Are Herbal Medicines Ripe for the Cancer Clinic?

Cathy Eng
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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 resectable 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 bio-modulator 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–κB (NF-κB) 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 tumoridal 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); Paonisia lactiflora Pall (Chinese peony) (P); Scutellaria baicalensis Georgi (skullcap

Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA. E-mail: ceng@mdanderson.org

Various doses of PHY906 have since been tested in phase I and II clinical trials in combination with escalating doses of irinotecan or capcitabine 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 correlates 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 mm³ 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-
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 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), hepato celular (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).

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**Table 1. Clinical trial development of PHY906.**

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

*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.
Glycyrrhiza glabra is derived from licorice root and reportedly binds glucocorticoid receptors, resulting in reduced renin and aldosterone activity and thus hypertension. Glycyrrhiza 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 anti-coagulation 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 as 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. Capetibinat 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 gastrointestinal toxicity and regeneration of stem cells. Reduction in gastrointestinal 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 II/III 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 baicalensis 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.

REFERENCES AND NOTES

16. Shivaani Kummer, Principle Investigator of the study, personal communication.


29. I thank Richard Lee for his assistance in finding unbiased botanical references.