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Old formula, new Rx: The journey of PHY906 as cancer adjuvant therapy

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ABSTRACT

Ethnopharmacological relevance: PHY906, is a decoction of a mixture of the four herbs *Scutellaria baicalensis Geori, Glycyrrhiza uralensis Fisch, Paeonia lactiflora Pall*, and *Ziziphus jujuba Mill*. A combination of these four herbs has been in continuous use in traditional Chinese medicine for over 1800 years for treating a variety of gastrointestinal distress such as diarrhea, cramps, nausea, vomiting etc.
Aim of the study: Preclinical and clinical studies to find PHY906 enhances the therapeutic indices of a broad spectrum of anticancer agents.
Materials and methods: Using various mouse tumor xenograft and allograft models, PHY906 has been shown to enhance the chemotherapeutic efficacy of a variety of anticancer agents in various cancers. The PHY906 clinical program consists of five trials in three different types of cancers in both the United States and Taiwan. To date, approximately 150 subjects have received PHY906 in combination with chemotherapy in these five clinical studies.
Results: Preclinical studies have shown that PHY906 enhances the therapeutic indices of a broad spectrum of anticancer agents. These findings have been examined in clinical studies for colorectal, liver, and pancreatic cancers when PHY906 is used as an adjuvant to chemotherapy and the results were promising; i.e. PHY906 could reduce chemotherapy-induced toxicities and/or increase chemotherapeutic efficacy. Furthermore, PHY906 did not affect the pharmacokinetics of the chemotherapeutic agents used. Some information has been obtained regarding the mechanism of action of PHY906 in preclinical studies. A comprehensive platform, PhytomicsQC that integrates chemical and biological fingerprints together with a novel biostatistical methodology has been developed to assess the quality of different batches of PHY906.
Conclusions: Over a ten-year period, the multiplex technology "PhytomicsQC" has been used to show batch-to-batch consistency of PHY906 production. Advanced clinical trials are ongoing to demonstrate the effectiveness of PHY906 as adjuvant therapy for cancer patients undergoing chemotherapy.

1. Introduction

Cancer is the second overall cause of death in the U.S. and many unmet needs exist within the field. Medical oncology has had a great impact in changing the practice of medicine in the past several decades by developing a few curative treatments for a variety of previously fatal malignancies. However, some commonly used drugs could have better therapeutic indices and greater potential for success if their harmful side effects could be reduced. Targeted therapy has become one of the main approaches for increasing a drug's therapeutic index as it was thought to improve the antitumor selectivity and reduces the side-effects of treatment by targeting a specific gene, enzyme or receptor. However, side effects from chemotherapy and targeted therapy are prevalent and such toxicities not only can prevent a patient from receiving the most effective chemotherapeutic doses, but also can adversely impact a patient's quality-of-life. Common side effects associated with chemotherapy and targeted therapy are gastrointestinal ailments such as diarrhea, nausea, and vomiting, as well as hand-foot syndrome, etc. (Forman, 1994; Llovet et al., 2008; Cheng et al., 2009; Chen et al., 2010). Any medicine that is able to ameliorate these multiple adverse effects without compromising antitumor efficacy of a drug would improve the quality of life for patients and also enhance the therapeutic indices of anti-neoplastic medicines (Calabresi and Chabner, 1996; Eisenberg et al., 1998; Armstrong and Gilbert, 2008).

Herbal medicines have been commonly used by cancer patients in Asia to combat various diseases (Quimby, 2007; Konkimalla

Abbreviations: AE, adverse event; APC, advanced pancreatic cancer; B.I.D., twice per day; CRC, colorectal cancer; DLT, dose-limiting toxicity; GAP, Good Agricultural Practices; GCP, Good Clinical Practice; GI, gastrointestinal; GLP, Good Laboratory Practice; GMP, Good Manufacturing Practice; HCC, hepatocellular cancer; IND, Investigational New Drug; IP, intraperitoneal; mOS, median overall survival; MTD, maximum tolerated dose; NDA, new drug application; OS, overall survival; PR, partial response; SAE, serious adverse event; SD, stable disease; TIC, three times per day; TTP, time for tumor progression.

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and Efferth, 2008; Liu et al., 2010; Liu and Saif, 2012). PHY906, a pharmaceutical grade of traditional Chinese herbal formulation Huang-Qin-Tang (HQT), composed of four distinct herbs: the roots of *Scutellaria baicalensis Georgi.* (scute), *Glycyrrhiza uralensis Fisch.* (licorice) and *Paeonia lactiflora Pall.*(peony), and the fruit of *Ziziphus jujuba Mill* (Chinese date), has been documented for nearly 1800 years for treating common gastrointestinal distress, including diarrhea, abdominal spasms, fever, headache, vomiting, nausea, extreme thirst, and subcardiac distention. Each of the four component herbs possesses a distinct pharmacological profile; these include anticancer and antiviral activity, hematological and immunological modulation, analgesic activity, liver protection, and appetite improvement. Teams led by Professor Yung-Chi Cheng at the Yale University School of Medicine and PhytoCeutica, Inc. have explored PHY906 as an adjuvant for cancer chemotherapy and targeted therapy. With the unique and defined procedures for its preparation, characterization, and quality control, PHY906 is different from HQT that is currently available in the market. Preclinical studies have indicated that PHY906 enhances the antitumor efficacies of a broad-spectrum of anticancer agents in a variety of murine xenograft and allograft models (Liu et al., 2000, 2001, 2002, 2003, 2004, 2006, 2007) whereas HQT did not show such activity.

In contrast to the traditional single molecule-single target approach in drug development, the mechanism of action of PHY906 is multifactorial. These different mechanisms may be mediated by one or more of the constituent chemicals of PHY906. In vivo studies with CPT-11 (Irinotecan, Camptosar®) indicated that PHY906 also can reduce the dose-limiting GI side effect (severe late-onset diarrhea) of CPT-11. In addition to the anti-inflammatory activity of PHY906 that is mediated through at least three mechanisms by different chemical constituents of PHY906 or their metabolites of PHY906 (Ye et al., 2007; Zhang et al., 2010), PHY906 can also restore damaged intestinal epithelium through promotion of intestinal progenitor or stem cell growth, mediated by increasing of several Wnt signaling components as well as potentiation of Wnt action (Lam et al., 2007, 2009, 2010). Several phase I/II clinical trials have been conducted in U.S. to explore the toxicity and clinical efficacy of PHY906. The results were highly encouraging. PHY906 was shown to provide cytoprotective effects without dampening the anti-tumor activity of chemotherapeutic agents in liver, pancreatic, and colorectal cancer patients under chemotherapy (Yen et al., 2009; Saif et al., 2007; Saif, 2008a,b; Saif et al., 2009, 2010a,b; Farrell and Kummar, 2003; Kummar et al., 2011).To ensure that consistent batches of PHY906 can be made, a comprehensive technology platform termed "PhytomicsQC" that integrated chemical fingerprints and biological fingerprints, analysed by novel statistical analysis, was developed to evaluate different batches of PHY906. It was demonstrated PHY906 can be made with consistency (Tilton et al., 2010).

2. Preclinical studies of PHY906 in murine tumor models

CPT-11, an inhibitor of topoisomerase I, is a widely used agent for the treatment of colorectal cancer. The dose-limiting side effect of CPT-11 is severe late-onset diarrhea (Goldber and Erlichman, 1988; Bleiberg and Cvitkovic, 1996). Based on traditional anti-gastrointestinal ailment claims in Chinese medicine documents, PHY906 offered a possibility for reducing the severe diarrhea associated with CPT-11 treatment, but only if PHY906 did not compromise CPT-11 antitumor effectiveness.

BDF-1 mice bearing murine colon 38 tumor were used as a surrogate system to test the above hypothesis. Mice were treated with a single dose of CPT-11 at its maximum tolerated dose of 360 mg/kg intraperitoneally in the presence or absence of twice daily gavage administration of PHY906 (125, 250, or 500 mg/kg) for 4 days. The animals were evaluated for tumor size, changes in body weight, mortality, and hematologic toxicity. The results indicated that PHY906 was able to reduce CPT-11-induced body weight loss in a dose-dependent manner with maximum protective effect occurring at a PHY906 dose of 500 mg/kg ($p < 0.01$).

Table 1
Preclinical studies of PHY906 with chemotherapeutic agents.

Chemotherapeutic agent	Indication
CPT-11	Colorectal cancer
Capecitabine	Colorectal and liver cancer
CPT-11/5-FU/LV	Colorectal cancer
VP-16	Lung cancer
L-OddC	Leukemia, pancreatic cancer
Gemcitabine	Pancreatic cancer
Oxaliplatin	Colorectal cancer
Sorafenib	Renal and liver cancer
Taxol	Lung, breast and ovarian cancer
Sunitinib	Renal and liver cancer

Mortality data from the same colon 38 allografts indicated that PHY906 alone does not exhibit any significant toxicity; 100% of the tumor-bearing mice survived with PHY906 treatment. In contrast, treatment with a single dose of CPT-11 resulted in 60% survival of the tumor-bearing mice after 14 days. However, this survival rate dramatically improved to 100% after receiving 4 days of PHY906 treatment in combination with CPT-11 (Kummar et al., 2011) (Fig. 1). This result suggested that PHY906 treatment can indeed protect mice against mortality induced by a single high dose of CPT-11.

Surprisingly, it appears that PHY906 has a dual effect on CPT-11: not only does it reduce CPT-11-induced toxicities such as bodyweight loss and mortality, but it also potentiates the antitumor activity of CPT-11 (Fig. 2A). The studies were expanded to other chemotherapeutic agents that have mechanisms of antitumor action different from that of CPT-11. In addition to the colorectal cancer model, the study also has been expanded into other tumor models such as hepatocellular carcinoma and pancreatic cancer (Fig. 2B and C), for which successful treatments do not exist. PHY906 has been shown to be a broad-spectrum adjuvant in that it either enhances the chemotherapeutic efficacy or reduces the toxicities, or both, of a variety of anticancer agents including 5-fluorouracil (5-FU), VP-16 (Etopophos®, Vepesid®), irinotecan (CPT-11, Camptosar®), L-OddC (troxacitabine, Troxatyl®), L-FMAU

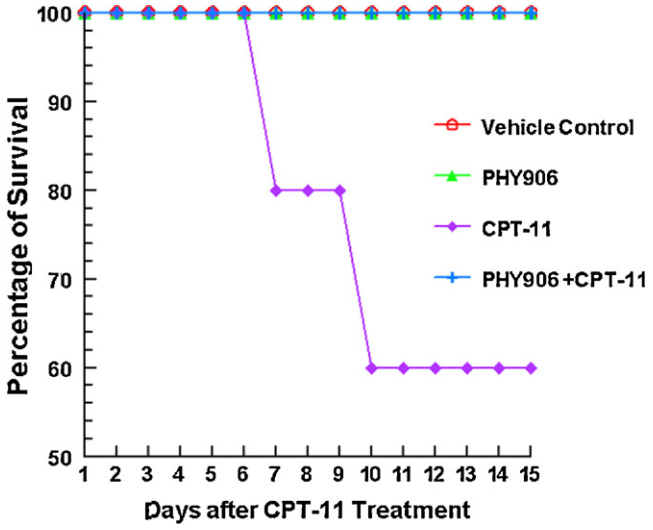

Fig. 1. Kaplan–Meier survival plot of Colon 38 bearing BDF-1 mice treated with CPT-11 vs. PHY906 plus CPT-11.
With permission from Kummar et al. (2011).