

PERSONALISED CANCER MEDICINE IN COLORECTAL CANCER - A SHORT OVERVIEW

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Summary

In this article, a short overview of the current clinical situation of colorectal cancer (CRC) personalised medicine is presented. CRC is a complex, heterogeneous disease that involves multiple signalling pathways and tumors that appear histologically identical, but may have different prognoses and different responses to treatment. Basically, the treatment for colorectal cancer varies by tumor location, stage at diagnosis, and patient's general condition. Recent newer polychemotherapy protocols, along with the use of inhibitors of the vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR) pathways, have enhanced the therapeutic responses and potentially also the patient's prognosis. These recent improvements in anticancer treatments and patient outcome in CRC were followed by a series of biomarker studies attempting to refine prognosis and predict patients who are likely to derive the most benefit from treatment. Consequently, validated predictive and prognostic biomarkers offer potential for personalised therapy for CRC patients. Microsatellite instability (MSI), as well as clinical pathological factors in stage II and III colorectal cancer, may now be considered to be a robust prognostic biomarker in the adjuvant setting. On the other hand, KRAS mutation status should be taken up as a part of routine clinical practice, as a predictive marker for response to EGFR-targeted therapies. The treatment of CRC is expected to become more and more routinely based on identified CRC subtypes and on validated prognostic and predictive biomarkers relatively soon (within several years), which should offer patients better therapeutic outcomes with less side effects.

Keywords: colorectal cancer; biomarkers; personalised medicine; chemotherapy; targeted therapy.

As regards its incidence and mortality, colorectal cancer (CRC) is a relatively common tumor (the third most common tumor) [1-3]. The colorectal cancer treatment strategy is still based on standard clinical and pathological parameters, where the assessment of the progression and spreading of the tumor and general conditions of the patient are given priority [4-7]. On the other hand, clinical observations indicate that this “equal” treatment strategy is not optimal because not all treated patients demonstrate analogous success. Its causes may lie both in patients’ genetic differences and in other molecular heterogeneity between histologically “identical” tumors in different patients. In addition, as a result of further accumulation of genetic changes (clonal evolution of tumor) the genetic profile of metastases in a particular patient may be different to the original primary tumor finding, which in turn may affect the outcome of treatment if it is based only on molecular characteristics of the primary tumor. All this indicates that, whenever possible, treatment should be individualized according to patient’s pharmacogenetic characteristics and the finding with respect to the predictive genetic alterations in autologous tumor cells. Such individualized approach (personalized cancer medicine) may result in more rational, higher-quality and more effective treatment with less adverse reactions. A genetic analysis and/or profile of both the patients and their tumors may provide information and/or parameters in connection with the pharmacodynamics, pharmacogenetics and sensitivity of tumor cells to potential oncological treatment modalities, which rationalizes the treatment strategy and the potential antitumor effect [6-12].

The pathogenesis of colorectal cancer is complex. The risk of occurrence and occurrence of colorectal cancer depends on the genetic characteristics of the individual (heritage and epigenetic changes), their diet, intestinal flora, and lifestyle. Colorectal cancer is hereditary in less than 5% of patients. For example, in patients with familial adenomatous polyposis, an adenomatous polyposis coli (APC) gene which act as a tumor suppressor gene is mutated and inherited. In case mismatch repair (MMR) genes are mutated and inherited, hereditary non-polyposis colorectal cancer (HNPCC) with microsatellite instability (the Lynch Syndrome) will occur, characterized by high genetic instability. Lynch syndrome follows an autosomal dominant inheritance pattern. People who have Lynch syndrome have a significantly increased risk of developing colorectal cancer but also an increased risk of developing other types of cancers [6,7,13-18].

In most patients with colorectal cancer (approximately 95%), the impact of heritage is not so high, so we refer to it as sporadic colorectal cancer. Most of these tumors derive from malignant altered adenoma; in addition to genetic mutations, these tumors also demonstrate chromosome instability (with potential loss of tumor suppression genes). This is a so-called phenotype of chromosome instability (CIN) and microsatellite stability (MSS). Among the smaller patient population with sporadic tumors (approximately 15%), malignant alteration is caused by high microsatellite instability (MSI-high), as a result of epigenetic changes or remodulation, which most often result in DNA mismatch repair gene promoter region CpG island hypermethylation (CIMP, CpG Island Methylator Phenotype). These genes are silenced by hypermethylation of the promoter region. Patients suffering from this molecular type of tumor predominantly have a tumor finding in the right colon. As these two “groups” of sporadic tumors have different molecular profiles, that is, mutated genes, number of mutations and cellular molecular activation routes and mechanisms, we are, for the time being, able to identify at least two types of sporadic colorectal cancer. This difference is to a certain degree reflected in the prognosis and strategy of systemic adjuvant treatment. For example, stage II MSI-H patients have a better prognosis than CIN patients, and they seem to have no benefit from adjuvant treatment with 5-fluorouracil (5-FU) [4-7,13-18].

Systemic chemotherapy treatment of metastatic colorectal cancer is based on chemotherapeutic agents 5-FU, irinotecan, and oxaliplatin. Various studies have investigated whether molecular differences between patients can predict response to standard chemotherapy drugs to facilitate a more personalized approach to chemotherapy. Analysis regarding the genes or their products that may be targeted by such cytostatics or may be involved in the metabolism of these cytostatics or in repairing the damage to (tumor) DNA molecule caused by these agents are not in routine use. This might be due to the low number of studies, conflicting results between the studies, but also in not having standardized accepted laboratory procedures. The molecular target of 5-FU is the thymidylate synthase (TS) enzyme. TS is an important part of the folate–homocysteine cycle and purine and pyrimidine synthesis. Tumors with low expression of TS are less proliferative and may therefore be associated with a better prognosis. The metabolism of 5-FU is mediated by thymidine phosphorylase and dihydropyrimidine dehydrogenase (DPD).

Several variants in DPD have been associated with toxicity and DPD deficiency can result in severe and even fatal 5-FU toxicity [4-7,19,20].

Irinotecan is a topoisomerase-1 (Topo1) inhibitor and Topo1 is overexpressed in 43–51% of colorectal cancers. A large randomized FOCUS trial showed that patients with high levels of Topo-1 expression had improved OS with first-line combination chemotherapy compared with patients with low or moderate Topo1 levels. Irinotecan is detoxified by the enzyme “UDP glucuronosyltransferase 1 family, polypeptide A1” (UGT1A1). There is no current evidence of any benefit or harm of modifying irinotecan regimes based on an individual patient’s UGT1A1 genotype [4-7,19,20].

The excision nuclease “Excision Repair Cross-Complementing 1” (ERCC1) is involved in the repair of platinum-induced DNA damage and early data suggest that there was an association between low ERCC1 expression and oxaliplatin effectiveness in patients with metastatic colorectal cancer. Enzyme “glutathione S-transferase” (GST) is involved in the oxaliplatin detoxification, and again, the relevance of specific polymorphisms seems clinically unclear [4-7,19,20].

On the other hand, predictive analysis is fortunately available for the monoclonal antibodies cetuximab and panitumumab. These two monoclonal antibodies may have an antitumor effect because they inhibit agonist binding to the epidermal growth factor receptor (anti-EGFR treatment) on colorectal cancer cells. Through this effect, these two monoclonal antibodies are able to inhibit the stimulation of tumor cells in case there are no activation mutations in downstream intracellular molecules of this activation pathway. The KRAS molecule is one of these downstream molecules in this molecular pathway. When KRAS gene is mutated, it stimulates this molecular pathway itself, irrespectively of the EGFR blockade. This is why the use of these monoclonal antibodies is conditional upon determining the KRAS and NRAS mutational status in autologous tumor cells. These two monoclonal antibodies can only be used in patients having non-mutated KRAS and NRAS genes. KRAS and NRAS testing is now part of routine clinical practice. The humanized monoclonal antibody bevacizumab inhibits the activity of the vascular endothelial growth factor (VEGF) where we have no predictive parameter or marker [4-7,19,20].

In conclusion, the existence of molecularly different cancer subtypes with different prognoses and potentially different treatment strategies may be said to be confirmed in colorectal cancer. A finding of MSI can be now consi-

dered to be a robust prognostic biomarker in the adjuvant setting, and KRAS and NRAS testing has been taken up as part of routine clinical practice as a predictive marker for response to EGFR-targeted therapies. Personalized medicine is making advances in colorectal cancer [6,7,20,21].

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Sažetak

Personalizirana medicina kolorektalnog raka: kratki pregled

U prikazanom radu dan je kratak pregled kliničke primjene personalizirane medicine kolorektalnog raka. Dijagnoza kolorektalnog raka bazira se na patohistološkim karakteristikama, ali rezultati molekularnih istraživanja ukazuju da se radi o skupini heterogenih tumora, koji se razlikuju u patogenezi, molekularnim aberacijama, prognozi i odgovoru na primijenjeno liječenje. Strategija liječenja raka kolorektuma još uvijek se prvenstveno temelji na smještaju tumora i procjeni uznapredovalosti i proširenosti tumora te općem stanju bolesnika. Razmjerno noviji polikemoterapijski protokoli kao i uporaba inhibitora vaskularnog endotelijalnog faktora rasta i receptora za epidermalni faktor rasta poboljšali su liječenje, a moguće i prognozu bolesnika. Ta novija poboljšanja paralelno prate i klinička ispitivanja s ciljem određivanja potencijalnih prognostičkih i prediktivnih biomarkera. Posljedično, validirani biomarkeri pružaju mogućnost personalizirane medicine za bolesnike s kolorektalnim rakom. Mikrosatelitska nestabilnost zajedno s kliničko-patološkim faktorima u stadiju bolesti II i III smatra se valjanim prognostičkim biomarkerom u strategiji adjuvantnog liječenja bolesnika stadija bolesti II i III. Nadalje, KRAS mutacijski status je parametar koji se mora odrediti ako se planira primjena inhibitora protiv receptora za epidermalni faktor rasta. Za očekivati je da će se unutar nekoliko slijedećih godina liječenje bolesnika s kolorektalnim rakom sve više i više temeljiti na nalazu molekularnih subtipova raka i prema validiranim prognostičkim i prediktivnim parametrima, jer bi takav pristup trebao osigurati bolju terapijsku učinkovitost i manje nuspojava.

Ključne riječi: kolorektalni rak; biomarkeri; personalizirana medicina; kemoterapija; ciljana terapija.

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