CANCER

Are Herbal Medicines Ripe for the Cancer Clinic?

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The use of complementary and alternative medicine (CAM) has become a core component of the daily challenges faced when treating cancer patients. PHY906 is a formulation of four herbal compounds traditionally used to treat nausea, vomiting, cramping, and diarrhea. Diarrhea is one of the major side effects of the cancer drug irinotecan. In this issue of *Science Translational Medicine*, Lam and colleagues report that administration of PHY906 with irinotecan in a mouse model of colon cancer resulted in a synergistic reduction in tumor burden, maintenance of body weight, and stem cell regeneration in the intestinal mucosa. Yet when considering CAM use in the treatment of cancer patients, one must take into account reproducibility of preclinical findings in clinical practice, quality assurance of herbal products, and potential toxicities associated with alternative therapies.

Internationally, colorectal cancer remains one of the leading causes of cancer-related morbidity and mortality. For example, in the United States, colorectal cancer is the second-leading cause of cancer-related mortality for men and women combined (*1*, *2*). It is estimated that only 10% of all patients with advanced surgically unresectable metastatic tumors will survive for 5 years after diagnosis. Hence, a substantial focus on colorectal cancer drug development has resulted in Food and Drug Administration (FDA) approval of six drugs over the past decade. Many of these drugs block cell division, causing cell death. Therefore, in addition to killing rapidly dividing cancer cells, these drugs also destroy normal cells that have a high rate of turnover, such as those of the digestive tract, yielding serious and sometimes lethal side effects. In this issue of *Science Translational Medicine*, Lam *et al.* (*3*) report on the potential role of the oral Chinese herbal supplement PHY906 in reducing chemotherapy (irinotecan)–induced gastrointestinal toxicity.

DRUGS THAT HEAL AND HURT THE GUT

For decades, 5-flurouracil (5-FU), a pyrimidine analog that indirectly blocks DNA synthesis in dividing cells, and its biomodulator leucovorin (LV) were the only options for patients regardless of whether they exhibited locally advanced or metastatic colorectal cancer. The first colorectal cancer drug to be approved outside of 5-FU was the topoisomerase I inhibitor CPT-11 (irinotecan, Camptosar). Topoisomerase enzymes modulate the structure of DNA in cells and are required for proper cell division. Inhibitors of this enzyme cause DNA damage in dividing cells and subsequent cell death. Irinotecan is effective as a single agent and was recognized for its ability to extend overall survival of colorectal cancer patients for 14.8 versus 12.6 months ($P = 0.04$) when given in combination with a weekly bolus delivery of 5-FU; the combination irinotecan/5-FU/LV drug mixture is referred to as IFL (*4*–*6*).

With IFL, patients suffered grade 3/4 toxicities, which include neutropenia (53.8% of patients) and early (<24 hours after receiving medication) and late (>24 hours after receiving medication) diarrhea (22.7% of patients) (*4*, *7*). However, early death rates (at <60 days after the first dose of IFL) were noted in two large National Cancer Institute–sponsored phase III clinical trials of the IFL regimen in patients with both early and advanced colorectal cancer. These deaths were attributed to a treatment-related gastrointestinal syndrome of nausea, vomiting, diarrhea, and abdominal cramping (*7*). Mucosal changes in the alimentary tract have been reported after irinotecan administration, resulting in increased amounts of the proinflammatory transcriptional regulatory protein nuclear factor–κβ (NF-κβ) and a variety of inflammatory cytokines (*8*). Vigilant patient monitoring was encouraged, and eventual treatment-related diarrhea guidelines were created that incorporated the use of loperamide and antibiotics, if warranted (*9*). Revisions in the irinotecan-based treatment schedule have resulted in the modification of weekly irinotecan dosing to the widely accepted regimen of bimonthly irinotecan administration (begun on Day 1) with an infusional delivery of 5-FU and LV on days 1 and 2, and then every 14 days (regimen name: FOLFIRI). The FOLFIRI regimen resulted in an improved tolerance of the therapy (*10*). However, although the incidence of grade 3/4 treatment–related diarrhea is reduced (10%) with this bimonthly schedule, treatment-related grade 1/2 diarrhea remains a common adverse event (53%) (*10*).

A VIABLE ALTERNATIVE?

The role of complementary and alternative medicine (CAM) continues to evolve in the daily lifestyle and treatment regimens of cancer patients. Reportedly 38% of adults in the United States use some form of CAM therapy, resulting in an astounding $27 billion in out-of-pocket expenses (*11*, *12*). Furthermore, 60% to 80% of cancer patients have used some form of CAM treatment during their cancer therapy (*13*, *14*). CAM use may be inclusive of holistic spiritual practice and physical exercise, as well as vitamin and herbal medicines for enhanced tumoricidal activity or reduction in treatment-related adverse events.

Chinese medicine has been practiced for more than a thousand years and often uses herbs to achieve its key goal of restoring the balance of energy in the body. The agent PHY906 is derived from Huang Qin Tang, a multicomponent Chinese herbal supplement with its origin dating back to 1800 years ago. Huang Qin Tang has been used for the treatment of nausea, vomiting, and abdominal cramping. Now, in the 21st century, Lam *et al.* (*3*) have used a mouse model of colon cancer to decipher the mechanism by which a well-characterized formulation of PHY906 reduces the toxic gastrointestinal side effects of irinotecan chemotherapy.

The preclinical development of PHY906 was led by the senior author, Yung-Chi Cheng, Professor of Pharmacology and Director of the Developmental Therapeutics Program at the Yale Cancer Center (*3*). PHY906 is composed of four primary herbs, *Glycyrrhiza uralensis Fisch* (Chinese licorice) (G); *Paeonia lactiflora Pall* (Chinese peony) (P); *Scutellaria baicalensis Georgi* (skullcap

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root) (S); and *Ziziphus jujuba Mill* (fruit from a buckthorn tree) (Z) in a 3:2:2:2 ratio (from Sun Ten Pharmaceuticals, Taiwan) (Fig. 1). PHY906 was originally investigated in a phase I/IIA clinical trial in which patients with metastatic colon or rectal cancer received either IFL or a single weekly dose of irinotecan (choice of regimen was at the discretion of the treating physician). Eligibility criteria required all patients to have had progressive disease while being treated with single-agent 5-FU. Patients were then randomized to escalating doses of PHY906 (1.2 g, 2.4 g, and 3.6 g) or were given a placebo in combination with the first dose of chemotherapy and then the alternative (PHY906 or placebo) with the second chemotherapy treatment (*15*). Standard phase I objectives included safety and tolerability. The secondary objective of the trials was to determine the benefit of PHY906 in reducing the late-onset diarrhea commonly associated with weekly irinotecan use. Unfortunately, this trial was not completed and was closed for further development (*16*).

Fig. 1. Herbal landscape. Shown (top left to bottom right) are *Glycyrrhiza* (Chinese licorice), *Lactiflora* (Chinese peony), *Scutellaria baicalensis* (skullcap), and *Ziziphus jujuba* (Chinese date tree or shrub).

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Various doses of PHY906 have since been tested in phase I and II clinical trials in combination with escalating doses of irinotecan or capecitabine in a variety of solid tumors, and capecitabine for pancreatic and hepatocellular carcinomas (Table 1) (*17*–*20*). In pharmacokinetic analyses, PHY906 did not affect the metabolism of irinotecan or its active metabolites SN38 or SN38G (*17*). Various plasma correlatives were assessed, including the concentrations of cytokines (interleukins) and other growth factors (tumor necrosis factor, vascular endothelial growth factor), but these did not correlate with outcome (*18*).

Liu *et al.* of the same investigative group previously reported preliminary findings obtained when PHY906 was tested in combination with either irinotecan or 5-FU+LV in a murine model of colon cancer; they found that the addition of PHY906 resulted in increased antitumor activity and decreased weight loss (*21*). In the current study, Lam *et al.* (*3*) now report the culmination of their final preclinical findings and show that PHY906 likely delivers its beneficial effects by reducing the amount of gastrointestinal mucosal damage that occurs after irinotecan administration. BDF1 female mice were transplanted subcutaneously with murine colon 38 cancer cells to create the BDF1 colon cancer mouse model. After 10 to 14 days, mice with tumors of 150-300 mm^3 were selected for analysis. The treatment groups (5 mice each) that were analyzed for change in tumor size included: (i) the control group; (ii) the irinotecan alone (350 mg/kg body weight) group; and (iii) the irinotecan + escalating doses of PHY906 (50, 150, 500, or 1000 mg/kg body weight) group. Prior to irinotecan administration, PHY906 was administered to the third experimental group of mice orally at a dose of 50, 150, 500, or 1000 mg/kg body weight twice daily on days 1 to 4. Over the same time period, the control BDF1 colon cancer mice (no drug treatment provided) were given phosphate-buffered saline (intraperitoneally) or water (orally).

The investigators reported several findings in favor of administering PHY906 in combination with irinotecan. Reduction in the size of the initial tumor was observed in mice that had been treated with irinotecan and PHY906. However, maintenance of initial body weight was noted only with PHY906 doses of 500 or 1000 mg/kg body weight. Hence, a dose of 500 mg/kg body weight delivered twice a day on days 0 to 3 was chosen for further evaluation. When loperamide alone was added to irinotecan at a dose of 2 mg/kg body weight, twice daily on days 0 to 9, loperamide did not result in a reduction in tumor size or benefit in maintaining initial body weight in comparison to PHY906. The mice were sacrificed two or four days after a single dose of irinotecan (360 mg/kg body weight, injected intraperitoneally). Intestinal tissue was removed, formalin fixed, paraffin embedded, and sectioned into 10-μm sections. Intestinal mucosal DNA damage was verified by hematoxylin and eosin staining on day 2 after irinotecan administration. Yet by day 4, the combination of irinotecan and PHY906 was shown to expedite the regen-

Table 1. Clinical trial development of PHY906.

Phase (ref)*	Type of cancer	*N*	PHY906	Chemotherapy	Grade 3/4 toxicities	Response
I (*17*)	Solid tumors	25	1200–2400 mg BID, days 1–4, then every 14 days	Irinotecan (180–250 mg/m2, day 1, then every 14 days)	Grade 3: Leukopenia and neutropenia	N/A
II (*18*)	Pancreatic	25	800 mg/m2, days 1–4, then every 14 days	Capecitabine (1500 mg/m2, days 1–7, then every 14 days)	Grade 3: Diarrhea, fatigue, and hand-foot syndrome	PR (*N* = 2) SD (*N* = 10)
I/II (*18*, *19*)	All solid tumors with expanded phase II pancreatic cohort	44	800 mg BID, days 1–4, then every 14 days	Phase I: Capecitabine (1000–1750 mg/m2, days 1–7, then every 14 days) Phase II: Capecitabine (1500 mg/m2, days 1–7, then every 14 days)	Grade 3/4: Diarrhea	N/A
I/II (*20*)	Hepatocellular carcinoma	42	Phase I: 600–1000 mg BID, days 1–4 and days 8–11, then every 21 days Phase II: 800 mg BID, days 1–4 and days 8–11, then every 21 days	Phase I: Capecitabine (750–1000 mg/m2 BID, days 1–14, then every 21 days) Phase II: Capecitabine (750 mg/m2 BID,days 1–7, then every 14 days)	Grade 3: Mucositis, hand-foot syndrome	Phase II: No CR or PR

*Abbreviations: ref, reference; BID, twice per day; mg/m2 is based on Body Surface Area (BSA); PR, partial response; SD, stable disease; CR, complete response; N/A, not available; *N*, number of cases.

eration of normal intestinal crypt cells. Paraffin embedded sections stained positive for lysozyme (paneth cells), chromogranin A (endocrine cells), and periodic acid-Schiff (goblet cells), indicating normal regeneration. PHY906 alone did not have an impact on the histology on Days 2 or 4.

Of interest is that the regenerated intestinal crypt cells appeared to be intestinal progenitor cells as determined by quantitative reverse transcription–polymerase chain reaction. In combination with irinotecan, PHY906 helped to reverse the reduction in mRNA expression of the *leucine-rich repeat–containing G protein–coupled receptor* 5 gene (*Lgr5*, which encodes a well-known marker of stem cell development) and the *olfactomedin 4* gene (*Olfm4,* which encodes a protein that is endogenously expressed in intestinal epithelial cells, specifically stem cells) observed in crypt cells from the colon cancer–ridden mice that received only irinotecan. Furthermore, with irinotecan, PHY906 caused an increase in expression of the *Achaete scute-like 2* gene (*Ascl2*), which encodes a component of the apoptotic Wnt signal transduction pathway and is commonly expressed in cells at the base of intestinal crypts (*22*). It is well known that proliferation of epithelial crypt cells is dependent on the Wnt pathway. These findings are poignant and support recent data indicating that deletion of the *Ascl2* gene in the intestine negatively impacts the expression of *Lgr5* and thus intestinal stem cell development (*22*). In adults, constitutive activation of the Wnt signaling pathway may result in enhanced expression of genes whose products make up the β-catenin complex, which is necessary for maintenance of epithelial cell layers as found in the gut. The Wnt pathway also leads to the increased expression of *adenomatous polyposis coli* (*APC*), a known tumor suppressor gene. Mutations in the *APC* gene may promote the development of colorectal cancer.

It appears, then, that PHY906 may ameliorate the intestinal mucosal damage initiated by irinotecan primarily by the regeneration of intestinal stem cells through the Wnt signal transduction pathway. Although these preclinical results are promising, whether these findings hold true in human subjects remains unknown.

PICKING POTENT HERBS FOR THERAPY

Several caveats come to mind when considering the development of a formulation of four different herbal compounds into one formula for clinical development. Quality assurance for the development of the drug is of grave concern. The authors (*3*) report that they used, as their method of quality assurance, the PhytomicsQC technology platform, which employs mass spectrometry and biological fingerprinting to generate a Phytomics Similarity Index (PSI), a type of quality control measure used to compare different botanical batches. In general, minimal literature exists regarding quality control for botanical ingredients in cancer treatment. To date, the PhytomicsQC platform may be the most comprehensive platform available. However, it is presumed that for optimal development, botanical supplements must be grown uniformly and under the same environmental conditions, and must be from the same lot number. Subtle conditions including soil constitution, ambient temperature, moisture content, and season of harvest may cause small differences in the activity of an herbal product.

Individually, two of the herbal components used by Lam *et al.* (*3*) have been reported to have preclinical anti-carcinogenic properties. *Scutellaria baicalensis* (Huang Qin or Chinese skull cap) is the most well known of the four herbal supplements. Dose-dependent growth inhibition by *Scutellaria baicalensis* was demonstrated in multiple cancer cell lines, including breast (MCF-7), hepatocellular (HepG2), prostate (PC-3), and colon (KM-12, HCT-15) (*23*). However, it has been reported that the activity of *Scutellaria baicalensis* may be affected by changes in temperature during cultivation (*24*).

Although the purified individual components of PHY906 have existed for several decades, herbal supplements are fraught with potentially harmful adverse effects. In in vivo models, treatment with *Scutellaria baicalensis* may result in rare instances of stupor, confusion, and seizure activity as a result of its ability to cross the blood brain barrier (*25*).

Preclinically, *Glycyrrhiza glabra* has demonstrated anticancer properties in a breast cancer cell line (MCF-7) in culture (*26*).

Glycyrrhiza glabra is derived from licorice root and reportedly binds glucocorticoid receptors, resulting in reduced renin and aldosterone activity and thus hypertension. *Glycyrrhizia glabra* also may result in other adverse toxicities, including electrolyte disturbances (such as low blood potassium and high blood sodium concentrations), decreased libido, and paralysis (*27*). Therefore, deglycyrrhizinated licorice extract (DGL) may be preferred. Adverse drug interactions may occur with diuretics, insulin, and anticoagulation medications.

Paeonia lactiflora Pall (Chinese peony) and *Ziziphus jujube mill* (red or dried Chinese dates) are not well studied for medicinal purposes. Their relevance and activity in the formulation of PHY906 are unclear.

At this time, it is difficult to ascertain whether it is practical to develop reagents such PHY906 as supportive compounds for chemotherapy-induced gastrointestinal toxicity. The findings reported by Lam *et al.* on the regeneration of intestinal stem cells by PHY906 after irinotecan administration are of interest if the treatment reduces chemotherapy-related toxicity in the patient. Currently, according to patient-education guidelines, loperamide is used routinely in the treatment of cancer chemotherapy–related diarrhea along with the identification and use of optimal chemotherapy schedules shown to reduce treatment-related toxicities.

Only one of the previously mentioned irinotecan-based trials was completed (*17*). Alsamarai and colleagues have presented only preliminary data, but plan to proceed to higher irinotecan doses than are commonly administered, and on an every-14-days schedule; this regimen likely will result in more severe neutropenia and diarrhea. Whether escalating doses of irinotecan are required for improved therapeutic efficacy in cancer patients is unclear. Capecitabine is widely accepted for therapeutic use in multiple malignancies and is well tolerated except in combination with irinotecan, as a result of excessive gastrointestinal toxicity (*28*).

The PHY906-associated histological findings observed in the murine model used by Lam *et al.* (*3*) might not be reproduced clinically in patients, because it would be difficult to ask patients to have a tissue biopsy to test for reduced gastrointestingal toxicity and regeneration of stem cells. Reduction in gastrointestingal toxicity can be assessed clinically, and most patients will already have standard supportive medications for treatment-related diarrhea, such as loperamide and Imodium. The development of PHY906 would be further supported if the investigators were able to demonstrate increased reduction in tumor burden. Yet, increased efficacy in response to a reduction in tumor burden or survival was not significantly appreciated in the previously reported phase I/II clinical studies (*17*–*19*).

Therapeutic advances in colon cancer treatment have culminated in the approval of biological agents such as monoclonal antibodies to vascular endothelial growth factor (bevacizumab) and epidermal growth factor receptor (cetuximab and panitumumab). Such biological or targeted therapies are considered standard options for metastatic colorectal cancer patients. These biological agents have their own unique toxicities separate from the less-targeted cytotoxic agents described above, which are often combined with the targeted reagents for additional therapeutic efficacy. The most common toxicity of bevacizumab is the development of hypertension, with rare instances of reversible posterior leukoencephalopathy syndrome, which results in cortical blindness and seizure activity. Cetuximab and panitumumab frequently cause electrolyte disturbances. Hence, the use of *Scutellaria baicalensi* and *Glycyrrhiza glabra* as supportive therapies to reduce treatment-related diarrhea may place the patient at risk for additional toxicities. As with all standard FDA-approved medications, all risks and benefits of CAM therapy must be openly discussed and reviewed with the patient.

Lam *et al*. have surmounted some of the initial challenges in formulating botanical supplements for therapeutic use in oncology. However, as with all other preclinical data, whether these reported findings from the murine model have relevance in patient care is uncertain. Nevertheless, the data generated with PHY906 in a mouse model of colon cancer may shed further light on our understanding of the mechanistic pathways of colorectal carcinogenesis.

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