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Synergistic Role of Curcumin With Current Therapeutics in Colorectal Cancer: Minireview

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Abstract

Despite the use of surgical resection and aggressive chemotherapy, nearly 50% of patients with colorectal carcinoma develop recurrent disease, highlighting the need for improved therapies. Curcumin (diferuloylmethane), the major active ingredient of turmeric (*curcuma longa*) with no discernable toxicity, has been shown to inhibit the growth of transformed cells and colon carcinogenesis at the initiation, promotion, and progression stages in carcinogen-induced rodent models. In a Phase I clinical trial, curcumin has been found to be extremely well tolerated and effective. In this review, we summarized the current status of our knowledge about the effectiveness of curcumin when given in combination with current chemotherapeutics such as 5-fluorouracil, oxaliplatin, and gemcitabine in treatment of gastrointestinal cancers with particular reference to colorectal cancer. Existing data suggest that curcumin in combination with chemotherapy is a superior strategy for treatment of gastrointestinal cancer.

INTRODUCTION

Colorectal cancer is the third most common cancer in both men and women, constituting 10% of new cancer cases in men and 11% in women (1). It is the second most common cause of death from cancer in the United States and other developed countries. Surgery and subsequent chemotherapy can cure over 75% of colon cancer patients, but more than 30% of these patients develop new neoplastic polyps, and 10% progress to frank second malignancy (2–4). The risk of second malignancy is higher for microsatellite instable tumor (5). Metastatic colorectal cancer has poor prognosis, with 5-yr survival of less than 10% (1). As a result of great efforts being made on improving chemotherapeutic interventions for metastatic colon cancer, the median survival has improved to over 20 mo in this group of patients (6). However, this comes at a cost of additional toxicities, some of which are even fatal. The validation of a nontoxic agent that could improve on the current chemotherapeutic regimen would therefore be highly desirable. Curcumin (diferuloylmethane), the major active ingredient of turmeric, derived from the dried roots of *Curcuma longa* with no discernable toxicity, could be one such agent. This review summarizes some of the most relevant information on utilization curcumin with and without current therapeutics in the treatment of colorectal cancer.

CURCUMIN IN COLORECTAL CANCER

In its pure crystalline state, curcumin is a diferuloylmethane existing in a stable enol form under alkaline conditions. Its chemical formula is 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Besides curcumin, turmeric powder contains other chemical constituents known as the curcuminoids, composed of demethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin (7,8). Curcumin, which is used as a coloring and flavoring additive in many South Asian cuisines, has been shown to inhibit the growth of transformed cells (9,10) and colon carcinogenesis at the initiation, promotion, and progression stages in carcinogen-induced rodent models (11–13). Curcumin has been found to inhibit chemically induced carcinogenesis in the skin, fore stomach, and colon when administered during initiation and/or postinitiation phases (14–17). Development of azoxymethane induced preneoplastic and neoplastic lesions of the colon are also inhibited in experimental animals fed a diet containing 0.2–1.6% curcumin (18,19). In addition, curcumin has been reported to prevent adenoma development in the intestinal tract of Min/+ mice, a model of human familial adenomatous polyposis (20). In a Phase I clinical trial, curcumin was shown to be effective in inhibiting tumor growth (21).

In addition to the possible direct/indirect effects of curcumin at the preinitiation and initiation stages (22–24), curcumin has been shown to affect the postinitiation and progression stages of colon carcinogenesis. Several in vivo and in vitro studies, including our own, have demonstrated that curcumin treatment inhibits cyclooxygenase-2 (COX-2) expression and activity, leading to a reduction in prostaglandin synthesis and loss of cancer cell growth (25–27). However, curcumin was also shown to be an effective inhibitor of cell growth in prostaglandin-synthesis deficient cancer cells (HCT-15), suggesting that curcumin may act via prostaglandin independent pathways (28).

Since metabolism and absorption of dietary agents can significantly impact their biological efficacy, studies have been performed to determine the biological availability of curcumin. Most preclinical and clinical studies have demonstrated a poor oral bioavailability of curcumin. On oral administered curcumin undergoes extensive first pass metabolism in the liver by conjugation to glucuronide and sulphate. Curcumin and its metabolites were measured by HPLC in the tissues, plasma, and feces in Min+/- mice after long-term ingestion of dietary curcumin (0.2%–0.5%) in doses that reduced adenoma multiplicity by about 40% (20,29). Most of the ingested curcumin was present in the feces as authentic curcumin sulfate, 20–25% was measured in the colonic mucosa, and 5–10% was present in the mucosa of small intestine. In mice fed 0.2% curcumin, 100 pm/g of curcumin was found in the liver, approximately 0.001% of that measured in the intestinal mucosa (20). After termination of dietary curcumin intake, tissue curcumin levels declined rapidly to unquantifiable amounts (within 3–6 h), whereas fecal levels declined more slowly (with a 23-h half-life) (20). In contrast, intraperitoneal (i.p.) injection of a bolus dose of ^{14}C -curcumin produced a 10-fold higher concentration in the intestinal mucosa than in the plasma; the half-life of ip administered curcumin was also highest in the intestinal mucosa (approximately 8 h) compared to all other organs (2–4 h). These studies have suggested that orally administered curcumin may exert its inhibitory effects primarily via luminal and/or intramucosal routes (although negligible levels were absorbed into the circulation via this

route) (29). Pilot studies in colon cancer patients (30,31) and results from experiments in rodents (20,32,33) also suggest that the systemic availability of curcumin is poor as a result of dietary ingestion. In spite of poor absorption into the circulation, intake of dietary curcumin reduces the growth of tumors remote from the site of absorption (34; for review see Ref. 35), and corrects biochemical defects in diseases such as cystic fibrosis (36).

The concentrations of curcumin required to elicit biochemical changes germane to chemoprevention in experiments in vitro are in the 5 to 50 μ mole/l range. Hence, for the development of curcumin as a potential colorectal cancer chemopreventive agent, it is of paramount importance to establish whether intestinal levels of curcumin in this concentration range are achievable in humans who receive oral curcumin, thus potentially eliciting pharmacologic changes, which, when maintained over prolonged periods of time, might elicit chemoprevention. Concentration of curcumin in human colorectum after daily consumption of 1.8 or 3.6 g are of an order of magnitude shown to elicit pharmacologic activity in cells in vitro (37–40).

The poor systemic availability of curcumin has raised concerns about its use for the chemoprevention or treatment of malignancies remote from the site of absorption (20). However, this would not preclude its use in prevention/treatment of gastrointestinal malignancies (20), as curcumin distribution in the gastrointestinal tract is, to a great extent, independent of systemic availability.

CURCUMIN AND CHEMOTHERAPEUTICS IN COLORECTAL CANCER

Despite the use of surgical resection and aggressive chemotherapy, nearly 50% of patients with colorectal carcinoma develop recurrent disease, highlighting the need for improved therapies (1). Suffice it to mention that chemotherapy has limited efficacy in treatment of advanced gastrointestinal malignancies, which comes at a cost of significant toxicities. Resistance to chemotherapy has been partly attributed to its activation of NF- κ B transcription factor leading to upregulation of various antiapoptotic genes (41–43). Therefore, improving efficacy of chemotherapeutic agents by addition of nontoxic agents such as curcumin is highly desirable. Curcumin has been shown to be synergistic with chemotherapy in inhibiting colorectal and pancreatic cancer cell growth. This synergistic effect appears to be partly due to inhibition of NF- κ B and growth factor receptors.

Gemcitabine, a pyrimidine analogue, is routinely used in the treatment of pancreatic cancer. In advanced pancreatic cancer, gemcitabine produces a very modest response rate in single digits with prolongation of survival by only a few weeks. Addition of various chemotherapies to gemcitabine has only resulted in increased toxicity with limited improvement in efficacy (44). Resistance of pancreatic cancer to gemcitabine has been attributed to activation of NF- κ B, leading to increased expression of cyclin D1 and vascular endothelial growth factor (VEGF) (45,46). Addition of curcumin to gemcitabine has been shown to suppress NF- κ B activation in pancreatic cells, resulting in downregulation of the NF- κ B-regulated gene products that inhibit apoptosis such as Bcl-2, Bcl-xL, X-linked inhibitor of apoptosis protein, and cellular inhibitor of apoptosis protein-1 (cIAP-1)] and stimulate proliferation (e.g. COX-2, cyclin D1, and c-*myc*), angiogenesis (VEGF and

interleukin-8), and invasion [matrix metalloproteinase-9 (MMP-9)] (47). Curcumin inhibits the growth of various pancreatic cancer cells at a dose that can be physiologically achieved when administered orally in various Phase I studies (48). This growth inhibition is found to be synergistic when combined with gemcitabine (47,48). In 1 of the experiments, groups of mice were randomized to receive vehicle only, curcumin (1 g/kg) orally daily, gemcitabine (25 mg/kg) ip twice weekly, and combination of curcumin and gemcitabine. They were sacrificed on Day 35, and tumor volume was assessed. The tumor volume in the combination of curcumin and gemcitabine group was found to be significantly lower than that caused by gemcitabine alone or those treated with vehicle (control group; $P < 0.05$ vs. gemcitabine; $P < 0.001$ vs. control) (47). This was accompanied by the concomitant inhibition of COX-2, MMP-9, and ICAM-1 expression (47). In view of these observations, it is reasonable to speculate that addition of curcumin to gemcitabine could be an effective therapeutic strategy for pancreatic cancer and should be further tested in clinical trials. Additionally, constitutive activation of NF- κ B has been shown to be responsible for maintaining resistance to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in various human cancer cells (49). TRAIL ligand is currently being evaluated clinical trials for treatment of variety of cancers including gastrointestinal cancers due to its selectivity for inducing apoptosis in cancer cells (50). In addition to inhibition of NF- κ B, curcumin is also shown to upregulate DR-5, a receptor for TRAIL, in various cancer cells including colorectal and hepatocellular cancers (51). Thus, curcumin further sensitized TRAIL sensitive cells and reverses TRAIL resistance in various GI cancer cells. Therefore, curcumin should be explored in combination with TRAIL in clinical trials.

Combination of 5-fluorouracil and oxaliplatin (FOLFOX) forms the backbone of colorectal cancer chemotherapeutics. One of the important mechanisms of chemotherapy induced growth inhibition of colon cancer growth is its ability to down-regulate the expression and activation of growth factor receptors, specifically EGF-receptor (EGFR) and its family members (referred to as EGFRs) as well as insulin like-growth factor (IGF)-1-receptor (IGF-1R). It is becoming increasingly evident that the development and progression of many malignancies, including colorectal cancer, are associated with constitutive activation of multiple signaling pathways, induced by many growth factor receptors, specifically, EGFRs and IGF-1R that promote proliferation, inhibit apoptosis, and induce metastasis (3–5). Therefore, it is likely that the maximal and most durable therapeutic benefit against tumor growth will be achieved with combination therapies that affect several targets. Thus, agent(s)/regimen(s) that target EGFRs and IGF-1R should be more effective than narrowly focused therapies, as they are likely to impact several aspects of tumor progression. This hypothesis was tested in an in vitro study in which addition of curcumin to FOLFOX resulted in a significantly greater inhibition of growth HCT-116 and HT-29 colon cancer cells that that observed following treatment with curcumin, curcumin plus 5-FU, or FOLFOX when compared with the untreated controls (52). A part of the growth inhibition due to combination of curcumin and FOLFOX could be attributed to inhibition of expression and activation of EGFR, HER-2, and HER-3 as well as IGF-1R (52). Curcumin-induced downregulation of EGFR was found to be due to inhibition of EGFR promoter activity, whereas the effect of FOLFOX on EGFR expression was thought to be posttranslational (52). Inhibition of IGF-1R activation by curcumin and FOLFOX was attributed to increased

sequestration of IGFs by IGFBP-3, whose levels were greatly increased by the combination of curcumin and FOLFOX (52). Curcumin in combination with 5-FU has also found been to cause a greater inhibition of growth of gastric cancer cells growth via G2/M arrest (53). Additionally, we reported that the combination of curcumin and ERPP, a universal inhibitor of EGFR and its family members (54), causes a significantly greater inhibition of growth of colon cancer cells in vitro than either agent alone (25). This has been partly attributed to attenuation of NF- κ B activity (25). More recently, we have observed that a combination of curcumin and dasatinib (BMS-354825; Bristol-Myers Squibb)—a newly developed, highly potent, ATP-competitive Src and Abl kinase inhibitor—causes a greater inhibition of growth of colon cancer cells accompanied by inhibition of EGFRs and IGF-1R activation and attenuation of NF- κ B activity (unpublished observation). Hence, addition of nontoxic curcumin can improve the efficacy of gastrointestinal cancer chemotherapy without any additional toxicity. Since curcumin accumulates in the gastrointestinal mucosa after oral administration, it could serve as a radiosensitizer and could also improve the efficacy of chemoradiotherapy for rectal and/or gastroesophageal cancers (55). A schematic representation of the mechanisms of how curcumin may exert its synergistic effect on current therapies for colorectal cancer is shown in Fig. 1. Herein, we propose that radiation and chemotherapy by themselves can stimulate NF- κ B activity, which may lead to increased cell survival (Fig. 1). However, curcumin and chemotherapy can both inhibit the activation of EGFR and its family members, resulting in inhibition of NF- κ B leading to increased apoptosis. Curcumin can also inhibit the activation of IGF-1R by stimulating the expression of IGFBP-3, which in turn leads to increased sequestration of IGFs rendering the ligand(s) unavailable for activation of IGF-1R (Fig. 1). Further experiments are undoubtedly needed to fully establish the therapeutic effectiveness of curcumin either alone or in combination with chemotherapeutics in gastrointestinal malignancies, with particular reference to colorectal cancer.

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FIG. 1.
Schematics of mechanism of synergism between curcumin and current therapeutics in colorectal cancer.