening toxicity in a patient displaying the UM phenotype was reported in the late 2000's (Mercier C et al., 2009). The role CDA could play in severe toxicities with capecitabine has been next confirmed in another larger study showing that deletion in the promoter region of the CDA gene with increased transcription was a predictive marker for hand-foot syndrome (Caronia et al., 2011). Lastly, the first toxic-death case in a capecitabine-treated patient harboring several polymorphisms on the CDA gene, including the Caronia deletion, has been published recently (Dahan et al., 2011), thus highlighting the fact that beside *DPYD*, other genetic polymorphisms should be screened to ensure a better safety when handling oral fluoropyrimidines.

3.1.2 Irinotecan

Irinotecan is a prodrug that can be either metabolized by the Cyp3A sub-family to form the inactive APC derivative, or be converted by carboxylesterase into SN38, a highly cytotoxic metabolite responsible for both the efficacy and the toxicity of irinotecan. SN38 is next mainly detoxified after conjugation by the UGT1A1 to yield inactive SN-38G that will be excreted by the kidneys and the bile eventually. Numerous polymorphisms have been described for the gene coding for UGT1A1, and variations in the promoter region consisting in 7 instead of 6 TA-repeats (UGT1A1*28) is admittedly associated with increased risk of severe toxicities in mCRC patients administered with high dose (e.g., above 250 mg/m^2) irinotecan (Kweekel et al., 2010). A strong influence of ethnicity has been observed with this allelic variant because its population frequency is as high as 43% heterozygotes in the Caucasians but much lower in the Asians (Innocenti et al., 2005; deJong et al., 2006). Several independent studies have demonstrated how individuals with the UGT1A1*28 genotype were up to 7-time more at risk to experience haematological or gastrointestinal severe toxicities when treated with irinotecan (Ando et al., 2000; Marcuello et al., 2004). Of note, some authors have reported an association between the UGT1A1*28 genotype and irinotecan efficacy (Toffoli et al., 2006), although other studies have failed in providing evidence for such a relationship (Kweekel et al., 2008). Along with the UGT1A1*28 genotype, other variations such has the UGT1A1*6 most frequently found in Asian populations has been associated with increased severe neutropenia after irinotecan intake (Han et al., 2006), although other studies failed in confirming such relationship (Ando et al., 2000). Additionally, polymorphisms affecting transmembrane pumps involved in the excretion of toxic metabolites could be related to drug resistance. Pharmacogenetics of the ATP-binding cassette proteins has been associated with changes in the pharmacokinetics of irinotecan, because they impact of the renal clearance of the drug and ultimatelly on

exposure levels. For instance, patients harboring the 34A>G SNP on the *ABCG2* gene could be more at risk of treatment failure, as compared with WT patients (Mc Leod et al., 2008). Conversely, other SNPs like the 421C>A polymorphism seems to have limited impact on irinotecan pharmacokinetics and clinical outcome (de jong et al., 2004) whereas some mutations were associated with higher incidence of drug-induced toxicities (Cha et al., 2009).

3.2 Pharmacokinetics of targeted therapies: The hidden biomarker?

For years, the importance of pharmacokinetic issues such as residual plasma levels or drug concentrations at the tumor site has been largely underestimated with targeted therapies. For instance, it took 5 years since its first approval in Chronic Myeloid Leukemia to acknowledge the fact that the residual concentrations of imatinib were predictive for the major molecular response in patients, thus highlighting the utility to perform drug monitoring and subsequently developing dose-tailoring strategies to ensure a better efficacy (Egorin et al., 2009). Although similar strategies are now developed with other small molecules such as pazopanib (Suttle et al., 2010), no such trend is currently proposed with monoclonal antibodies, despite the fact that dose/exposure/efficacy and dose/exposure/toxicities relationships have been described (Lu et al., 2009, Keiser et al., 2010). Both non-clinical and clinical studies suggest that 90% of target inhibition should be continuously achieved to ensure a maximum efficacy, thus stressing the usefulness to monitor residual concentrations of monoclonal antibodies such as panitumumab, as for other target therapies (Yang et al., 2010). For instance, plasma residual concentrations of 10-30 ug/ml are considered necessary with bevacizumab for an optimal efficacy (Data on File Genentech Inc). However, little is known about the pharmacokinetics of monoclonal antibodies and there is a clear lack for markers of inter-patient variability. Proteolytic degradation along with target-mediated drug disposition are the main patterns implicated in the clearance of monoclonal antibodies, and several factors such as antibodies anti-therapeutic antibodies, target expression, number of metastatic sites or inflammatory syndromes are likely to modify drug levels in plasma. Of note, genetic polymorphism affecting immunoglobulin G fragment receptor Fc-γ-R has been identified as a putative marker for rituximab clearance, but the clinical importance of *Fc-γ-R* genotype could be more related to the Antibody-Dependent Cell Cytotoxicity (ADCC) of rituximab that involves Fc-γ-R, rather than a pharmacokinetics issue (Cartron et al., 2002). In digestive oncology, Fc-γ-R genotype has been identified in mCRC patients treated with cetuximab as predictive for PFS, but as for rituximab, this could be related to changes in the ADCC described sometimes with cetuximab rather than changes in pharmacokinetics (Zhang et al., 2007), and other studies failed in confirming the impact this polymorphism could have with the anti-EGFR therapy (Graziano et al., 2008).

4. Conclusions: One patient, one disease, one drug, one dosage…. Can we finally do it?

Developing strategies to implement personalized medicine in digestive oncology is now an irreversible trend (Ciccolini et al., 2011). However, identifying predictive biomarkers associated with either treatment efficacy or tolerance remains an uneasy task, because CRC patients are usually treated with up to 6 different drugs in combination over several lines.

Consequently, and despite the abundant literature published, the heterogeneity in the clinical settings can hinder the relevance of some markers, thus preventing standardized guidelines to be issued. However, oncogenetic, pharmacogenetic and pharmacogenomic tools are now developed as a new mean to help oncologists to choose the optimal strategy for each patient, regarding the staging of the disease, the status of the various response markers, and eventually information about specificities in pharmacokinetics and detoxification patterns, once the right drugs have been chosen. However, this later and critical step remains today the forgotten item in routine clinical setting. Although implementing KRAS pharmacogenomic testing is now a systematic practice prior to administrate cetuximab or panitumumab to mCRC patients, little is done to further develop pharmacogenetics-based dose tailoring strategies to reach next the right exposure likely to ensure an optimal efficacy/toxicity balance. Screening for *DPYD* or *UGT1A1* genetic polymorphisms, despite countless clinical reports demonstrating their role in life-threatening toxicities, and therefore the usefulness of preliminary testing in patients undergoing 5-FU, capecitabine or irinotecan-based regimen to anticipate treatment-related toxicities, is far from being a common practice. However, when performed, pharmacoeconomic studies suggest that implementation of such screening is cost-effective, thus suggesting that routine pharmacogenetics should benefit both to the patients and to the institute ultimately, by dramatically cutting the costs dedicated to managing the treatment-related toxicities (Mercier et al., 2009). Of note, no regulatory official step has been undertaken to date to prompt oncologists to require such tests when prescribing cytotoxics to mCRC patients. Changes in the drug label informing physicians about the toxic risks with irinotecan related to the *UGT1A1* genetic polymorphism has been done by the F.D.A in the mid-2000's and official warning issued as a as a level-2 priority, but with little impact in clinical practice, partly because the UGT1A1 test is not reimbursed in the U.S. by most insurance companies (Ikediobi et al., 2009, Meckley et al. 2010), and partly because of the lack of tools to customize the irinotecan dosage once the *UGT1A1* status has been obtained. As of today, it is acknowledged that the UGT1A1*28 genotype is a concern in patients scheduled for irinotecan dosage above 200 mg/m² only, with little further guidelines made available about adaptive dosing strategies to treat patients harboring this polymorphism (Hoskins et al., 2007) because. Usually, an empirical 25-50% reduction in irinotecan starting dose is recommended in patients with the homozygous variant. Similarly, screening for *DPYD* genetic polymorphism is an exceptional, rather than a routine test in most institutes. DPD testing can be required at best once the severe toxicities have already shown in a patient treated with a 5-FU-containing regimen to keep or discard the fluoropyrimidine in the forthcoming course. As for UGT1A1, little tools are available to tailor dosage based upon the DPD status of the patient. However, a case-control study has demonstrated the immediate advantages patients could benefit from prospective DPD testing associated with adaptive-dosing, with a sharp reduction in the incidence of 5-FU-related toxicities in patients screened for DPD deficiency with tailored dosage as compared with patients treated with standard regimen (Yang et al., 2009). Of note, efficacy remained the same in this study despite markedly lower doses in patients with DPD deficiency, thus illustrating how pharmacogenetics-based adaptive dosing could improve indeed the efficacy/toxicity balance of canonical 5-FU. In this respect, prospective clinical trials investigating pharmacogenetics of drugs given in mCRC patients with strong PK, PK/PD and

PK/PD/PGx modeling support should help to develop easy-to-implement tools designed to individualize dosing based upon the patients genotypes or phenotypes.

5. References

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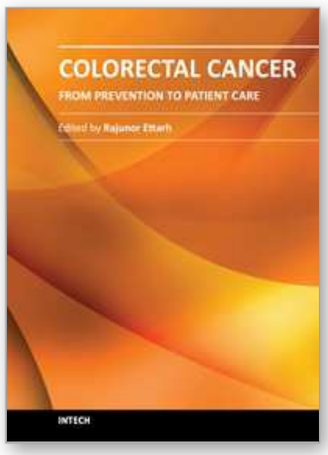

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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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