

PHARMACOGENETICS OF CYTOTOXIC THERAPY IN COLORECTAL CANCER

Viktorija Erdeljić Turk

University Hospital Zagreb, Department of Medicine, Zagreb, Croatia

Summary

Colorectal cancer is a relatively common tumor with incidence that has been increasing during recent decades. Despite the rapid advances in treatment of colorectal cancer, the best way to combine and sequence all available drugs to optimize treatment is not yet established. The majority of cytotoxic drugs used in therapy of colorectal cancer have a dose related effect and narrow therapeutic index. Hence, dosing of cytotoxic drugs is considered very important. Current modalities for therapy and dose selection give restricted possibilities to equalise inter-individual variations which are dependent on physiological, genetic and environmental factors. In this article, an overview of current possibilities of personalized medicine in therapy of colorectal cancer is presented. This includes review of the most important gene polymorphisms important for safety and efficacy of cytotoxic therapy in colorectal cancer, and evaluation of their importance for the current clinical practice. Despite raising knowledge, providing individual treatment with low toxicity and significant benefits is still an unsolved problem. Reasons for this are the lack of knowledge on distribution of these polymorphisms in the population, importance of non-genetic factors, price of genetic testing and still limited data from controlled clinical trials confirming the clinical usefulness of pharmacogenetic testing. Although the initial costs of cancer management and personalized medicine may be high, in the future they may result in significant benefits from both a clinical and economical perspective.

Keywords: colorectal cancer; pharmacogenetics; biomarkers; personalised medicine.

Background

Colorectal cancer is a relatively common tumor with incidence that has been increasing during recent decades, and the lifetime risk for colorectal cancer in industrialized countries is about 5% [1]. The last 5 to 10 years have seen unprecedented advances in the treatment of colorectal cancer. Therapeutic strategies involve seve-

ral different classes of drugs with significant anti-tumor activity in colorectal cancer: cytotoxic therapy which includes 5-fluorouracil, capecitabine (oral precursor of 5-fluorouracil), irinotecan and oxaliplatin, and targeted therapy which includes bevacizumab, aflibercept, regorafenib, cetuximab and panitumumab [2]. Despite the rapid pace of clinical research, the best way to combine and sequence all of these drugs to optimize treatment is not yet established.

The majority of cytotoxic drugs have a dose related effect and narrow therapeutic index. Hence dose selection is considered very important. Even small dose variations can lead to significant toxicity in some patients, and to hypodosing in others. There is an important inter-individual variability in the capacity of drug metabolism and elimination [3]. The choice of therapy is still based on standard clinical and pathological parameters represented by Dukes and TNM (Tumor Node Metastasis) grading systems. The dose is mostly chosen based on age, height and body mass by calculation of BSA (Body Surface Area) [4,5]. However, this gives restricted possibilities to equalise inter-individual variations which are dependent on physiological, genetic and environmental factors (drug-drug interactions, drug-food interactions). The influence of genetic factors on response variability is far greater than sex, age or interactions with other drugs. The distribution frequency of correct responses to drug usage in a population is far from normal distribution, which means that the presence of treatment non-responders and over-responders (increased toxicity) is much more common than has been assumed so far [6]. The clinical problems that arise from inter-individual variability in drug metabolism are mostly related to toxic effects of cytotoxic drugs, mainly affecting hair growth, gastrointestinal system and bone marrow, but also include resistance to therapy involving various mechanisms.

Personalised cancer medicine

Personalised medicine is a new concept arising from the need for more rational and effective treatment with less adverse reactions. It is based on the combination of therapeutic drug monitoring (TDM) and genotyping with the objective to evaluate metabolic capacity of the host and/or the characteristics of the tumor [7]. Cytotoxic anticancer drugs fit many of the criteria commonly defined as prerequisites for utilising TDM approaches. Firstly, the extent of inter-individual pharmacokinetic (PK) variability exhibited is large in the majority of cases. This large inter-individual PK variability is likely to be related to genetic differences as well as variations in the functional status of the cancer patients. Furthermore, relationships have been

described between plasma concentrations and pharmacodynamic (PD) end-points such as percentage decrease in neutrophil counts between pre-treatment and nadir values [8]. Genetic factors contribute to the phenotype of drug response. A significant proportion of variability in drug response can be attributed to genetic factors through modulation of drug PKs and/or PD. So, the rationale behind pharmacogenetic studies is to investigate genes encoding drug transporters, drug-metabolising enzymes and drug targets that can predict the usefulness of a particular drug so as to increase the number of responders and decrease the number of subjects affected by adverse drug reactions. Nevertheless, the sources of variability in drug response are multifactorial and apart from genetics, factors such as pathophysiology, environment, diet, drug–drug interactions, drug allergies, medication errors and poor compliance, may all have a profound impact on PKs and/or PDs, thereby affecting therapeutic outcome

Pharmacogenetics is not only important for targeted drugs which effectiveness is often dependent upon a genetic mutation. Inter-individual differences in toxicity and response are observed in practically all available anticancer treatment regimens. Identification of subgroups of patients which differ in their prognosis and response to treatment could be helpful to identify the best available therapy for individual patient.

The first studies on pharmacogenetics and colorectal cancer outcomes were conducted and published approximately 20 years ago [9]. Since then, many possible biodeterminants have been studied with many expectations, but the final step of clinical validation has remained an unmet objective for almost all putative biomarkers [10]. Consequently, providing individual treatment with low toxicity and significant benefit is still an unsolved problem. Reasons for this are the lack of knowledge on distribution of these polymorphisms in the population, importance of non-genetic factors, price of genetic testing and still limited data from controlled clinical trials confirming the clinical usefulness of pharmacogenetic testing.

Important gene polymorphisms in cytotoxic colorectal cancer therapy

Although significant research on polymorphisms important for the metabolism of cytotoxic drugs has been done, the translation of pharmacogenetic outcomes into clinical practice has proved to be surprisingly disappointing, with relatively few exceptions. These exceptions include genetic polymorphisms important for the metabolism of fluoropyrimidines (5-FU and capecitabine) and irinotecan.

Fluoropyrimidines

Fifty years after the first synthesis of 5-FU it is still a standard component of adjuvant and palliative therapy having a proven impact on survival time in patients with colorectal cancer [11]. Experimental studies have shown that 5-FU is converted to an active metabolite which is a potent inhibitor of DNA synthesis. It forms a complex with thymidylate synthase enzyme and 5,10-methylenetetrahydrofolate (CH₂THF) cofactor, responsible for the catalytic conversion of deoxyuridine monophosphate to deoxythymidine monophosphate which is a substrate for deoxythymidine triphosphate necessary for the process of DNA synthesis [12]. Despite significant progress in understanding the 5-FU activity mechanisms, the identification of molecular markers potentially clinically useful in predicting 5-FU treatment efficacy and toxicity and is still the subject of research. Approximately 10–40% of 5-FU develop severe, and sometimes life-threatening, toxicity (neutropenia, nausea, vomiting, severe diarrhoea, stomatitis, mucositis, hand-foot syndrome, and neuropathy) [13].

5-FU is the sole anticancer agent for which TDM has been validated in more than one randomised trial, in terms of improved therapeutic index [14-16]. Individual FU dose adjustment based on pharmacokinetic monitoring resulted in significantly improved objective response rate, a trend to higher survival rate, and fewer grade 3/4 toxicities. Approach that includes both patient's phenotype and genotype up to now Has not been studied and proven useful enough to be translated into everyday oncology practice. However, testing polymorphisms of 2 enzymes involved in fluoropyrimidine metabolism have found their way into clinical practice. These two enzymes are dihydropyrimidin dehydrogenase (DPD) and thymidylate syntase (TS).

Dihydropyrimidin dehydrogenase

5-FU as a prodrug, in order to achieve its intracellular cytotoxic activity, requires metabolic activation. Inter-individual variability in the response of patients to 5-FU treatment may in fact be associated with a decrease in the activity of enzymes responsible for catabolism of the drug, which will result in an increase in drug concentration and longer half-life, and thus an increased risk of serious toxic effects. Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates >80% of administered 5-FU. The activity of DPD is dependent upon polymorphisms in the DPYD gene. Its activity is extremely variable in tumoral tissue and this variation might make a difference to the efficiency of 5-FU treatment, since intratumoral drug concentration is one of the most important factors for the determination of the antitumoral effect [17]. Deficiency in DPD activity, however, leads to severe toxicity correlated to 5-FU which may even be fatal. The partial or total lack

of this enzyme has, in fact, been associated with severe toxicity (mucositis, granulocytopenia, and neuropathy), and in several cases even death, after 5-FU administration (18). Partial DPD activity deficiency in the general population is about 5%-10%, and its total loss is very rare, about 0.2% [19]. However, it has been estimated that 23-38% of 5-FU toxicity can be attributed to DPD polymorphisms [20]. The acquired uncertain evidence is derived mostly from retrospective clinical studies and suggests that low expression of the *DPYD* gene may be a sensitivity marker in tumour cells for fluoropyrimidines and thus allow us to predict the degree of response to treatment. However, currently quality clinical data have become available that confirmed the predictive value of *DPYD* expression determination in order to predict the efficacy of 5-FU therapy in colorectal cancer patients [21].

An assay for DPD polymorphisms testing is commercially available as well as for TYMS polymorphisms. However, pre-emptive testing is not recommended.

The *US Food and Drug Administration* (FDA) has added statements to the drug labels for 5-fluorouracil and capecitabine that contraindicate use in patients with DPD enzyme deficiency. The FDA drug label also warns to use precaution with intravenous 5-fluorouracil in these patients. The *Dutch Pharmacogenetics Working Group* has evaluated therapeutic dose recommendations for 5-fluorouracil, capecitabine, and tegafur (5-fluorouracil prodrug combined with uracil; not available in United States). The Working Group recommends the use of an alternative drug for homozygous carriers of a decreased-activity allele and a reduced dose or alternative drug to capecitabine or 5-fluorouracil for heterozygous carriers of a decreased-activity allele [22]. Recently, *Clinical Pharmacogenetics Implementation Consortium Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing* have been issued on dosing recommendations for fluoropyrimidines based on *DPYD* genotype, recommending that in heterozygous for high risk alleles the dose of fluoropyrimidines should be reduced by 50% and in homozygous instead of fluoropyrimidines alternative therapy should be used [23].

Tymidilate synthase

TYMS polymorphisms which result in increased expression of the enzyme are increasing the risk of 5-FU toxicity and decreasing the therapeutic response. In particular, TS overexpression has been found to be significantly associated with a low response to treatment based on 5-FU, both as adjuvant [24] and metastatic therapy [25]. Colorectal cancer patients with low levels of TYMS gene expression had a significantly higher rate of response to therapy and longer median survival compared to patients with higher TS expression in tumor tissue (leichman-19). Subsequent meta-

analyses confirmed the importance of TS expression on overall response rate and overall survival [26,27]. Available data suggest that high-risk TYMS polymorphisms are associated with 1.4-2.4 higher risk for 5-FU toxicity. Still, the positive predictive value of these tests is limited (50%) [28]. There is a need for further analyses to allow identification of *TYMS* transcription regulatory mechanisms including the role played by combinations of different genetic variants and their expression variability in populations. No recommendations have been issued on dosing of **fluoropyrimidines by TS phenotype**.

Other gene polymorphisms possibly important for fluoropyrimidine efficacy and toxicity for various enzymes have currently been explored (eg. dihydropyrimidinase, beta-ureidopropionase, methylenetetrahydrofolate reductase), but available research data are insufficient for conclusions on their potential clinical usefulness.

Irinotecan

Irinotecan is a synthetic analogue of a naturally occurring alkaloid, camptothecin. It was first approved for clinical use in Japan in 1994 for the treatment of small-cell lung cancer and hematologic malignancies, and then in 1995 in France for the treatment of advanced colorectal cancer. Tumour-specific somatic mutations and abnormal gene expression have been reported to be associated with irinotecan therapeutic efficacy and toxicity. However, the available studies do not provide unequivocal confirmation that somatic mutations have a significant impact on the outcome of irinotecan treatment, which prevents their usage as predictive markers. Generally, genetic variations may influence both the pharmacokinetics and pharmacodynamics of irinotecan [29,30].

It is recognised that there is large PK and PD inter-individual variability in patients receiving irinotecan with limited dependence on dosing based on BSA [31]. PK variability is linked to variability in biliary excretion and inherited variations in metabolic pathway which controls degradation of irinotecan.

Uridine diphosphate glucuronosyltransferase

The active metabolite of irinotecan, SN-38, is glucuronidated mainly in the liver by the uridine diphosphate glucuronosyltransferase enzymes (UGTs), primarily the *UDP-glycosyltransferase 1* family (UGT1As) isoenzyme, responsible in humans for bilirubin conjugation with glucuronic acid. UGTs are one of the most important classes of enzyme proteins participating in the coupling reaction phase II of xenobiotic metabolism. First evidence from clinical trials on the role of *UGT1A1*28* in the development of toxicity resulting from administration of irinotecan was published

by Ando et al [32]. It is estimated that there are 8-10% homozygous people for this allele in the population. Homozygous patients for the UGT1A1*28 allele have increased risk for severe neutropenia and severe delayed-type diarrhoea after treatment with irinotecan [33].

Early research and meta-analyses have suggested that the toxic effect of irinotecan is dose dependent and that this effect is not likely in patients receiving low doses of irinotecan (100-125 mg/m² weekly). Subsequent meta-analysis showed that UGT1A1*29 allele polymorphism is significantly associated with risk of neutropenia in all dose regimens. Still, this risk is significantly higher with higher doses of irinotecan ≥ 250 mg/m² (RR 7.0, 95%ci 3.10-16.78) as compared to lower doses (80-145 mg/m² weekly, RR 2.43, 95%CI 1.34-4.39) [34]. It is still unclear if neutropenia prevention would be possible with previous identification of homozygous patients. Only 1/10 are homozygous and it is unclear how much of the added risk for neutropenia can be attributed to irinotecan, especially in lower dosage. However, some studies have shown significant differences in prevalence of severe neutropenia in patients homozygous for UGT1A1*28 allele as compared to controls (48% vs 10%, respectively), higher hospitalization rate and higher mortality [35]. Subsequent systematic reviews and meta-analyses are generally supportive of the clinical utility of genotyping *UGT1A1*28* prior to commencement of irinotecan therapy in order to decrease the risk of severe neutropenia and diarrhoea through the pre-emptive dose reduction of irinotecan for *UGT1A1*28* homozygotes [36,37], and indicate that there is unlikely to be an important association between *UGT1A1* genotype and overall response rate with irinotecan, however, this does not provide direct evidence that a dose reduction for *UGT1A1*28* homozygous patients will not lead to an important reduction in overall response rate [38].

There is still no consensus on the need for dose reduction in homozygous patients. In conclusion, the clinical utility of pre-emptive UGT1A1*28 allele testing is not yet known. One proof-of-concept study has been conducted that showed that the maximum tolerated dose of irinotecan in UGT1A1*29 allele homozygous patients was significantly lower as compared to normal variants (400 mg vs. 840 mg). The authors concluded that identification of UGT1A1*28 genotype is useful for irinotecan dose individualisation [39]. An assay for UGT1A1 polymorphisms testing is commercially available (*Invader UGT1A1 Molecular Assay*), specifically for testing the *UGT1A1*1* (wild-type) and the *UGT1A1*28* genotype. However, the proposed benefit of testing colorectal cancer patients for *UGT1A1* genotype is that the risk for adverse drug-related side effects among patients found to be homozygous for the *UGT1A1*28* genotype can be reduced by lowering their initial and/or subsequent doses of irinotecan. The concomitant harm is that a reduction in irinotecan dosage

may also reduce the effectiveness of chemotherapy in tumour suppression and long-term survival [40].

There are other gene polymorphisms important for irinotecan metabolism that currently being explored (eg. carboxylesterase, topoisomerase-1, aprataxin, etc.) but the available data are insufficient for conclusions on their potential clinical usefulness.

Oxaliplatin

Combination therapy with 5-FU/leucovorin plus oxaliplatin (FOLFOX) is currently a standard in treating gastric cancer and colorectal cancer with a 40% positive response ratio during first relapse therapy [41]. Despite the efficiency of combined therapy, a high percentage of patients show drug resistance to a higher or lower degree, which suggest that the therapeutic efficiency of FOLFOX is characterised by high variability. Insufficient intra-tumour concentration of platinum compounds is a critical factor determining both primary and secondary resistance. Potential platinum uptake or influx transporters include copper transporter proteins [42], organic cation transporters belonging to the SLC22 family [43] and an undefined cis-configuration specific platinum influx transporter (44), in addition to drug transporters facilitating the active efflux of platinum compounds including adenosine triphosphate and additionally adenosine triphosphate (ATP) binding cassette (ABC) multidrug transporters, and copper-transporting P-type adenosine triphosphatases (ATPases) [45]. Clinical studies concerning transporters for platinum derivatives have concentrated on evaluation of the connection between intratumour expression of certain transporters and the results of treatment after chemotherapy based on platinum derivatives. *In vivo* clinical research is required to elucidate the meaning of genetic variability of membrane transporters and channels for gene expression and their influence on the pharmacokinetics and effectiveness of oxaliplatin-based therapy.

Other pathways important for oxaliplatin PK and PD are being evaluated (eg. glutathione S-transferases, nucleotide excision repair pathway apoptosis regulation). However, available research data are insufficient for conclusions on their potential clinical usefulness.

Barriers to the clinical implementation of pharmacogenomics

Although the testing context for pharmacogenetic tests is different from other genetic tests, decisions to use any new clinical tests in medical practice will require evaluation of not only the benefit linked to improved drug safety and efficacy, but also a host of ethical questions. Due to the uncertainties of future developments in the field, thoughts on the ethical aspects are somewhat preliminary at this point.

However, some aspects of pharmacogenetics are likely to have a potentially profound impact on medical practice, research and on society as a whole. Therefore, much thought has been invested in the anticipation of ethical, legal and social aspects of pharmacogenetics [46]. A number of other barriers remain with implementing clinical pharmacogenetics, including clinical utility, cost-effectiveness, professional education, and regulatory and reimbursement issues [47]. The greater the barriers to the clinical adoption of pharmacogenetics, the greater the evidence and size of the improvement in clinical outcome required. The problem to date is that the evidence and importance of most pharmacogenomic associations are not sufficient to overcome the barriers to the clinical implementation. Although long overdue, many of these potential barriers are now being subjected to closer examination and as a result, a framework for successful clinical uptake of pharmacogenomics is emerging.

Conclusion

The purpose of individualized therapy is to choose the most effective treatment and the optimal dosage for each patient, while minimizing toxicity and side effects of therapy. A limited number of pharmacogenetic markers are identified in colorectal cancer. In most studies they are explored individually which has led to somewhat conflicting results. The simultaneous testing of multiple markers predictive of response could help to identify more accurately the true role of these polymorphisms in colorectal cancer therapy [48]. Although the initial costs of cancer management and personalized medicine may be high, in the future they may result in significant benefits from both a clinical and economical perspective.

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Sažetak

Farmakogenetika citotoksičnog liječenja kolorektalnog karcinoma

Rak kolorektuma relativno je čest tumor s rastućom incidencijom zadnjih desetljeća. Unatoč brzom napretku u liječenju kolorektalnog raka, još nije jasno na koji način je najbolje kombinirati i kojim redoslijedom koristiti dostupne lijekove. Većina citotoksičnih lijekova koji se primjenjuju u liječenju kolorektalnog raka imaju učinak ovisan o dozi i malu terapijsku širinu te je određivanje doze lijeka vrlo značajno. Važeći načini izbora terapije i određivanja doze daju ograničene mogućnosti ublažavanja interindividualnih varijacija ovisnih o fiziološkim, genetičkim i okolišnim čimbenicima. U ovom članku dan je pregled trenutačnih mogućnosti individualiziranja liječenja kolorektalnog raka. To uključuje pregled najznačajnijih genetskih polimorfizama bitnih za sigurnost i učinkovitost citotoksične terapije u liječenju kolorektalnog raka te evaluaciju njihove značajnosti za trenutačnu kliničku praksu. Unatoč sve većem znanju, omogućavanje individualiziranog liječenja uz ograničavanje toksičnosti a potenciranje učinkovitosti još je neriješeni problem. Razlog za to su manjak znanja o distribuciji polimorfizama u populaciji, važnosti negenetičkih čimbenika, cijena genetičkog testiranja i još uvijek ograničeni podaci iz kontroliranih kliničkih studija koji bi potvrdili kliničku korisnost farmakogenetičkog testiranja. Iako inicijalni troškovi liječenja kolorektalnog raka i personalizirane medicine mogu biti visoki, u budućnosti bi kombinacija ovih pristupa mogla rezultirati značajnim prednostima iz kliničke i ekonomske perspektive.

Ključne riječi: kolorektalni rak; farmakogenetika; biomarkeri; personalizirana medicina.

Corresponding author:
Viktorija Erdeljić Turk
verdeljic@gmail.com>