Curcumin as an Anti-Cancer Agent: Review of the Gap Between Basic and Clinical Applications

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Abstract: Curcumin, commonly called diferuloyl methane, is a hydrophobic polyphenol derived from rhizome (turmeric) of the herb Curcuma longa. Extensive research over the last half century has revealed important functions of curcumin. In vitro and in vivo research has shown various activities, such as anti-inflammatory, cytokines release, antioxidant, immunomodulatory, enhancing of the apoptotic process, and anti-angiogenic properties. Curcumin has also been shown to be a mediator of chemo-resistance and radio-resistance. The anti-cancer effect has been seen in a few clinical trials, mainly as a native chemoprevention agent in colon and pancreatic cancer, cervical neoplasia and Barretts metaplasia. Some clinical studies with healthy volunteers revealed a low bioavailability of curcumin, casting doubt on the use of curcumin only as food additive. Our clinical experience with curcumin, along with the anti-metabolite gemcitabine in the treatment of patients with advanced pancreatic carcinoma, produced an objective response in less than 10% of patients, with a minor effect on survival. However, the safety of this combination was proved. Curcumin's potent anti-proliferative activity interacting with several intracellular signal transduction pathways may potentiate the anti-tumor effect of gemcitabine. The preclinical data lead to various, but still scarce, clinical studies (some on-going) that demonstrated the possible efficacy of this treatment as a chemopreventive or chemotherapeutic agent. This review will focus on the clinical evidence, including our experience with curcumin as a chemopreventive and therapeutic agent and the in vitro background results.

Keywords: Curcumin, anti-tumor activity, chemopreventive.

INTRODUCTION

Cancer and inflammation is a new research field that moves from basic to clinical applications. The paradigm of inflammatory cells infiltrating into the stromal microenvironment of tumors where pro-inflammatory cytokines play important roles in promoting tumor cell proliferation, invasion, migration and metastasis is well established in preclinical models. The cancer prevention effect of anti-inflammatory drugs, such as aspirin and other salicylates, is well documented, although the evidence has come from randomized controlled trials performed for purposes other than cancer reduction [1]. Salicylates also regulate the NF-kappa pathways in cells. Clear evidence that aberrant regulation of NF-kappaB and the signaling pathways that control its activity are involved in cancer development and progression, as well as in resistance to chemotherapy and radiotherapy, lead to studies of chemotheraphy and Cox-2 inhibitor combinations for treating patients with advanced cancer [2,3]. The side-effects of these anti-inflammatory drugs limits their widespread use in cancer prevention. The possible use of a diet with anti-inflammatory activity is captivating.

Over the past decade, research into diet and cancer has concerned the general public and raised interest from the media. The American Department of Health and Human Services together with the Department of Agriculture has reported malignant neoplasms as one of the main causes of deaths and suggested targeting a 16% reduction in mortality of men and 9% in women through the adoption of desirable dietary behaviors [4]. Chemicals derived from plants, known as phytochemicals, have gained attention as potential cancer prevention agents, even as part of cancer treatment after epidemiological supporting data and experiments in preclinical models of carcinogenesis. Polyphenols are in the first line of phytochemicals that have been studied for their potential preventive and therapeutic effects. Polyphenols are derived from many components of the human diet, including dark chocolate, peanuts, green and black teas, red wine, olive oil and the spice, turmeric. Many of these natural substances, traditionally used in ancient medicines for their anti-inflammatory and antioxidant actions, are now being investigated for their cardioprotective or cancer preventive abilities [5]. Although research in the field of phytochemicals is growing extensively, the gap between research and widespread use by the public is growing as well. This situation calls for specific physician attention, giving the right advice to their patients who are starving for diet-phytochemicals to improve their health.

Turmeric is a spice derived from the rhizomes of the plant Curcuma longa, which is a member of the ginger family (Zingiberaceae). Rhizomes are horizontal underground stems that send out shoots as well as roots. The bright yellow color of turmeric comes mainly from fat-soluble, polyphenolic pigments known as curcuminoids. Curcumin, chemically known as diferuloylmethane (C21H20O6), the principal curcuminoid found in turmeric, is generally considered to be its most active constituent. Other curcuminoids found in tumeric include demethoxycurcumin and bisdemethoxycurcumin [6]. Curcuma longa grows naturally throughout the Indian subcontinent and in tropical countries, particularly Southeast Asia. Turmeric has been used as a component of Indian Ayurvedic medicine since 1,900 BCE. Its use was confined to the Asian continent until the 12th-13th centuries AD. In modern times, curcumin continues to be used as an alternative medicinal agent in many parts of Southeast Asia for the treatment of common ailments, such as stomach upset, flatulence, jaundice, arthritis, sprains, wounds, and skin infections, among many others. Curcumin has entered scientific clinical trials at the phase I and II levels only in the last 10–15 years. Beside its anti-cancerous effects, curcumin has been reported to have beneficial effects in arthritis, allergy,
asthma, atherosclerosis, heart disease, Alzheimer’s disease and diabetes. This widespread effect might be due in part to its ability to modulate the immune system [7].

These pleiotropic activities of curcumin derive from its complex chemistry as well as its ability to influence multiple signaling pathways, including survival pathways such as those regulated by NF-kappaB, Akt, and growth factors, and cytoprotective pathways dependent on Nrf2; and metastatic and angiogenic pathways. Curcumin is a free radical scavenger and hydrogen donor, and exhibits both pro- and antioxidant activity. It also binds metals, particularly iron and copper, and can function as an iron chelator. Curcumin is remarkably non-toxic and exhibits limited bioavailability [8].

Although curcumin is poorly absorbed after ingestion, multiple studies have suggested that even low levels of physiologically achievable concentrations of curcumin may be sufficient for its chemopreventive and chemotherapeutic activity. Thus, curcumin regulates multiple targets (multitargeted therapy), which is needed for the treatment of most diseases, it is expensive and has been found to be safe in human clinical trials. In spite of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent [9]. This gap between the high level of many pre-clinical studies and the limitation of its right clinical use due to poor aqueous solubility, together with low bioavailability, lead to many uncertainties of its therapeutic effect in the Western population.

In the last 20 years, very few clinical trials have been published, but the stream is growing with many enrolling patients. In the current review, a short description of the main pre-clinical data will be given, followed by a description of the clinical evidence, including our experience, with curcumin as a chemopreventive and therapeutic agent for cancer patients.

ACTIVITIES/MechaNISM OF CURCUMIN

The mechanisms implicated in the inhibition of tumorigenesis by curcumin are diverse and appear to involve a combination of anti-inflammatory, antioxidant, immunomodulatory, proapoptotic, and anti-angiogenic properties via pleiotropic effects on genes and cell-signaling pathways at multiple levels. [5,8,10-12].

The anti-inflammatory and antioxidant activities of curcumin have been observed in in vitro studies that showed the inhibition of lipo-oxygenase and cyclo-oxygenase activities that can induce inflammation. The inhibition of Reactive Oxygen Species (ROS) has also been observed [13,14]. The ROS inhibition as well as the level of redox homeostasis enzymes, such as glutathione peroxidase and superoxide dismutase, by curcumin is complex, with the dual effect dependent on time and concentration [13,14]. This dual effect may be attributed to changes in oxidative stress and antioxidant gene expression levels leading to inhibition or promotion of cell death. Results from a study done on lung cancer models suggest that curcumin may exhibit organ-specific effects to enhance ROS formation in the damaged lung epithelium of smokers and ex-smokers. Ongoing clinical trials may need to exclude smokers and ex-smokers in chemopreventive trials of curcumin [15-17]. Interestingly, an in vivo study done with rats showed protection against renal study done with rats showed protection against renal damage induced by acetaminophen by the antioxidative effect of curcumin. This improvement was attributed to the increased antioxidant enzyme activity and the reduction in malondialdehyde levels [18].

COX-2 overexpression has been implicated in the carcinogenesis of many tumors. In contrast to selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib which inhibit the catalytic activity of the isoenzyme, curcumin inhibits the transcription of the COX-2 protein, reducing its level in the cells [19]. The gene inhibition of COX-2 is probably the main anti-inflammatory activity of curcumin. An in vitro study of human cervical cancer cells showed downregulation of COX-2, inducible nitric oxide synthase (iNOS) and cyclin D [7]. This combination of anti-inflammatory and antioxidant activity caused inhibition of vascular endothelial growth factor-mediated angiogenesis in human intestinal microvascular endothelial cells [5,9,20]. An in vivo study on a model of pancreatic carcinoma in nude-mice showed a reduction of 70% in tumor size on a diet rich in curcumin and omega-3 fatty acids through downregulation of the expression and activity of iNOS, COX-2 and 5-lipoxygenase (LOX-5) and upregulation of p21. This inhibitory effect was synergistic when the two food supplements were given together [43]. Curcumin and some of its analogues also inhibit COX-1 transcription [19], perhaps influencing the tumor environment as well.

Curcumin has a low systemic bioavailability after oral consumption and may limit access of sufficient concentrations for pharmacologic effects in tissues outside the gastrointestinal tract. Nevertheless, many pre-clinical studies have shown anti-carcinogenic effects in different tumor cell-lines and animal models. For example, Labbozzetta et al. [21] demonstrated in a multidrug-resistant (MDR) variant of the MCF-7 breast cancer cell line (MCF-7R) that the anti-tumor activity of curcumin was substantial in both cell lines. They discuss how curcumin may exert anti-tumor effects in breast cancer through ER-dependent and ER-independent mechanisms; and act as a drug transporter-mediated MDR reversal agent [21].

The efficacy of curcumin as an anti-cancer agent was also shown in bladder cancer cell lines [22] and in prostate cancer [23,27]. Moreover, the in vivo study revealed that curcumin induced apoptosis in situ, inhibiting the development into bladder carcinoma.

Whether curcumin can overcome chemoresistance and enhance the activity of thalidomide and bortezomib used to treat patients with multiple myeloma was investigated in vitro and in a xenograft model in nude mice [24,25]. The results showed that curcumin inhibited the proliferation of human multiple myeloma cells regardless of their sensitivity to dexamethasone, doxorubicin, or melphalan.

In a separate study of human mammary epithelial carcinoma cells, prostate cancer cells and B-lymphoma cells grow in vitro, curcumin was found to induce apoptosis selectively in the malignant cell lines by increasing p53 expression at the G2 phase of the cell cycle and by releasing cytochrome c from mitochondria [26]. An interesting finding in this study was that curcumin appeared to be sparing of the
normal epithelial cells by arresting them at the G0 phase of the cell cycle by downregulation of cyclin D1 and its related protein kinases (Cdk4/Cdk6) or upregulation of the inhibitory protein p21 \( \text{Waf1} \).

The mechanisms of curcumin-induced apoptosis have been tested from different aspects. One interesting finding in a recent publication is the activation of the caspase enzymes as a trigger for apoptosis [28]. In this study, the anti-proliferation and induced apoptosis effects of curcuminoids were investigated in Detroit 562 cells (human pharynx carcinoma) and HONE-1 (human nasopharyngeal carcinoma) cells. Through these approaches, apoptosis was induced by curcuminoids in the pharynx and nasopharyngeal cancer cells via the caspase-3-dependent pathway. However, a different dependency was observed, whereby proliferation inhibition and apoptosis depend upon the amount of curcuminoid treatment in the cancer cells.

An interesting aspect of curcumin's activity is its radioprotective effect on normal cells and radiosensitizing effects on cancer cells. This opposing mechanism is not entirely understood. It has been suggested that curcumin's ability to reduce oxidative stress and inhibit transcription of genes related to oxidative stress and inflammatory responses may afford protection against the harmful effects of radiation, while the radiosensitizing activity might be due the upregulation of genes responsible for cell death [14,18,20,29,33].

Finally, curcumin as a protector against chemotherapy side effects is a new area of research. Neurotoxicity induced by ROS can appear as an adverse effect of chemotherapy treatment with platinum compounds, such as cisplatin. Genotoxic/antigenotoxic effects of curcumin in PC12 cells exposed to cisplatin [24] showed that curcumin significantly reduced the total frequency of micronuclei induced by cisplatin. Determining the cytotoxic and genotoxic/antigenotoxic effects of curcumin in a neuronal model is important for assessing possible hazards when combined with other chemical agents, including chemotherapy drugs used in cancer therapy.

Basic research demonstrates different aspects of curcumin that are important to further clinical studies. Recently, Jiao et al. [39] observed that, in cultured cells, curcumin exhibits properties of an iron chelator. They observed that curcumin repressed synthesis of hepcidin, a peptide that plays a central role in the regulation of systemic iron balance. These results demonstrate that curcumin has the potential to affect systemic iron metabolism, particularly in a setting of subclinical iron deficiency. This may affect the use of curcumin in patients with marginal iron stores or those exhibiting the anemia of cancer and chronic disease. This phenomenon needs to be considered in any tumor treatment clinical trials.

In summary, the anti-tumor effect of curcumin has been attributed in part to the suppression of cell proliferation, reduction of tumor load and induction of apoptosis in various cancer models, both in vitro and in vivo. Curcumin inhibits multiple levels within the transcriptional network to restrict cell proliferation. It induces p53-dependent apoptosis in various cancers of the colon, breast, bladder, neuron, lung, ovary, etc. [9], while both p53-dependent and -independent G2/M phase arrest by curcumin has been observed in colon-rectal cancer cells [8-10,18-20,29,32-34]. Curcumin promotes caspase-3-mediated cleavage of β-catenin and decreases β-catenin/Tcf-Lef transactivation capacity for c-Myc and cyclin D1 [35]. It also activates caspase-7 and caspase-9 and induces polyadenosine-5'-diphosphate-ribose polymeerase cleavage through the downregulation of NF-κB in multiple myeloma cells [36,37]. Furthermore, curcumin inhibits EGFR activation, Src activity and inhibits activity of some nuclear receptors [11,14,27,33]. Curcumin demonstrates inhibitory effects on Cox-2 and cyclin D1, mediated through NF-κB, and restricts tumor cell growth [32,38] (see Table 1 and Fig. 1).

Table 1. Summary of Main Activities Of Curcumin [5,8,10,13-17,41-46]

<table>
<thead>
<tr>
<th>General Activity</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Chemosensitizing activity of curcumin</td>
<td>*Inhibition of NF-κB</td>
</tr>
<tr>
<td>*Radiosensitization and radioprotection</td>
<td>*Downstream of NF-κB: Inhibition of cyclin D1</td>
</tr>
<tr>
<td>*Chemopreventive, chemotherapeutic</td>
<td>*Downstream of NF-κB: Inhibition of COX-2</td>
</tr>
<tr>
<td>*Inhibition of angiogenesis and metastasis</td>
<td>*Downstream of NF-κB: Suppression of Bcl-2 and Bcl-XL</td>
</tr>
<tr>
<td>*Immunologic modulation</td>
<td>*Inhibition of cytokines inhibits the pro-survival kinase Akt</td>
</tr>
<tr>
<td></td>
<td>*Effects of curcumin on tumor suppressor p53</td>
</tr>
<tr>
<td></td>
<td>*Induction of phase II enzymes</td>
</tr>
<tr>
<td></td>
<td>*Modulation of growth factors and their signaling pathway</td>
</tr>
<tr>
<td></td>
<td>*Inhibition of STAT3 activation by curcumin</td>
</tr>
<tr>
<td></td>
<td>*Effect of curcumin on mitogen-activated protein kinases</td>
</tr>
</tbody>
</table>

**CLINICAL STUDIES WITH CURCUMIN**

The various properties of curcumin and its well-documented antioxidant properties were used to test its efficacy in various illnesses. Curcumin has been extensively investigated for its potential cardiovascular protection, and has been used in neurodegenerative disorders, especially Alzheimer's disease and Parkinson's disease. In addition, curcumin's potential activity in cystic fibrosis has received considerable media attention [5-6,10]. A majority of chemotherapeutic agents, including those isolated from plants (such as taxol, vincristin, etc.), not only induce cancer cell apoptosis but also severely damage the normal cells of the host. Curcumin is a part of our daily food habit and its use in large quantities since ancient times has proved that it is a safe product.

Curcumin treatment, exhibits great promise as a therapeutic agent and is currently being investigated in human clinical trials for a variety of conditions, including multiple myeloma, pancreatic cancer, myelodysplastic syndrom and colon cancer (Table 2).
Inhibits deregulation cellular proliferation, dedifferentiation and proliferation by alerting key signaling molecules that ensured that the cell death proceeds efficiently; enhancement of apoptotic death.

Table 2. Summary of Main Clinical Trials and On-Going Studies

<table>
<thead>
<tr>
<th>No.</th>
<th>Subject</th>
<th>Specific cancer or premalignant condition</th>
<th>No. of patients</th>
<th>Amount of curcumin</th>
<th>Main results</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Palliative care</td>
<td>Different types</td>
<td>62</td>
<td>Ointment</td>
<td>Reduction of necrosis smell and itching of external lesions</td>
<td>[40]</td>
</tr>
<tr>
<td>2.</td>
<td>Cancer prevention</td>
<td>Different types of premalignant conditions</td>
<td>25</td>
<td>1-8 g daily</td>
<td>Histological improvement in some lesions</td>
<td>[41]</td>
</tr>
<tr>
<td>3.</td>
<td>Cancer prevention</td>
<td>Familial adenomatous polyposis (FAP)</td>
<td>5</td>
<td>Curcumin 450 mg + quercetin daily</td>
<td>Decrease in number and size of polyps</td>
<td>[42]</td>
</tr>
<tr>
<td>4.</td>
<td>Pancreatic cancer</td>
<td>Pancreatic cancer</td>
<td>17</td>
<td>8 g daily, combined with gemcitabine</td>
<td>The combination is feasible; 45% stable disease and response</td>
<td>[44]</td>
</tr>
<tr>
<td>5.</td>
<td>Pancreatic cancer</td>
<td>Advanced pancreatic cancer (Phase II)</td>
<td>25</td>
<td>8g/daily</td>
<td>Information on cytokines release and 8% clinical response</td>
<td>[45]</td>
</tr>
<tr>
<td>6.</td>
<td>Colorectal</td>
<td>Advanced, refractory colon carcinoma (Phase I)</td>
<td>15</td>
<td>440-2200 mg/day</td>
<td>Safe product with no side-effects; 33% had short period of stable disease</td>
<td>[46]</td>
</tr>
<tr>
<td>7.</td>
<td>Colorectal</td>
<td>Rectal cancer before surgery</td>
<td>12</td>
<td>450, 1800 or 3600 mg</td>
<td>Pharmacodynamic study</td>
<td>[47]</td>
</tr>
</tbody>
</table>

On going | Location | Tumor/premalignant condition |
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>U of Pennsylvania</td>
<td>After colon polyps resection</td>
</tr>
<tr>
<td>2.</td>
<td>John Hopkins</td>
<td>FAP</td>
</tr>
<tr>
<td>3.</td>
<td>UCLA</td>
<td>Lichen planus</td>
</tr>
<tr>
<td>4.</td>
<td>MD Anderson</td>
<td>Myeloma</td>
</tr>
<tr>
<td>5.</td>
<td>MD Anderson</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>6.</td>
<td>Sourasky Medical Center</td>
<td>Pancreatic cancer</td>
</tr>
</tbody>
</table>
CANCER PREVENTION

A phase I clinical study performed in Taiwan investigated curcumin’s potential anti-carcinogenesis activity in patients with preinvasive malignant or high-risk premalignant conditions [41]. Twenty-five patients with recently resected superficial bladder carcinoma, Bowen disease of the skin, uterine cervical intraepithelial neoplasia, intestinal metaplasia of the stomach, or oral leukoplakia were given doses of 1–8 g of curcumin daily for three months. Histological improvement of the premalignant lesions was noted in one of two patients with presumed bladder carcinoma in situ, two of seven patients with oral leukoplakia, one of six patients with stomach intestinal metaplasia, one of four patients with cervical intraepithelial neoplasia, and two of six patients with Bowen disease of the skin. Limitations for drawing definite conclusions from this study are the small number of patients with each high-risk condition, different daily doses of curcumin, and possible bias from the interpreting pathologists, as the study was not blinded.

Familial adenomatous polyposis (FAP) is an autosomal dominant condition characterized by the development of numerous bowel adenomas that can transform to adenocarcinoma. Regression of the adenomas in this syndrome occurs with the administration of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, but these compounds can have considerable side effects. In a report from the Cleveland Clinic in Florida of five patients with FAP [42], curcumin in combination with quercetin was given to the patients. Quercetin is a phytochemical, acting as an antioxidant, that is part of the coloring found in the skins of apples and red onions. It has been isolated and is sold as a dietary supplement. It is also a natural antihistamine and anti-inflammatory [5]. Curcumin and quercetin were administered three times per day to the five FAP patients, and all showed a decrease in the number and the size of polyps compared with baseline figures [42].

The dose variability in the different studies (450 mg daily in the Cleveland study, 1-8 g/daily in the Taiwan study, represents one of the main difficulties of studies done with nutritional supplements - knowing the correct effective dose.

Two studies are currently testing the chemoprevention effect of curcumin in colon cancer. A phase II study of patients with Familial Adenomatous Polyposis is taking place at the NCI/Johns Hopkins University [56], and another study is being done by the University of Pennsylvania where patients with previously resected adenomatous colonic polyps are being given curcumin for the prevention of colorectal cancer [56]. An interesting chemoprevention phase II study to treat patients with oral lichen planus with curcuminoids or placebo is on-going at the University of California in San Francisco [56].

PANCREATIC CANCER

The anti-metabolite gemcitabine is the standard chemotherapy for advanced pancreatic cancer. Yet it produces an objective response in less than 10% of patients, with a minor effect on survival. Curcumin can potentiate the anti-tumor effect of gemcitabine, as shown in pre-clinical models of pancreatic cancer [56]. Epelbaum et al. [44] treated 17 patients with a combination of curcumin and gemcitabine. Six patients had locally advanced tumors and 11 had metastatic disease, all in the liver. Gemcitabine 1,000 mg/m² was given on day 1 every week for 7 weeks with a one week break, followed three weeks of treatment and a one week break in the next cycles. Eight grams of curcumin (500 mg capsules) were given daily, divided into 4 g twice a day (morning and evening), throughout the treatment period, and patients received a median of two (range, 1/3-14) cycles of gemcitabine. Five (29%) patients discontinued the curcumin after a few days to two weeks due to intractable abdominal fullness or pain, and one patient died during the first cycle due to an unrelated cardiac event. Curcumin and gemcitabine were delivered concomitantly for a period of 1 to 12 months in the remaining 11 patients. The dose of curcumin was reduced to 4 gram/day in three because of abdominal complaints. One patient had grade II neutropenia and one had grade I thrombocytopenia, but no other toxicities were observed. One (9%) of the 11 evaluable patients had partial response (7 months), 4 (36%) had stable disease (2, 3, 6 and 12 months) and 6 (55%) had tumor progression. Time to tumor progression was 1 to 12 months (median 2), and overall survival 1 to 24 months (median 6). The results suggest that a combination of gemcitabine and curcumin for patients with advanced pancreatic cancer is feasible. However, the daily oral dose of curcumin should be less than 8 grams.

Dhillon et al. [45] conducted a Phase II study of only curcumin supplement as 1st line treatment in patients with advanced pancreatic cancer. Twenty-five patients received 8 g of curcumin daily until disease progression, with restaging every two months. Serum cytokine levels for interleukin (IL)-6, IL-8, IL-10, and IL-1 receptor antagonists and peripheral blood mononuclear cell expression of NF-kappaB and cyclooxygenase-2 were monitored. Twenty-one patients were evaluated for response: One had ongoing stable disease for >18 months and, interestingly, one patient had a brief, but marked, tumor regression accompanied by significant increases in serum cytokine levels. No toxicities were observed. Curcumin downregulated expression of NF-kappaB, cyclooxygenase-2, and phosphorylated signal transducer, and activated transcription 3 in peripheral blood mononuclear cells from patients.

In these two studies, curcumin was given in a daily dose of 8 grams. The common side effect of intractable abdominal fullness or pain was only seen in the study that combined curcumin with chemotherapy. Clinical knowledge of curcumin is limited. Up to now, phase II studies have been performed only with pancreatic carcinoma patients. The results are interesting, raising the need for a phase III study, combining lower doses of curcumin with chemotherapy in the treatment of pancreatic carcinoma.

To the best of our knowledge, there are two on-going studies in pancreatic cancer. A phase II trial of gemcitabine, curcumin and celebrex in patients with advanced or inoperable pancreatic cancer is being carried out at the Sourasky Medical Center in Tel Aviv, Israel [56], and an open label study of patients with locally advanced pancreas cancer is being conducted at MD Anderson in Houston, Texas. In this trial, the daily dose of curcumin is 8g [56].
COLORECTAL CANCER

A phase I clinical trial was conducted by Sharma [46] on 15 patients with advanced colorectal carcinoma, refractory to 5-Fu containing chemotherapy. Patients were stratified to receive various dose of curcumin once daily orally, in a proprietary capsule form at doses between 440 and 2200 mg/day, containing 36–180 mg of curcumin, for four months. Oral Curcuma extract was well tolerated, and dose-limiting toxicity was not observed. Neither curcumin nor its metabolites were detected in blood or urine, but curcumin was recovered from feces. Curcumin sulfate was identified in the feces of one patient. Lymphocytic glutathione-s-transferase (GST) activity and the levels of the adduct (M1G) formed by the reaction of malondialdehyde with deoxyguanosine in DNA were assessed as biomarkers of curcumin activity. The patients receiving higher doses did not observe any change in GST activity. Correlation was not observed with levels of based M1G on a variety of different stratifications. A decline in the cancer biomarker carcinoembryonic antigen was seen in one patient with local colon carcinoma. Radiologically stable disease was demonstrated in five patients for 2–4 months of treatment. The results suggest that Curcuma extract can be administered safely to patients at doses of up to 2.2 g daily, equivalent to 180 mg of curcumin; and curcumin has low oral bioavailability in humans and may undergo intestinal metabolism.

Garcia et al. [47] studied curcumin levels in the colorectum and the pharmacodynamics in 12 patients with confirmed colorectal cancer in various staging. Patients were assigned to 450, 1800 or 3600 mg of curcumin per day for seven days prior to surgery. Biopsy samples of normal and malignant colorectal tissue were obtained at diagnosis and at 6–7 hours after the last dose of curcumin. Blood was taken 1 hour after the last dose of curcumin. The administration of curcumin 3600 mg decreased M1G levels from 4.8±2.9 adducts per 107 nucleotides in malignant colorectal tissue to 2.0±1.8 adducts per 107 nucleotides. COX-2 protein levels in malignant colorectal tissue were not affected by curcumin. The results suggest that a daily dose of curcumin 3.6 g achieves pharmacologically efficacious levels in the colorectum with negligible distribution of curcumin outside the gut. These results suggest that a daily dose of 3600 mg is safe in humans. This dose has been shown to furnish agent levels in the target organ, which may be adequate to elicit antioxidative changes commensurate with long-term benefits, mainly as chemopreventive agent.

In a case report by Braumann et al. [48], a treatment combination of oxaliplatin, 5-Fu and leucovorin, together with 5 g of curcumin daily, was given to a 75-year old woman with colon carcinoma metastatic to the liver. Good partial remission without side effects was reported after five months of treatment.

OTHER CANCERS AND ONGOING STUDIES

Kuttan et al. reported using turmeric as an ointment to treat skin cancers, breast cancer and mucosal cancers (oral cavity, vulva) [40]. This research group found that curcumin ointment produced remarkable symptomatic relief in patients with external cancerous lesions. This treatment lead to better quality of life. Reduction in smell (necrotic) was noted in 90% of cases, even in extensively ulcerated cases of breast cancer, and reduction of itching and dryness of weeping ulcers was observed in 70% of those cases. In a small number of patients (10%), a reduction in lesion size was reported. In many patients the effect continued for several months. An adverse reaction was noticed in only one of the 62 patients evaluated. However, there was no control group, no assessment of anti-inflammatory activity, and no chemical analysis of the medicinal preparation. The report include only 62 patients from 153 treated patients and did not include any patient or tumor details, such as pathology, stage, etc.

Based on the positive results of curcin in animal models of myeloma, a phase I study of multiple myeloma patients is taking place at M.D. Anderson Cancer Center, giving curcumin with or without bioperine [56].

In spite of the large number of basic research and various trials which have been conducted, the optimal dose for cancer prevention or cancer treatment is still not known.

TOXICITY

Curcumin is remarkably well tolerated, but its bioavailability is poor. It does not appear to be toxic to animals [49,51] or humans [49,50,51], even at high doses. Turmeric is generally recognized as safe by the FDA, and curcumin has been granted an acceptable daily intake level of 0.1-3 mg/kg-BW by the Joint FAO/WHO Expert Committee on Food Additives, 1996 [53]. In terms of dietary use in different countries, according to a study from Nepal, dietary consumption of turmeric up to 1.5 g per person per day, equivalent to 50 mg/day of curcumin, does not appear to be associated with adverse effects in humans [52]. In India, where the average intake of turmeric can be as high as 2.0-2.5 g per day (corresponding to 60-100 mg of curcumin daily), no toxicities or adverse effects have been reported at the population level [41]. Preclinical models and clinical trials have documented minimal toxicity from the administration of curcumin or turmeric. In a study performed in India, the administration of 1.2-2.1 g of oral curcumin to patients with rheumatoid arthritis daily for two-six weeks did not cause any toxicity [54]. Cheng [41] administrated 8 g daily of curcumin for three months to patients with pre-invasive malignancies, with no adverse effects. In a trial published by the NCI [54], curcumin was well tolerated at all doses up to 3.6 g daily for up to four months. Adverse events were mainly nausea and diarrhea grade I-II.

CONCLUSION

Curcumin is a component of turmeric that has been used through the ages as a “herbal general medicine” to relieve discomfort and inflammation associated with an extraordinary spectrum of infectious and autoimmune diseases. In basic cancer research, its effects appear pertinent to all stages of carcinogenesis. Curcumin’s beneficial effects have been shown in both chemical and genetic models, providing strong preliminary data for the justification of clinical studies in humans.

In contrast, several studies have suggested that curcumin may not only be ineffective, but may have adverse activities
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in selected settings. For example, in chemical studies, curcumin induced DNA fragmentation and base damage in the presence of copper and cytochromes of cytochrome p450 that are present in lung, lymph, liver, and skin [55].

All these preclinical data lead to various, but still scarce, clinical studies (some on-going). The gap between basic research and clinical application is still growing. The clinical studies were mainly done and are on-going in gastrointestinal (GI) malignancies. The results published until now have shown that the treatment is safe and provide some positive clues of curcumin as a chemo-preventive agent. The data justified a phase III trial in one of the GI carcinomas.

The design of randomized clinical trials should also consider the likelihood of individuals in the non-curcumin arm of the trial consuming turmeric or curcumin of their own volition. Another problem that needs to be clear in future studies is the exact therapeutic dose and the preventive dose for various cancers. Clinical studies in non-GI malignancies are still needed.

Although curcumin's low systemic bioavailability after oral dosing may limit access of sufficient concentrations for pharmacologic effects in tissues outside the gastrointestinal tract [34,38,46], novel delivery methods are in preclinical development to overcome this barrier.

REFERENCES


[56] Information sources; *http://clinicaltrials.gov/ct/search?term = curcumin;