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HIGHLIGHT ARTICLE

Is there a Role for Herbal Medicine in the Treatment of Pancreatic Cancer?

Highlights from the "44th ASCO Annual Meeting". Chicago, IL, USA. *May 30 - June 3, 2008*

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Summary

One of the greatest challenges in the treatment of pancreatic cancer remains its inherent lack of beneficial response to cytotoxic chemotherapy. According to the encyclopedic knowledge on herbal medicine regimen and clinical experience accumulated for centuries, traditional Chinese medicine can provide new avenues for alternative treatments of pancreatic diseases. Chinese herbal extracts have been widely used for the treatment of various cancers, but objective information on their efficacy in pancreatic cancer is lacking. This article provides a summary of herbal medicine, presented at the Annual Meeting of ASCO, 2008. The clinical applications of these active compounds warrant further investigation in randomized, controlled clinical trials.

Introduction

Data from recent studies on the mechanistic link between cancer and inflammation has led to a considerable interest in developing novel therapeutic candidates targeting the inflammatory signaling pathway. It is now the current paradigm that inflammatory cells infiltrate into the stromal microenvironment of tumors where pro-inflammatory cytokines play important roles in promoting tumor cell proliferation, invasion, migration and metastasis. The development of novel therapeutic approaches in this area of research has gained momentum, especially pathways that target the nuclear factor-kappa B (NF-kappa B), which has demonstrated certain inhibitory effects on cytokine productions responsible for tumor proliferation [1].

Certain herbal medicines have been administrated as an anti-inflammatory regimen for many years, and some of their active components or ingredients have been characterized, enhancing our knowledge about their biologic functions through *in vitro* and *in vivo* studies. The isolated active component curcumin [2] and the traditional Chinese formulation PHY906 [3] were presented at the 44th ASCO Annual Meeting, and are discussed here.

Figure 1. Tumeric.

Figure 2. Tumeric powder commonly used as a spice.

Curcumin

Curcumin is a polyphenol compound from the Indian herb, *Curcuma longa L*, and the dietary spice tumeric which is used for wound healing, skin and gut diseases (Figures 1 and 2) [4]. Its molecular structure is composed of both phenol and diarylheptanoid (Figure 3).
Curcumin is reported to have a wide range of beneficial properties, including anti-inflammatory, antioxidant, chemopreventive and chemotherapeutic activity [4]. The 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-kappa B, Akt, and growth factors; cytoprotective pathways dependent on Nrf2; and metastatic and angiogenic pathways, including MMPs [5, 6, 7]. Curcumin is a free radical scavenger and hydrogen donor, and exhibits both pro- and anti-oxidant activity. It also binds metals, particularly iron and copper, and can function as an iron chelator.
Curcumin has been shown to potentiate the antitumor effect of gemcitabine in pre-clinical models of pancreatic cancer. Curcumin is relatively non-toxic and exhibits limited bioavailability. Curcumin is currently used in human clinical trials for a variety of malignancies, including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, and colon cancer.

A Phase II Study of Curcumin and Gemcitabine in Patients with Advanced Pancreatic Cancer. Abstract #15619 [2]

Study Design

A phase II study of gemcitabine in combination with curcumin in patients with advanced pancreatic cancer was presented at ASCO 2008 [2]. Patients received 8 g/day of curcumin (Sabinsa Co., Piscataway, NJ, USA) orally in combination with gemcitabine 1,000 mg/m^2 i.v. weekly for 3 out of 4 weeks. Primary endpoint was time to tumor progression, while toxicity profile and other efficacy parameters constitute the secondary endpoints.

Demographics

Seventeen patients (6 with locally advanced tumor and 11 with metastatic disease) received a median of 2 (range: 1/3-14) cycles of gemcitabine.

Efficacy Results

Eleven patients were evaluable. Time to tumor progression was 1 to 12 months (median 2 months), and overall survival was 1 to 24 months (median 6 months). One patient (9.1%) had partial response (7 months), 4 (36.4%) had stable disease (2, 3, 6 and 12 months) and 6 (54.5%) had tumor progression.

Toxicity Profile

Five patients (29.4%) discontinued curcumin after a time period ranging from few days to 2 weeks due to intractable abdominal fullness or pain. Eleven patients (64.7%) received curcumin and gemcitabine concomitantly for a period of 1 to 12 months, including three patients in whom the dose of curcumin was

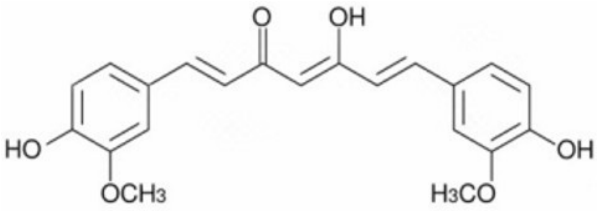

Figure 3. Structure of curcumin.

Figure 4. The four herbs in PHY906.

reduced to 4 g/day because of abdominal complaints; no data were reported on the 17th patient. Hematological toxicities were minimal as expected with gemcitabine, including one grade 2 neutropenia and one grade 1 thrombocytopenia. No other toxicities have been observed.

Conclusions

The preliminary results suggest that a combination of gemcitabine and curcumin for patients with advanced pancreatic cancer is feasible. However, oral doses less than 8 g/day should be considered. Further studies to evaluate the ability of curcumin to enhance the chemotherapeutic efficacy of gemcitabine in cancer patients are warranted.

PHY906

PHY906 is a 4-herb traditional Chinese medicine formulation (Figure 4) with a history of more than 1,800 years of human use [8].

Each of the PHY906's 4 component herbs possess a distinct pharmacological profile, including anticancer and antiviral activity, hematological and immunological stimulation, analgesic activity, liver protection, and appetite improvement. Together, PHY906 has historically been used to treat diarrhea, abdominal spasms, fever, headache, vomiting, nausea and extreme thirst. Many of these ailments are also toxicities resulting from chemotherapeutic treatment [8].

In addition to exploring the use of PHY906 in the alleviation of chemotherapy-induced side effects, such as diarrhea, PHY906 has also been investigated as an adjuvant with anti-cancer drugs in a broad-spectrum of malignancies, including colorectal, liver, and pancreatic cancers. There are multiple possible molecular mechanisms that appear to contribute to PHY906's pharmacological activity, including inhibition of NF-kappa B [8].

Investigators at the Yale Cancer Center presented their preclinical studies indicating

that PHY906 has synergistic anti-tumor activity with capecitabine (Xeloda; Roche, Nutley, NJ, USA) in PANC-1 cell lines [9] which prompted a phase I/II study of for capecitabine combined with PHY906 for patients with advanced pancreatic cancer [3].

A Phase I/II Study of PHY906 plus Capecitabine in Patients with Advanced Pancreatic Cancer. Abstract #15538 [3].

a) Phase I Study

Preliminary results of the phase I study were presented at the Annual Meeting of ASCO, 2008 [3]. Patients with advanced solid tumors who failed standard therapy or for which no standard therapy exists, with Eastern Cooperative Oncology Group (ECOG) performance status equal to or less than 2, and adequate organ function were enrolled. Patients received PHY906 800 mg *bid* (days 1-4) with escalating doses of capecitabine (1,000 mg/m^2, then 1,250 mg/m^2, then 1,500 mg/m^2, then 1,750 mg/m^2 *bid* on days 1-7) followed by 7 days rest, until maximum tolerated dose was reached (Figure 5). Each cycle is 14 days long. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 criteria (http://ctep.cancer.gov/forms/CTCAEv3.pdf). Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) every 6 weeks [10].

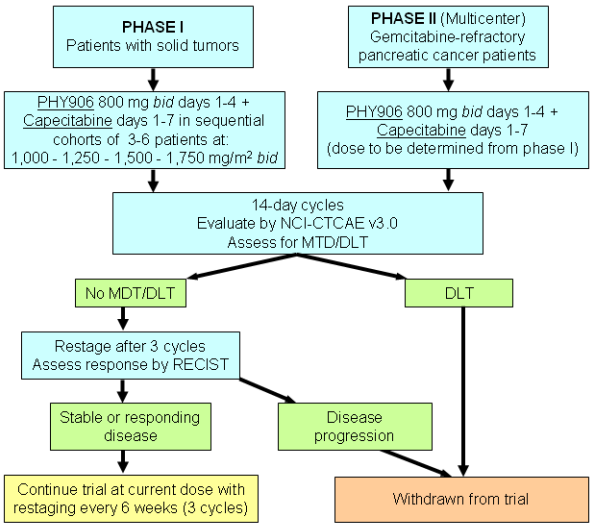

Figure 5. Treatment schema of a phase I/II study of PHY906 plus capecitabine in patients with advanced pancreatic cancer [3].
DLT: dose-limiting toxicity
MTD: maximum tolerated dose
NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
RECIST: Response Evaluation Criteria in Solid Tumors

Demographics

A total of 23 patients have received 100 cycles (median: 5 cycle/patient; range: 1-18 cycle/patient) with PHY906 in 4 capecitabine (7 days on and 7 days off schedule) escalation cohorts: 1,000 mg/m^2 (n=6), 1,250 mg/m^2 (n=3), 1,500 mg/m^2 (n=6), and 1,750 mg/m^2 (n=8).

Toxicity

Dose-limiting toxicity was observed in 1 of 6 patients at 1,000 mg/m^2 dose (grade 4 AST/ALT). No dose-limiting toxicities were seen at higher doses.

Efficacy

One patient with cholangiocarcinoma had partial response at cycle 3 and 9 patients experienced stable disease lasting 6 or more weeks (7 pancreas; 2 colon).

b) Phase II Study

Currently, a phase II study is recruiting patients with gemcitabine-refractory pancreatic cancer to evaluate the efficacy and quality of life and to further confirm toxicity [11].
In addition, correlative chemokine (IL-2, IL-4, IL-5, IL-10, TNF-alpha, IFN-gamma) levels, as surrogates for NF-kappa B expression, will be quantified by cytometric bead array to help elucidate PHY906 mode of action.

Discussion

Herbal medicine formulations have been derived from empirical observations in humans over the millennia. Unlike Western medicine that generally uses purified compounds and targets a single physiological

endpoint, traditional herbal medicine compositions usually comprise multiple herbs and components that interact and act simultaneously through multiple molecular targets and cellular mechanisms. These multiple herbs serve various functions; some may be responsible for efficacy while others may decrease toxicity or increase bioavailability.

There is, as yet, no FDA-approved oral botanical drug for pancreatic, or other cancer in the U.S.. The clinical applications of these active compounds warrant further randomized, controlled clinical trials in patients with pancreatic cancer.

Keywords Antineoplastic Agents, Phytogenic; capecitabine; Curcumin; Drugs, Chinese Herbal; Medicine, Chinese Traditional; NF-kappa B; Pancreas; Pancreatic Neoplasms; PHY 906

Conflict of interest The author has no potential conflicts of interest

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