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COLORECTAL CANCER: AN INTRODUCTION

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Summary

This introductory type of article provides a brief overview of the current clinical status of sporadic colorectal cancer (CRC). CRC ranks as one of the most prevalent and incident cancers and is also between the deadliest ones worldwide, along with lung and breast cancers. A majority of CRCs are sporadic, with age being the most important risk factor. CRC appears to be a complex, heterogeneous disease that involves multiple signaling pathways and tumors that appear histologically identical may have different prognoses and different responses to treatment. CRC develops through gradual accumulation of genetic and epigenetic changes, resulting in the transformation of normal colonic mucosa into invasive cancer. Basically, the treatment for colorectal cancer varies by tumor location, stage at diagnosis and patient's general condition. Any available data about the genes and/or molecular pathways that regulate activities such as cell growth, death or apoptosis, DNA repair, malignant alteration, etc. should also be taken into consideration. Recent 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 prognoses. The treatment of CRC is expected to become more and more routinely based on identified molecular CRC subtypes and on validated prognostic and predictive biomarkers relatively soon (within several years), which should provide to patients better therapeutic outcomes with less side-effects.

***Keywords**:* colorectal cancer; biomarkers; chemotherapy; targeted therapy; radiotherapy; personalized medicine.

Colorectal cancer (CRC) ranks as one of the most common cancer types diagnosed worldwide and also as one of leading causes of cancer death [1-3]. Clinical experience, supported by various pathohistological, chromosomal, and molecular biology data and analysis, indicate that CRC is a heterogeneous disease, so patients with clinicopathologically similar tumors and with the same disease stage might differ strikingly in terms of treatment response and survival, respectively [4-9].

The aim of this short overview is to recapitulate the data which indicate that CRC is a heterogeneous group of tumors and to present the topics presented by the lecturers and discussed at this meeting. The topics were the following: CRC incidence, importance of optimal nutrition, molecular pathogenesis, novel diagnostic procedures and algorithms, pathohistological recommendations and algorithms, surgical approaches, systemic therapy, radiation therapy, drug pharmacogenomics and patient pharmacogenetics, therapy side-effects, and the importance of a multidisciplinary team in making therapeutic decisions and in taking care of patients.

Our understanding of colorectal cancer as a disease is in fact continuously evolving. There are a number of known genes controlling growth factor pathways that may drive the development and progression of colorectal cancer. 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. 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. The lifestyle and nutritional recommendations, particularly for sporadic CRC prevention, include increasing dietary fiber intake, reducing red and processed meat consumption and alcoholic drinks, as well as regular physical exercise [8-11].

Two to three major genetic pathways are implicated in colorectal cancer. Most of sporadic CRC (at least two thirds) derive from malignant altered adenoma. In addition to genetic mutations leading to the activation of several protooncogens and to the inactivation of several tumor suppressor genes such as APC (adenomatous polyposis colis), TP53 gene and LOH (loss of heterozygosity), these tumors also demonstrate chromosome instability. This is a so-called phenotype or pathway of chromosome instability (CIN) and microsatellite stability (MSS) [8,9].

A subset of about 15% of CRC display a distinct type of genomic instability, referred to as microsatellite instability (MSI) pathway. Instability in two or more of several distinct marker loci (MLH1, MSH2, MSH6, PMS2) is defined as MSI-high (MSI-H) tumor, whereas those with one unstable marker are designated MSI low (MSI-L). Tumors with no positive marker at any of the investigated loci are classified as microsatellite-stable (MSS). The MSI subtype is caused by a defective DNA mismatch repair (MMR) system. The technical determination of the MSI status is based either on PCR analysis or immunohistochemistry (IHC). In about one third of cases, the MSI-H phenotype results from a germline mutation in one of the MMR genes. More commonly, MSI-H is sporadic and due to somatic or epigenetic events, for example due to MLH1 gene promoter methylation [8,9,12].

The epigenetic inactivation of the MLH1 gene in CRC is generally associated with an extensive hypermethylation of many other promoter regions, also known as the CpG island methylation phenotype or pathway (CIMP). The CIMP subtype includes a broader spectrum of tumors than the MSI subtype. Technological advances allowing for genome-wide DNA methylation profiling have revealed recently, that aberrant DNA methylation is not restricted to promoters, but occurs genome-wide, including intragenic and intergenic regions. Promoter methylation is often linked to the silencing of genes, whereas intragenic methylation is positively correlated with gene expression [8,9].

All these subtypes may require different clinical management and treatment strategies. For example, in patients with stage II disease mismatch repair deficiency (dMMR) is a predictive biomarker for lack of significant benefit from adjuvant single-agent fluoropyrimidine chemotherapy in this population [4,6].

Another CRC classification system, based on the cancer genome atlas (TCGA) analysis, considers the rate of somatic mutations that can vary considerably among tumors. About 16% of tumors were found to be hypermutated (defined as >12 mutations per 106 bases) with somatic events in either DNA mismatch repair genes— manifesting also as the MSI-H phenotype — or in a related DNA repair gene (such as POLE) not entirely. TGFBR2 and BRAF were frequent targets of mutation, too, found in about 50% of hypermutated, but less than 5% of non-hypermutated tumors. In contrast, the group of non-hypermutated tumors is very well associated with CIN+ tumors. The most frequently mutated genes among them were APC, TP53, KRAS, PIK3CA, FBXW7, and NRAS, indicating that hypermutated and non-hypermutated tumors progress through different sequences of genetic events and pathways [8,9,13].

Moreover, recent unsupervised approach using gene modules resulted in the identification and/or proposition of five distinct molecularly defined CRC subtypes, which adds a new layer of complexity to CRC heterogeneity and opens new opportunities for understanding the disease [8,14].

All this emerging data confirm that CRC, despite similar histology across cases, is a heterogeneous group of tumors that can be subdivided by their molecular features and treated differently; e.g., microsatellite instable (MSI) versus microsatellite stable (MSS), RAS mutated versus wildtype, BRAF mutated versus wildtype, and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) mutated versus wildtype [4,8,9,13,14].

A majority of newly diagnosed patients present with stage I – III disease that is confined to the bowel and regional lymph nodes, whereas about a third is diagnosed with metastatic disease. Early stage CRC might be curable with surgery alone or in combination with systemic adjuvant chemotherapy and radiotherapy (for rectal

cancer). Radiotherapy can be applied as neoadjuvant or as adjuvant. Nevertheless, a considerable proportion of these patients experience disease recurrence after surgical resection (and adjuvant therapy) or develop metastatic disease, indicating again that supplemental parameters and biomarkers for risk estimation in clinical practice beyond the TNM classification and pathological risk factors are needed. In developed countries, there is a trend of improvement in CRC mortality, probably due to an earlier diagnosis through screening, more precise diagnostic equipment and algorithms, and better treatment modalities [4-7,15].

The backbone of chemotherapy in CRC is 5-fluorouracil (5-FU), a pyrimidine analog that disrupts DNA and RNA synthesis. When 5-FU is administered intravenously, it is given with leucovorin, a folate analog that stabilizes thymidylate synthetase and enhances the cytotoxicity of 5-FU. Oral capecitabine is a prodrug, that is enzymatically converted to 5-FU in the body and can be used instead of 5-FU. 5-FU is active as a single agent, but its efficacy and patients' survival are improved in a metastatic setting when combined with oxaliplatin, a platinum derivative and alkylating agent, or with irinotecan, a topoisomerase I inhibitor that affects DNA repair. In selected patients, a feasible treatment option may be a combination of all three agents (FOLFOXIRI). There is evidence for improved response rate and survival with the latter chemotherapy protocol, but at the cost of increased toxicity (side-effects), including neurotoxicity and neutropenia. Various studies have investigated whether molecular differences between patients can predict response to standard chemotherapy drugs to facilitate a more personalized approach to chemotherapy. Analyses 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. In a disease metastatic setting, including the abovementioned cytotoxic drugs, both the vascular endothelial growth factor (VEGF)-A-targeted antibody bevacizumab and the epidermal growth factor receptor (EGFR)-targeted antibodies cetuximab and panitumumab have clear efficacy when combined with particular cytotoxic chemotherapeutic regimens, the latter group in KRAS and NRAS-wildtype disease only. For bevacizumab, we have no predictive parameter or marker. Another biologic agent that targets the VEGF pathway is aflibercept, a recombinant protein with VEGF receptors 1 and 2 that targets VEGF-A, VEGF-B, and placental growth factor (PlGF). The US Food and Drug Administration (FDA) also approved the novel agent regorafenib for chemotherapy-refractory mCRC in 2013. Regorafenib is an oral tyrosine kinase inhibitor that has multiple targets, including VEGF receptors 1, 2, and 3 [4-7,16-19].

In conclusion, treatment and outcomes for patients with mCRC have been steadily improving with the introduction of newer polychemotherapy protocols along

with the use of inhibitors of the vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR) pathways. Molecular heterogeneity of CRC is believed to be one of the main factors responsible for the considerable variability in patients' response to treatment. 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 [4-6, 8, 9, 20].

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Sažetak

Kolorektalni rak – uvodnik

U prikazanom uvodnom radu dan je kratak pregled kliničkih aktualnosti u sporadičnom kolorektalnom raku (KR). KR je u svijetu, zajedno s rakom pluća i rakom dojke, jedan od najčešćih tipova raka kako po incidenciji tako i u prevalenciji. Nažalost, među zloćudnim tumorima je jedan i od češćih uzroka smrti. Većina KR je sporadična, s dobi kao jednim od najvažnih faktora rizika. 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. KR se razvija kroz postepenu akumulaciju genskih i epigenetskih promjena, s posljedicom transformacije normalni stanica mukoze u invazivni rak. Strategija liječenja raka kolorektuma se prvenstveno temelji na smještaju tumora, procjeni uznapredovalosti i proširenosti tumora te općem stanju bolesnika. Ipak, sve češće kada je moguće, u obzir se uzimaju geni i/ili molekularni putevi koji reguliraju aktivnosti kao npr. rast i diobu stanica, njihovu smrt ili apoptozu, popravak molekula DNA, i druge slične stanične aktivnosti. 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. 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; kemoterapija; ciljana terapija; radioterapija; personalizirana medicina.

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