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Mini-review

Natural compounds and combination therapy in colorectal cancer treatment

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ABSTRACT

Colorectal cancer (CRC) therapy using conventional chemotherapeutics represents a considerable burden for the patient's organism because of high toxicity while the response is relatively low. Our review summarizes the findings about natural compounds as chemoprotective agents for decreasing risk of CRC. It also identifies natural compounds which possess anti-tumor effects of various characteristics, mainly *in vitro* on colorectal cell lines or *in vivo* studies on experimental models, but also in a few clinical trials. Many of natural compounds suppress proliferation by inducing cell cycle arrest or induce apoptosis of CRC cells resulting in the inhibition of tumor growth. A novel employment of natural substances is a so-called combination therapy - administration of two or more substances - conventional chemotherapeutics and a natural compound or more natural compounds at a time. Some natural compounds may sensitize to conventional cytotoxic therapy, reinforce the drug effective concentration, intensify the combined effect of both administered therapeutics or exert cytotoxic effects specifically on tumor cells. Moreover, combined therapy by targeting multiple signaling pathways, uses various mechanisms to reduce the development of resistance to antitumor drugs. The desired effect could be to diminish burden on the patient's organism by replacing part of the dose of a conventional chemotherapeutic with a natural substance with a defined effect. Many natural compounds are well tolerated by the patients and do not cause toxic effects even at high doses. Interaction of conventional chemotherapeutics with natural compounds introduces a new aspect in the research and therapy of cancer. It could be a promising approach to potentially achieve improvements, while minimizing of adverse effects associated with conventional chemotherapy.

1. Introduction

1.1. Colorectal cancer, prevalence and risk

Colorectal carcinoma (CRC) is a 3rd most common type of cancer (after lung and breast cancer) and the fourth leading cause of cancer death worldwide [1]. CRC occurs predominantly in persons over 50 years of age, about 690,000 people annually die for this disease. The Czech Republic, together with Slovakia (first in rank) and Hungary (second in rank), is one of the worst affected regions in the world. According to a 2012 comparison of GLOBOCAN data, the Czech Republic occupies the 3rd place. With the early detection of the disease is a five-year survival of 80%, while at the diagnosis of more advanced forms the prognosis is poor, the average survival time is 11 months. Data from the National Oncological Registry for 2013 show the incidence of CRC in the Czech Republic of 52/100 thousand in men and 39/100 thousand for women [2]. Mortality for 2013 in men reached 23/100 thousand and 18/100 thousand in women. From the long-term point of view, CRC mortality decreases slightly due to early detection of the disease.

CRC predisposition is an inherited susceptibility with an estimated risk 12–35% attributed to genetic factors [3] [4]. The genetic risk factors vary between two extreme situations: rare high-penetrance mutations which have significant increment of risk for hereditary syndromes and common variants (polymorphisms)

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which have weak effects on sporadic risk in individuals without family history in CRC [5]. Risk of CRC can be reduced with dietary habits and lifestyle [6]. Diet appears to be one of the ways by which various carcinogens challenge the DNA repair daily [7]. Dietary habits also modulate the intensity of early colon carcinogenic events [6]. Since genetic polymorphisms modulate the cancer risk by the activity of enzymes metabolizing xenobiotics and DNA repair proteins, it might be a critical step in the mutational process. Even at high-risk population the risk of tumor development can be modified by natural compounds. For example, in Chinese women that are at a higher risk of breast cancer due to a genetic predisposition, there has been reported that regular green tea consumption is associated with reduced risk of breast cancer [8]. A recent clinical trial phase II reported that in younger postmenopausal women (50–55 years) at high risk of breast cancer, a percent of mammographic density was significantly reduced by 4.40% with decaffeinated green tea extract supplementation as compared with the placebo group [9].

1.2. Conventional treatment

Current treatment of CRC is based on surgery and chemotherapy. Chemotherapeutics interfere with the cell cycle, the most sensitive are rapidly dividing cells and cells with reduced DNA repair capacity [10]. The chemotherapeutic agents are classified according to their mechanism of action on mitosis inhibitors, DNA replication inhibitors, and other cytotoxic agents. Adjuvant chemotherapy (therapy given in addition to the primary therapy to maximize its effectiveness) is not recommended for rectal cancer stage II or III [11]. The most commonly used chemotherapeutic agents are platinum derivatives (oxaliplatin), antimetabolites (capecitabine, 5-fluorouracil), topoisomerase inhibitors (irinotecan) and Tegafur/uracil (UFT), which inhibit the catabolism of 5-fluorouracil. First line chemotherapy in advanced CRC is based on 5-fluorouracil (5-FU) with leucovorin (folinic acid), alone or in combination with oxaliplatin [12]. In metastatic CRC the treatment consists of 5-FU or its combination with irinotecan [13]. The overall response rate to 5-FU monotherapy in advanced CRC is limited to 10–15% [14]. A potential way to improve therapy and postpone adverse effects is combination or multicomponent therapy [15]. 5-FU combined with other cytotoxic drugs could not only improve the response rates, but also reduce the undesirable reaction of these drugs [15]. In many cases, as described further, the combination therapy shows a better outcome –enhancement of the cytotoxic effect of the conventional therapy to cancer cells (for example curcumin [16]). The other problem with chemotherapy is toxicity and drug resistance.

The non-specific action of chemotherapeutics is connected with a number of side effects. Chemotherapeutics affect not only the tumor cells but also non-malignant cells. Chemotherapy destroys rapidly dividing cells - tumor cells, but also hair follicle cells, mucous membranes of the oral cavity and gastrointestinal tract, erythrocytes and leukocytes [17]. The adverse effects of the treatment differ among patients, depending on the type of used chemotherapy. As mentioned above, the first line chemotherapeutics in CRC therapy is 5-FU [12]. The most common adverse effects of 5-FU are: nausea, vomiting, diarrhea, mucositis of the oral cavity (mucosal and submucosal tissue damage), headaches, skin pruritus, myelosuppression (suppression of hematopoietic function of the bone marrow, leukopenia, pancytopenia and thrombocytopenia), anemia, cardiotoxicity, agranulocytosis, alopecia (hair loss), photosensitivity, hand-foot syndrome, depression and anxiety [18] [19].

For the capecitabine, a 5-FU precursor, which is enzymatically metabolized in the body to effective 5-FU, some of the serious adverse effects are occurring quite commonly (in more than 10% of patients) [20]. Common side effects of oxaliplatin therapy are neuropathy (peripheral nerve disorder resulting from drug neurotoxicity, starting with limb tingle), proprioceptive disorders (body coordination), ototoxicity (loss of hearing), nausea, vomiting, diarrhea, neutropenia, hypokalemia (low concentration of potassium in blood), rhabdomyolysis (acute skeletal muscle breakdown, followed by renal failure) [21]. Adverse effects of cytotoxic therapy impair the quality of patient's life and may adversely affect the course of the treatment, the treatment outcome, and treatment costs. We may hypothesize, that combination of conventional chemotherapeutics with well tolerated natural non-toxic compounds may contribute to better response to therapy and better quality of patient's life.

1.3. Chemopreventive approaches, natural compounds in food, antioxidant supplements, prebiotics and probiotics, healthy dietary habits

Natural compounds (sometimes called phytochemicals or phytonutrients) are biologically active substances present in plants (pigments), such as carotenoids, flavonoids, anthocyanins or terpenoids. Some of these beneficial substances are not found only in plants, but also in mushrooms, bacteria or marine organisms. Plants are protected against external influences or against predators by phytochemicals, mostly by antioxidant mechanisms. On the other hand, some other plant-derived substances may be toxic to the human body (phytotoxins), e. g. aristolochic acid [22]. For many natural compounds a precise mechanism of their action is not known and is being investigated. Many natural compounds that show the chemopreventive effect on DNA we uptake with food, but the ingested dose may not represent an effective amount. Food is both a source of macronutrients (proteins, fats, carbohydrates) and micronutrients (vitamins, minerals), but it also contain a large number of natural compounds – a complex mixture of bioactive compounds - of that our organism can benefit of [23].

The concept of so-called chemoprevention can be defined as the use of natural substances capable of preventing or interacting with the development of processes leading to the onset of neoplasia, during its initiation, promotion and progression, or the capability to discontinue its development [24]. Primary chemoprevention is an approach focused on cancer risk in the high-risk population, for example the prevention of lung tumors in smokers or the prevention of breast cancer development in women with positive biomarkers BRCA1 and BRCA2. Secondary chemoprevention focuses on patients diagnosed with a pre-malignant lesion that could grow into an invasive tumor. Tertiary chemoprevention is focused on prevention of recurrence after experienced cancer [25] [26].

One of the studied chemopreventive approaches is based on supplementation with compounds exhibiting antioxidant properties, as it is based on the assumption that oxidative stress and free radical formation in normal cells are one of the causes of cancer [27]. However, some clinical studies testing chemopreventive strategies have provided controversial outcomes. The SELECT 2011 study (Selenium and Vitamin E Cancer Prevention Trial), in which 35.5 thousand of patients with positive prostate cancer markers were administered with selenium, alpha-tocopherol (vitamin E), both agents together, or placebo, had to be prematurely stopped because it came out that vitamin E significantly increases the risk of prostate cancer [28]. From the 2004 meta-analysis of beta-carotene, vitamins A, C, E and selenium in cancer of the esophagus, stomach, colon and rectum, pancreas and liver appears that antioxidant supplementation has either no effect, or even increases mortality [29]. A study from 2011 says that green tea polyphenols which possess anti-cancer activity exhibit both antioxidant (radical