Clinical Studies

Phase I/II Study of PHY906/Capecitabine
in Advanced Hepatocellular Carcinoma

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Abstract. *PHY906 is a Chinese medicine formula with
claims for the treatment of severe gastrointestinal distress.
PHY906 enhanced the therapeutic index of various
chemotherapeutic agents in human hepatocellular carcinoma
xenografts. Accordingly, here a phase I/II clinical study was
conducted with the combination of capecitabine in patients
with advanced, unresectable hepatocellular carcinoma. More
than 60% of patients had either stable disease or better after
two treatment cycles. Median overall survival was 9.2
months. Asian patients had a higher median overall survival
(16.5 months) than non-Asian patients (6.2 months, p=0.03).
Patients' quality of life did not deteriorate significantly
during treatment. This finding supported further investigation
of PHY906 as an adjuvant therapy of capecitabine in a
larger hepatocellular cancer population.*

Hepatocellular carcinoma (HCC) is a leading cause of death
from cancer worldwide. The median survival time of patients
with unresectable and recurrent HCC ranges from 3-7
months (1-3). The etiology of the disease is multifactorial;
hepatitis B (HBV) and C virus (HCV) infections are
strongly linked to its development (4-6). The number of
cases of HCC has increased over the last few years in the
US, mainly due to HCV infection (7-10). In most cases, the
occurrence of HCC arises in a background of decompensated
liver diseases and cirrhosis. HCC patients usually present
with advanced disease where surgical resection and/or
chemical embolism is not feasible; thus, treatment options
for such patients are limited (11-13).

In November 2007, sorafenib (Nexavar®) became the first
drug approved for the first-line treatment of advanced HCC.
Previously, doxorubicin (Adriamycin®) was widely used, but
its effectiveness was moderate whether employed as a single
agent or in combination with other chemotherapeutic drugs,
e.g., etoposide, thalidomide, mitoxantrone, cisplatin (14-23).
Combinations of doxorubicin and gemcitabine (Gemzar®)
were slightly more effective (24, 25).

Capecitabine (Xeloda®), an oral 5-fluorouracil prodrug for
the treatment of metastatic colorectal and breast cancer, has
modest activity against HCC when given alone (26, 27).
Antitumor activity and tolerable adverse events were observed
when capecitabine was used in combination with doxorubicin
plus cisplatin or oxaliplatin for advanced HCC (28, 29).
When capecitabine plus bevacizumab or capecitanine plus
bevacizumab/oxaliplatin was used in advanced HCC, the
combinations were effective and tolerable (30, 31).

PHY906 is a traditional Chinese medicine formulation that
has been used for approximately 1800 years for a variety of
maladies, most notably severe gastrointestinal distress, *e.g.*
nausea, vomiting, diarrhea and abdominal spasms (32, 33). It
is prepared under c-GMP conditions and has been well
characterized by both chemical and biological fingerprints
(Figure 7). PHY906 consists of a mixture of four herbs
(*Scutellaria baicalensis* Georgi*, Glycyrrhiza uralensis* Fisch.*,
Paeonia lactiflora* Pall., and the fruit of *Ziziphus jujube*
Mill.). Given the historical use of PHY906, we hypothesized
that this formulation could be useful in ameliorating some of
the severe side-effects associated with cancer chemotherapy.

In preclinical studies, PHY906 was used with different
cancer chemotherapeutic agents including capecitabine,
irinotecan (CPT-11), 5-fluorouracil, VP-16, oxaliplatin,

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thalidomide, taxol, gemcitabine, and sorafenib in various animal models; these include colon 38 and PAN-2 (murine pancreatic cancer line) in BDF-1 mice and HepG2 (human HCC tumor line) and PAN-1 (human pancreatic cancer line) in nude mice (12, 34-37). PHY906 treatment did not compromise the effectiveness of the chemotherapeutic drugs. In fact, in nearly all cases, the combination regimen was found to have greater therapeutic efficacy than PHY906 or the chemotherapeutic agent alone (34-37). The enhancement of the antitumor activity of capecitabine by PHY906 in the HepG2/nude mouse model was particularly significant (p=0.0018; Figure 7).

In this report, we document the results of a phase I/II study in patients with advanced, unresectable HCC who have been treated with the combination of a traditional Chinese medicine (PHY906) and a widely-used Western anticancer agent (capecitabine).

Patients and Methods

This study was a multicenter, open-label, dose escalation phase I/II safety and efficacy clinical trial of PHY906 given concomitantly with capecitabine to patients with advanced HCC. Phase I was designed to determine a safe and tolerable dosing regimen of PHY906 plus capecitabine, and phase II was designed to determine whether PHY906 enhances the response rate of capecitabine, time to disease progression (TTP) and overall survival time (OS). The quality-of-life (QoL) of patients undergoing treatment was monitored.

The study was conducted at the City of Hope National Medical Center (Duarte, CA, USA), Stanford University School of Medicine (Stanford, CA, USA), Yale Cancer Center (New Haven, CT, USA) and the VA Healthcare System (West Haven, CT, USA). All patients signed a written informed consent.

Patient selection and evaluation. Eligible patients (male or female) were 18-80 years of age with either a histological or cytological diagnosis of HCC or who met all of the following criteria: (a) α-fetoprotein levels higher than 600 ng/ml, (b) the presence of cirrhosis or chronic hepatitis B or C, and (c) the characteristic enhancement pattern of liver tumors on triphasic computed tomography (CT) scan or magnetic resonance imaging (MRI). No more than two prior chemotherapeutic regimens were allowed. Patients having prior radiation, chemoembolization, and/or alcohol injections were eligible. Responses were evaluated utilizing WHO criteria. Measurable disease was defined as lesions of ≥20 mm, utilizing conventional techniques, or as ≥10 mm, utilizing spiral CT scanning. Patients had to have had progression of disease during the observation interval prior to participation in this study. Re-evaluation was repeated every 6 weeks (two cycles of therapy) with CT scans and evaluation of tumor markers. Baseline performance status was Eastern Cooperative Oncology Group (ECOG) 0-2. Patients with cirrhosis were classified as Child-Pugh A or B. Adequate hematological, hepatic, and renal functions were defined as: hemoglobin ≥10.0 g/dl, white blood count (WBC) ≥2.0×10^9/l, absolute neutrophil count ≥1.0×10^9/l, platelet count ≥50.0×10^9/l, total bilirubin ≤3.0 × study center institutional upper limit of normal (ULN), asparate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5x ULN, creatinine clearance ≥30 ml/min. Exclusion criteria included prior treatment with capecitabine or the presence of an uncontrolled

concurrent illness including active infections, symptomatic congestive heart failure or unstable angina, pulmonary fibrosis, or pulmonary interstitial disease.

Treatment plan. This study was an open-label, dose-escalation study of capecitabine plus PHY906 in patients with unresectable hepatocellular carcinoma. Three patients were to be enrolled in each cohort. If no patient experienced dose-limiting toxicity (DLT) at a particular dose level, three patients would be enrolled at the next highest dose level. If one out of three patient developed DLT, three additional patients would be treated with the same dose level. Dose escalation would be terminated at the dose level associated with the occurrence of DLT in ≥2 out of 6 patients. No intra-individual dose escalation would be performed, *i.e.*, patients themselves at a specific dose level would not be allowed to escalate to the next dose level. Patients who did not complete two courses of treatment would be replaced in the study, except for those who experienced DLT.

Capecitabine (750 or 1,000 mg/m^2 *bid*) was administered orally starting on day 1, and continued for 14 consecutive days followed by 7 days rest. PHY906 (600, 800, or 1,000 mg *bid*) was administered orally on days 1-4 and 8-11 of each 21-day course. Treatment was repeated every 21 days. Dose delays and modifications were based on observed toxicity. Duration of treatment was determined by the development of unacceptable toxicity, disease progression, or concurrent illness that prevented further administration of treatment.

Evaluation of toxicity. Toxicity was determined utilizing the NCI Common Toxicity Criteria Version 3. Hematology assessments were performed within 14 days before the first dose of capecitabine, weekly for the first two cycles and during the last week of each subsequent cycle, and results were available before the next scheduled treatment. Hematological assessments included hemoglobin, hematocrit, complete blood cell count with differential, and platelet count. Patients were required to have at least one dose of study drug for evaluation of safety and toxicity. Patients having unresolved drug-related toxicity at the time of scheduled treatment were permitted a two-week delay in treatment. Drug-related febrile neutropenia or persistent grade 2 neurotoxicity warranted dose reduction for subsequent treatments. Follow-up assessments included toxicity duration and documentation of disease progression. All patients were followed up for overall survival.

Evaluation of response. To qualify for efficacy evaluation, patients had to have had completed two courses, must have had a CT scan and received at least 75% of the recommended amount of study drug. Disease response (WHO criteria) was assessed in the third week of every second cycle. Response definitions were: complete response (CR), disappearance of all lesions; partial response (PR), ≥50% decrease in the sum of all products (SOP) of the two longest perpendicular diameters of lesions compared to the baseline sum longest diameter; stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease; progressive disease (PD), ≥25% increase in the SOP of lesions compared to the smallest SOP recorded since the treatment started, or the appearance of one or more new lesions. Patients with symptomatic deterioration were considered to have PD.

Quality of life (QoL). QoL assessments (FACT-Hep, version 4) were completed by patients at the end of each 21-day course of therapy. The FACT-Hep assessment for QoL consists of 5 subscales:

Table I. *Patient enrollment and prior treatment*.

Study stages	Phase I			Phase II
	Cohort I	Cohort II	Cohort III	
Dose	Cap 1,000 mg/m^2 *bid* PHY906 1,000 mg *bid*	Cap 750 mg/m^2 *bid* PHY906 600 mg *bid*	Cap 750 mg/m^2 *bid* PHY906 800 mg *bid*	Cap 750 mg/m^2 *bid* PHY906 800 mg *bid*
No. of patients recruited	3	8	7	24
No. of toxicity-evaluable patients	3	8	7	24
Prior treatment				
• Chemoembolization	0	3	3	12
• Other treatments	1	4	2	2
• None	1	1	2	3
• Not available	1	0	0	7
No. of efficacy-evaluable patients	2	4	5	18
Prior treatment				
• Chemoembolization	0	2	1	10
• Other treatments	1	2	2	0
• None	1	0	2	4
• Not available	0	0	0	4
No. of efficacy non-evaluable patients	1	4	2	6
Prior treatment				
• Chemoembolization	0	1	2	2
• Other treatments	0	2	0	0
• None	0	1	0	1
• Not available	1	0	0	3
Reason for termination				
• Adverse effects	1	1	0	2
• Progress disease	0	2	2	3
• Non-compliance	0	1	0	1

Cap, Capecitabine.

(i) physical well-being; (ii) social and family well-being; (iii) emotional well-being; (iv) functional well-being; (v) a hepatobiliary cancer subscale that assesses specific symptoms of hepatobiliary carcinoma and the side-effects of treatment.

Statistical analysis. No formal statistical analysis was performed. Data are summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum) for continuous variables and frequency and percentage for discrete variables. For the safety analysis, data are presented for all patients.

Results

Forty-two patients with HCC were enrolled: 18 in phase I and 24 in phase II. Three patients began with a combination of capecitabine 1,000 mg/m^2 *bid* and PHY906 1,000 mg *bid* in phase I cohort 1. This dose of capecitabine is the 'standard' dose given to colorectal or breast cancer patients. Cohort I was terminated due to the occurrence of two drug-related DLTs. Both capecitabine and PHY906 doses were subsequently reduced to 750 mg/m^2 *bid* and 600 mg *bid*, respectively, in cohort 2. Eight patients were enrolled (two were replacements). One patient had a study drug-related DLT and one patient had

a non-study-drug-related DLT. The dose of PHY906 was subsequently increased to 800 mg *bid* with a fixed dose of capecitabine (750 mg/m^2 *bid*) for cohort 3. Seven patients were enrolled in cohort 3 including one replacement. All patients were eligible for safety evaluation; two who received the cohort 1 treatment regimen and 9 who received the cohort 2 or cohort 3 regimen and 18 patients from phase II were for efficacy. As listed in Table I, 13 patients were terminated early due to adverse effects (N=4), progressive disease (N=7), or non-compliance in following the drug regimen (N=2).

Of the 42 patients, 7 (16.7%) had received no prior treatment, 18 (43%) received prior chemoembolization, 9 (21.4%) received other pre-treatment, and the pre-treatment statuses of 8 patients were unavailable. Among 27 efficacy-evaluable patients, 13 (48%) received prior chemoembolization, 4 (15%) other prior treatments, and previous treatment information was unavailable for 4 (15%). Baseline characteristics of all 42 patients are listed in Table II.

Patient demographics, liver disease classification, prior treatment characteristics, and performance status. Among 42 toxicity-evaluable patients administered capecitabine (1,000

Table II. *Baseline characteristics of the patients.*

Baseline characteristics	PHY906 1,000 mg *bid* + Capecitabine 1,000 mg/m^2 *bid* N=3 No.	PHY906 600 mg *bid* + Capecitabine 750 mg/m^2 *bid* N=8 No.	PHY906 800 mg *bid* + Capecitabine 750 mg/m^2 *bid* N=31*(%) No.	Total N=42 No.
Gender				
Male	3	7	29 (93.5)	39 (92.9)
Female	0	0	2 (6.5)	2 (4.8)
Ethnicity				
White	1	3	17 (54.8)	21 (50)
Black	0	0	1 (3.2)	1 (2.4)
Hispanic	1	0	2 (6.5)	3 (7.1)
Asian	1	5	11 (35.5)	17 (40.5)
Age (years)				
Median	67	58	60	60
Range	55-71	47-75	32-85	32 - 85
Cirrhosis				
Yes	3	7	17 (54.8)	27 (64.3)
No	0	1	14 (45.2)	15 (35.7)
Previous treatment				
Yes	1	7	19 (61.3)	27 (64.3)
No	1	1	5 (16.1)	7 (16.7)
Not available	1	0	7 (22.6)	8 (19)
ECOG				
0 or 1	3	6	30 (96.8)	39 (92.9)
2 or 3	0	2	1 (3.2)	3 (7.1)
Child Pugh				
A	1	6	18 (58.1)	25 (59.5)
B	2	2	13 (41.9)	17 (40.5)
Hepatitis virus infection				
HBV	1	5	8 (25.8)	14 (33.3)
HCV	0	2	12 (38.7)	14 (33.3)
HBV and HCV	0	0	1 (3.2)	1 (2.4)
None	2	1	10 (32.3)	13 (31)

*N=7 from phase I, cohort 3 and N=24 from phase II.

or 750 mg/m^2)/PHY906 (600 or 800 mg), 21 were Caucasians, 17 Asians, three Hispanics, and one African-American. Thirty-nine patients were male and two female. Twenty-five patients (59.5%) were classified Child-Pugh A and 17 (40.5%) Child-Pugh B. Thirty-nine patients had ECOG performance scores of 0 or 1, and three had a score of 2 or 3. Twenty-seven patients (64.3%) had undergone prior surgery, chemotherapy, local chemoembolization, or local treatment, *e.g.* ethanol ablation or radiation therapy.

Safety evaluation. All 42 patients were evaluable for toxicity. Of the first three patients recruited into cohort 1, two developed drug-related grade 3 DLT: one with colitis, hyperbilirubinemia and stomatitis, and one with hand-foot skin reaction. Enrollment of further patients into this cohort was therefore terminated and both capecitabine and PHY906 doses were adjusted downward.

Eight patients were recruited, with two replacements, into cohort 2 and received two courses of treatment. Among these 6 enrolled patients, one patient experienced a study-drug related DLT (grade 3 mucositis). Since the dose of PHY906/ capecitabine in cohort 2 was drastically reduced from that of cohort 1, the cohort 2 dosing level was considered not to represent the maximum tolerated dose (MTD). Accordingly, a new cohort of 6 patients to be dosed at capecitabine 750 mg/m^2 *bid* /PHY906 800 mg *bid* (cohort 3) were added to the study. Seven patients (one a replacement) were recruited into cohort 3. One patient had a study-drug-related DLT (grade 3 elevated alkaline phosphatase (ALP). The dose of capecitabine/PHY906 evaluated in this cohort was the recommended dose for phase II.

The combination of PHY906 (600 mg or 800 mg *bid*) and capecitabine (750 mg/m^2 *bid*) was well tolerated (N=39). The toxicity profile is given in Table III. Twenty-eight out of 39 patients (71.8%) reported adverse events (AEs). The most common grade 1 drug-related AEs were diarrhea (28.2%), fatigue (23.0%), abdominal pain (10.3%), pruritus (10.3%), and nausea (10.3%). The most frequently experienced grade 2 drug-related AEs were leukopenia (7.7%), fatigue (7.7%) and hyperbilirubinemia (7.7%). The

Table III. *Most common drug-related adverse events*.

Adverse events	PHY906 1000 mg *bid* + Capecitabine 1000 mg/m² *bid* Cohort 1 N=3 No.	PHY906 600 mg *bid* + Capecitabine 750 mg/m² *bid* Cohort 2 N=8 No.	PHY906 800 mg *bid* + Capecitabine 750 mg/m² *bid* Cohort 3/Phase II N=31 No. (%)
Abdominal pain			
Grades 1 and 2	0	2	2 (6.5)
Grades 3 and 4	0	0	0 (0)
Dehydration			
Grades 1 and 2	0	0	1 (3.2)
Grades 3 and 4	0	1	1 (3.2)
Diarrhea			
Grades 1 and 2	2	5	8 (25.8)
Grades 3 and 4	0	0	0 (0)
Fatigue			
Grades 1 and 2	1	2	9 (29.0)
Grades 3 and 4	0	0	0 (0)
Mucositis/stomatitis			
Grades 1 and 2	0	0	1 (3.2)
Grades 3 and 4	1	1	2 (6.5)
Neutropenia			
Grades 1 and 2	0	1	2 (6.5)
Grades 3 and 4	1	0	1 (3.2)
Leukopenia			
Grades 1 and 2	0	2	1 (3.2)
Grades 3 and 4	1	0	0 (0)
Thrombocytopenia			
Grades 1 and 2	0	0	0 (0)
Grades 3 and 4	0	1	0 (0)
Hyperbilirubinemia			
Grades 1 and 2	0	1	3 (9.7)
Grades 3 and 4	1	1	0 (0)
Hand-foot syndrome			
Grades 1 and 2	0	3	0 (0)
Grades 3 and 4	1	0	1 (3.2)
Rash			
Grades 1 and 2	0	2	2 (6.5)
Grades 3 and 4	0	0	0 (0)
ALP increased			
Grades 1 and 2	0	0	0 (0)
Grades 3 and 4	0	0	1 (3.2)
AST increased			
Grades 1 and 2	0	0	0 (0)
Grades 3 and 4	0	0	1 (3.2)
Blood LDH dehydrogenase increased			
Grades 1 and 2	0	1	0 (0)
Grades 3 and 4	1	0 (0)	0 (0)
Blood lactic acid increased			
Grades 1 and 2	0	0	0 (0)
Grades 3 and 4	1	0	0 (0)
Hyperglycemia			
Grades 1 and 2	0	0	0 (0)
Grades 3 and 4	0	0	1 (3.2)

ALP, Alkaline phosphatase; AST, asparate aminotransferase; LDH, lactate dehydrogenase.

most frequently experienced grade 3 drug-related AEs were mucositis/stomatis (7.7%), dehydration (5.1%), neutropenia (2.6%), hyperbilirubinemia (2.6%), and hand-foot skin reaction (2.6%). No patient experienced drug-related grade 4 or 5 toxicities. One patient experienced grade 4 hyperbilirubinemia, one grade 4 hypoglycemia, one grade 4 hyponatremia, three patients died from disease progression, and one patient died from hepatic encephalopathy; these
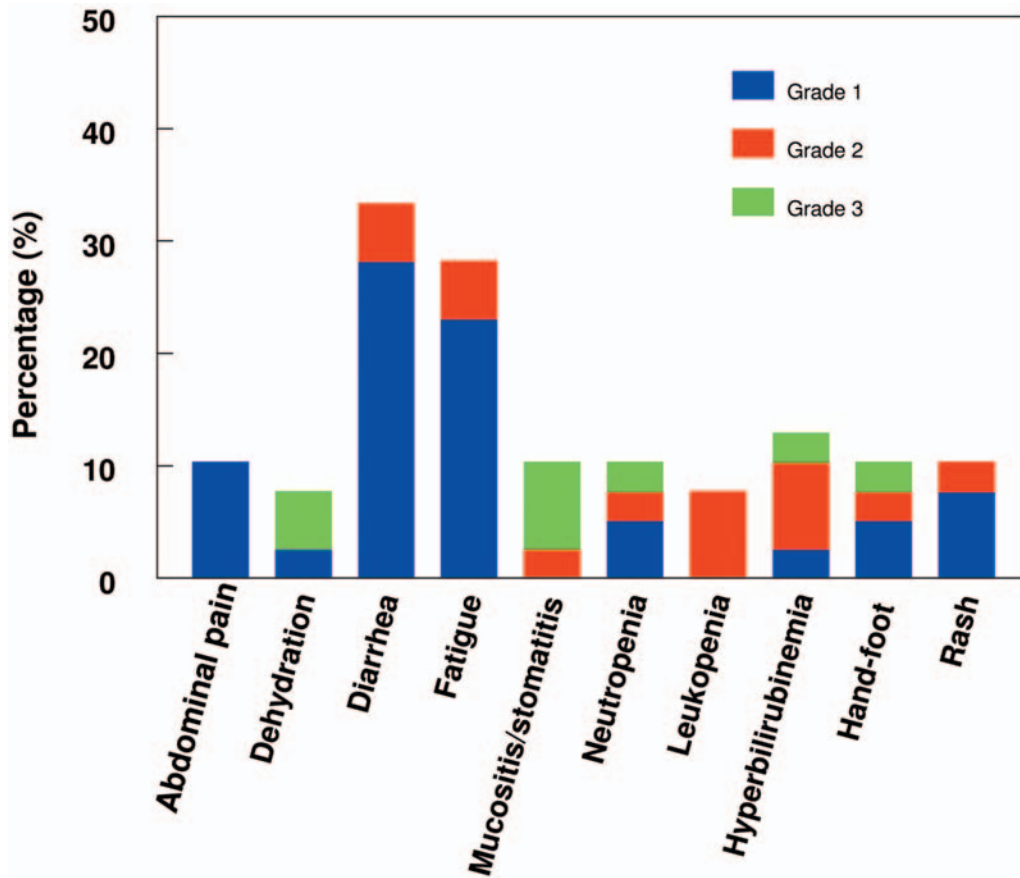
Figure 1. *Most common drug-related adverse events in patients treated with PHY906 (600 or 800 mg) plus capecitabine (750 mg/m^2) (N=39).*

adverse events (AEs) were not related to capecitabine/ PHY906 administration. Figure 1 summarizes the most common drug-related AEs in 39 patients.

Among 27 efficacy-evaluable patients, 5 each had one drug-related grade 3 toxicity: neutropenia, dehydration, ALP elevation, hyperglycemia, or hand-foot skin reaction. One patient experienced two drug-related grade 3 toxicities (poor appetite and AST elevation). Among 20 efficacy-evaluable Child-Pugh A patients, four patients each experienced one drug-related grade 3 toxicity: neutropenia, dehydration, ALP elevation, or hyperglycemia. No correlation was observed between grade-3 drug-related toxicity and ethnicity, Child-Pugh status, hepatitis, or previous treatment.

Efficacy evaluation. While 29 out of the 42 patients were evaluable for a response (N=2 received the cohort 1 regimen, N=4 received the cohort 2 regimen, and N=23 received the cohort 3 regimen), only patients who received capecitabine 750 mg/m^2 (cohort 2 and 3 regimens) are analyzed (N=27) in this report.
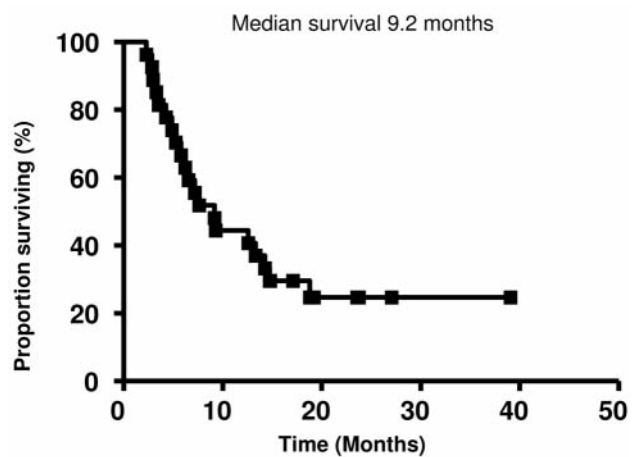

Figure 2. *Kaplan-Meier survival curve of patients treated with PHY906 (600 or 800 mg) plus capecitabine (750 mg/m^2) (N=27).*
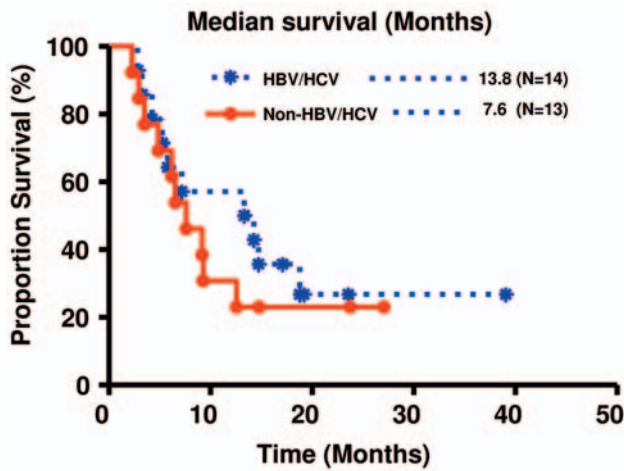
Figure 3. *Kaplan-Meier survival curves of HBV/HCV vs. non-HBV/HCV patients treated with PHY906 (600 or 800 mg) plus capecitabine (750 mg/m^2).*
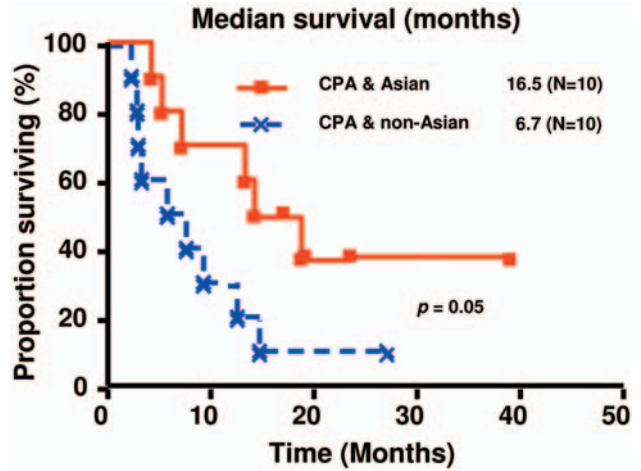

Figure 6. *Kaplan-Meier survival curve of Asian vs. non-Asian patients (both Child-Pugh A) treated with PHY906 (600 or 800 mg) plus capecitabine (750 mg/m^2).*
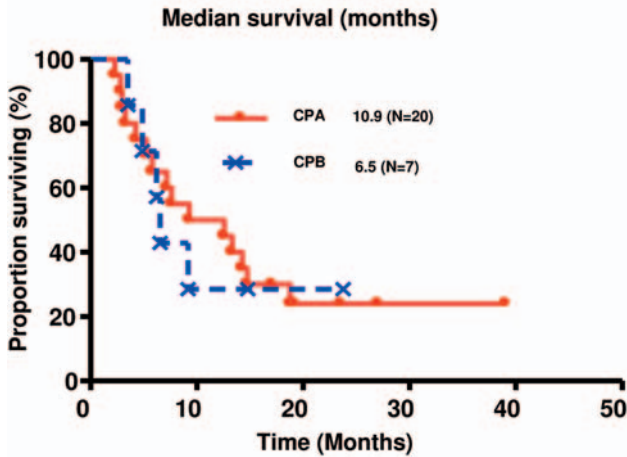

Figure 4. *Comparison of survival curves of Child-Pugh A patients vs. Child Pugh B patients treated with PHY906 (600 or 800 mg) plus capecitabine (750 mg/m^2).*
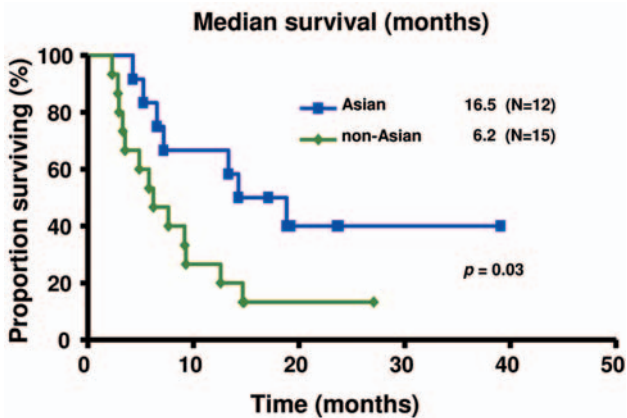

Figure 7. *Antitumor effect of PHY906 and capecitabine on HepG2 tumor-bearing mice.*

Figure 5. *Survival curve of Asian vs. non-Asian patients treated with PHY906 (600 or 800 mg) + capecitabine (750 mg/m^2).*

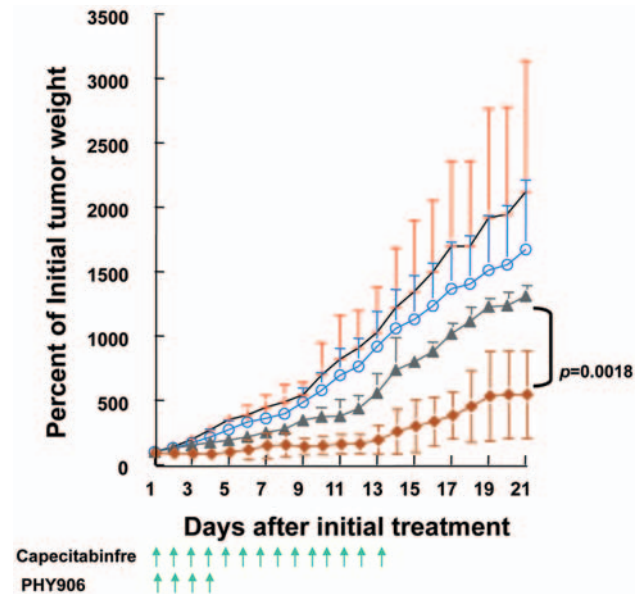*Objective responses.* Among four patients treated with capecitabine 750 mg/m^2/PHY906 600 mg, two patients had minor response (MR, tumor reduced by 33.5% and 34%, respectively), one had SD, and one had PD after two cycles of treatment. At the capecitabine 750 mg/m^2/PHY906 800 mg dose level (N=23), no CR or PR were seen; two patients had

Table IV. *Comparison of patient characteristics, outcome, and selected grade 3 or 4 drug-related side-effects in sorafenib and PHY906/capecitabine studies.*

Patient characteristics, outcome and side-effects	Sorafenib Phase II	Sorafenib Phase III	PHY906 (600/800 mg)+ Capecitabine[1]	PHY906 (600/800 mg)+ Capecitabine[2]
No. of Patients	299	150	27	20
% of Child-Pugh A	95	97	74	100
% of HBV	19	71	37	50
% of HCV	29	11	26	20
Study sites (%)	EU/US (88/9)	Asia (100)	US (100)	US (100)
Response % (PR/MR/SD)	2.3/0/71	3/0/54	0/14.8/51.9	0/0/65
Median TTP (months)	5.5	2.8	3.4	2.8
Median OS (months)	10.7[3]	6.5[4]	9.2	10.9
12-month survival rate (%)	44	28	41	50
Grade 3/4 drug-related toxicities (%)				
Hand-foot skin reaction	8	11	3.7	0
Diarrhea	8	6	0	0
Fatigue	4	3	0	0
Hypertension	2	2	0	0
Abdominal pain	2	NA	0	0
Hypophosphatemia	11	NA	0	0
Thrombocytopenia	4	NA	0	0

[1]Phase II patients treated with either 600 mg or 800 mg of PHY906 together with capecitabine (750 mg/m^2); [2]subset of (1). All the patients in this group were classified as Child-Pugh A; [3]median OS for the placebo group in the US/EU trial was 7.9 months, N Engl J Med *359*: 4, 378-390, 2008; [4]Median OS for the placebo group in the Asia trial was 4.2 months, Lancet Oncol *10(1)*: 25-34, 2009.

an MR (39.7% and 44% tumor reduction, respectively), 13 exhibited SD, and 8) had PD. The median time to progression was 3.4 months and median overall survival (OS) was 9.2 months. The 12-month survival rate was 44.5% (Figure 2).

Hepatitis status, liver disease classification, ethnicity and overall survival time. Of the patients eligible for efficacy evaluation (N=27), 10 had HBV and 8 had HCV. Figure 3 indicates that non-hepatitis patients exhibited a median OS of 7.6 months; for patients with hepatitis B or C, the median OS was 13.8 months.

Seventy-four percent (N=20) of the 27 efficacy-evaluable patients were classified as Child-Pugh A. Median OS values for Child-Pugh A and Child-Pugh B patients were 10.9 and 6.5 months, respectively (Figure 4). No difference in the 6-month survival rate was observed between Child-Pugh A and Child-Pugh B patients. However, the 12-month survival rate for was 51% for Child-Pugh A patients and 29% for Child Pugh B patients.

Median OS values for Asian and non-Asian subgroups were 16.5 and 6.2 months, respectively (*p*=0.03, Figure 5). Median OS values for Asian and non-Asian Child-Pugh A patients were 16.5 and 6.7 months, respectively (*p*=0.05, Figure 6). No significant correlation was observed for either nuclear grade or degree of differentiation of tumor.

QoL. QoL scores for 8 phase II patients at the end of treatment with capecitabine 750 mg/m^2 *bid*/PHY906 800 mg *bid* did not deteriorate significantly from baseline scores. Changes in score, either positive or negative, did not exceed 25% (data not shown). Thus, PHY906/capecitabine treatment resulted in limited deleterious side effects, *e.g.* hand-foot syndrom, diarrhea and vomiting.

Discussion

From many previous trials, including those with capecitabine, it is evident that HCC is resistant to chemotherapy (26-31). Capecitabine, as a monotherapy, has been used off-label in HCC, yielding response rates of up to15% (26, 27). Myelosuppression and skin toxicity are the most common side-effects seen with capecitabine-containing combinations, with severe GI toxicity being the most limiting side effect. Sorafenib in HCC patients also exhibits drug toxicities; these include fatigue, weight loss, rash or superficial skin shedding, hand or foot skin reaction, hair loss, diarrhea, anorexia, nausea and abdominal pain (38, 39). Diarrhea was reported in 55% of patients who received sorafenib (40, 41). Agents that reduce the toxicities of these chemotherapeutics without compromising their antitumor activities would provide an added benefit to patients.

PHY906, a traditional Chinese medicine formulation, has been in continuous use for a variety of gastrointestinal ailments since 300 AD. In preclinical studies, PHY906 did not appear to have toxicities that overlap with those of other agents used for HCC chemotherapy (34-37). More significantly, in a

double-blind, randomized, placebo-controlled, cross-over phase I/II clinical trial with a two-step dose escalation of PHY906 in colon carcinoma patients treated concomitantly with irinotecan/5-fluorouracil/leucovorin, PHY906 reduced the incidence of vomiting, nausea, and grade 3/4 diarrhea (42).

The mechanisms of PHY906 action are multifactorial. PHY906 has inhibitory activity on multidrug-resistant protein (MDR) and CYP450; both of these inhibitions may facilitate the oral uptake of chemotherapeutic agents (34-37). Examination of the tumor tissues and compounds involved suggest that the integrity of blood vessels and the pathways of HIF-α and Fos/Juk transcription are affected by PHY906. *In vitro* studies also reveal that PHY906 has inhibitory activities against NF-κB and matrix metalloproteases (MMPs), which are possible contributors to the enhancement of the antitumor action of chemotherapeutic agents. Possible mechanisms of action for the reduction of gastrointestinal toxicity by PHY906 are the inhibition of tachykinin NK-1, opiate δ receptors and acetylcholinesterase based (43).

In the present phase I/II study, the PHY906/capecitabine combination resulted in only a few grade 3 drug-related toxicities and no grade 4 or 5-drug related toxicities; the combination was generally well tolerated. The rate of nausea and emesis rate seen with PHY906/capecitabine was lower than would be expected using capecitabine alone. Moreover, fewer patients discontinued treatment in the current combination trial as a consequence of adverse effects (9.5%) than were reported in trials using capecitabine or sorafenib monotherapy (29%) (26, 27, 38, 39).

Based on the results of SHARP and Asian phase III studies, sorafenib has been approved for HCC treatment. Ninety-five percent of patients enrolled in these studies were classified as Child-Pugh A and had no previous treatment. The median OS of patients enrolled in the SHARP and Asian studies were 10.7 and 6.5 months, respectively, while that of placebo was 7.9 and 4.2 months, respectively (38, 39). The patients enrolled in the current study would generally be expected to have a poorer prognosis as 26% of the patients were classified Child-Pugh B and >64% had had previous treatments. However, the median OS in our study was 9.2 months, with fewer grade 3 or 4 drug-related toxicities than seen with sorafenib (38). Moreover, the median OS among Child-Pugh A (n=20) patients was 10.9 months with no grade 3 or 4 sorafenib-type toxicities (Table IV). In our study, Asian Child-Pugh A patients had a median OS of 16.5 months – a marked increase over that seen with sorafenib in the same cadre of patients.

Our results suggest that the PHY906/capecitabine combination provides a survival benefit and has a tolerable safety profile in advanced HCC patients and has promise as a treatment for this disease. Use of the PHY906/capecitabine combination may prove to be particularly efficacious for Asian Child-Pugh A HCC patients. In light of the very poor prognosis of HCC patients and the 100% tumor progression rate seen with sorafenib therapy, the PHY906/capecitabine combination provides an additional opportunity to stabilize the disease for relatively longer periods of time.

Use of the PHY906/capecitabine combination may not be limited to HCC. A phase II clinical trial in patients with advanced and recurrent pancreatic cancer refractory to gemcitabine is currently ongoing and preliminary reports indicate that the combination is safe and well tolerated (44).

Conclusion

The data provided in this report illustrate that a widely-used traditional Chinese medicine formulation, PHY906, can be used in combination with a widely-used western cancer chemotherapeutic agent, capecitabine, to successfully treat patients with advanced HCC. The results with Asian patients are particularly noteworthy.

Acknowledgements

References

1 Llovet JM and Bruix J: Molecular targeted therapies in hepatocellular carcinoma. Hepatology *48*: 1312-1327, 2008.

2 Jemal A, Murray T, Wood E *et al*: Cancer Statistics. CA Cancer J Clin *55*: 10-30, 2005.

3 Di Bisceglie AM, Rustgi VK, Hoofnagle JH *et al*: Hepatocellular carcinoma. Ann Intern Med *108*: 390-401,1998.

4 Tsukuma H, Hiyama T, Tanaka S *et al*: Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med *328*: 1797-1801, 1993.

5 Chen CH, Chen CJ, Yen MF *et al*: Ultrasound screening and risk factors for death from hepatocellular carcinoma in a high-risk group in Taiwan. Int J Cancer *98*: 257-261, 2002.

6 Velazquez RF, Rodriguez M, Navascues CA *et al*: Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology *37*: 520-527, 2003.

7 El-Serag HB and Mason AC: Risk factors for the rising rates of primary liver cancer in the United States. Arch Intern Med *160*: 3227-3230, 2000.

8 Hassan MM, Frome A, Patt YZ *et al*: Rising prevalence of hepatitis C virus infection among patients recently diagnosed with hepatocellular carcinoma in the United States. J Clin Gastroenterol 35:266-269, 2002.

9 Kulkarni K, Barcak E, El-Serag H *et al*: The impact of immigration on the increasing incidence of hepatocellular carcinoma in the United States. Aliment Pharmacol Ther 20:445-450, 2004.

10 Davila JA, Morgan RO, Shaib Y *et al*: Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology *127*: 1372-1380, 2004.

11 Nerenstone SR and Ihde DC, Freidman MA: Clinical trials in primary hepatocellular carcinoma: current status and future directions. Cancer Treat Rev *15*: 1-31, 1988.

12 Venook AP: Treatment of hepatocellular carcinoma: too many options? J Clin Oncol *12*: 1323-1334, 1994.

13 Burroughs A, Hochhauser D and Meyer T: Systemic treatment and liver transplantation or hepatocellular carcinoma: two sides of the therapeutic spectrum. Lancet Oncol *5*: 409-418, 2004.

14 Ihde DC, Kane RC, Cohen MH *et al*: Adriamycin therapy in American patients with hepatocellular carcinoma. Cancer Treat Rep *61*: 1385-1387, 1977.

15 Vilaseca J, Guardia J, Bacardi R *et al*: Doxorubicin for liver cancer. Lancet *1*: 1367, 1978.

16 Chlebowski RT, Brzechwa-Adjukiewicz A, Cowden A *et al*: Doxorubicin (75 mg/m^2) for hepatocellular carcinoma: clinical and pharmacokinetic results. Cancer Treat Rep pp. 487-491, 1984.

17 Sciarrino E, Somonetti RG, LeMoli S *et al*: Adriamycin treatment for hepatocellular carcinoma. Experience with 109 patients. Cancer *56*: 2751-2755, 1985.

18 Melia WM, Johnson PJ and Williams R: Induction of remission in hepatocellular carcinoma: a comparison of VP-16 and adriamycin. Cancer *51*: 206-210, 1983.

19 Lewis BJ and Freidman MA: Current status of chemotherapy for hepatoma. *In*: Chemotherapy of Hepatic Tumors. Ogawa M (ed.). Princeton, NJ, Excerpta Medica pp. 63-74, 1984.

20 Lai KH, Tsai YT, Lee SD *et al*: Phase II study of mitoxantrone in unresectable primary hepatocellular carcinoma following hepatitis B infection. Cancer Chemother Pharmacol *23*: 54-56, 1989.

21 Okada S, Okazaki N, Nose H *et al*: A phase 2 study of cisplatin in patients with hepatocellular carcinoma. Oncology *50*: 22-26, 1993.

22 Simonetti RG, Liberati A, Angiolini C *et al*: Treatment of hepatocellular carcinoma: a systematic review of randomized controlled trials. Ann Oncol *8*: 117-136, 1997.

23 Mathurin P, Rixe O, Carbonell N *et al*: Overview of medical treatments in unresectable hepatocellular carcinoma – an impossible meta-analysis? Aliment Pharmacol Ther *12*: 111-126, 1998.

24 Yang TS, Lin YC, Chen JS *et al*: Phase II study of gemcitabine in patients with advanced hepatocellular carcinoma. Cancer *89*: 750-756, 2000.

25 Yang TS, Yang CH, Hsieh RK *et al*: Gemcitabine and doxorubicin for the treatment of patients with advanced hepatocellular carcinoma: a phase I-II trial. Ann Oncol *13*: 1771-1778, 2002.

26 Patt YZ, Hassan MM, Aguayo A *et al*: Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer *101*: 578-586, 2004.

27 von Delius S, Lersch C, Mayr M *et al*: Capecitabine for treatment of advanced hepatocellular carcinoma. Hepatogastroenterology *54(80)*: 2310-2314, 2007.

28 Shin D, Lee J, Park J *et al*: Systemic chemotherapy with capecitabine, doxorubicin and cisplatin for metastatic hepatocellular carcinoma. J Clin Oncol *23*: 16s (suppl; abstr 4177), 2005.

29 Boige V, Raoul J-L, Pignon J-P *et al*: Multicentre phase II trial of capecitabine plus oxaliplatin (XELOX) in patients with advanced hepatocellular carcinoma: FFCD 03-03 trial. Br J Cancer *97*: 862-867, 2007.

30 Hsu C-H, Yang T-S, Hsu C *et al*: Phase II study of bevacizumab + capecitabine in patients with advanced/metastatic hepatocellular carcinoma: final report. J Clin Oncol *26*: (abstr 4603), 2008.

31 Sun W, Haller DG, Mykulowycz K *et al*: Combination of capecitabine, oxaliplatin with bevacizumab in treatment of advanced hepatocellular carcinoma (HCC): a phase II study. J Clin Oncol *25*: 18s (abstr 4574), 2007.

32 Hsu HY and Hsu CS: Commonly used Chinese herb formulas with illustrations. Los Angeles, CA: Oriental Healing Art Institute, 1980.

33 Chinese Botany, vol. 7, 1st ed. Shanghai, China: Shanghai Science and Technology Publishing Company, 1999.

34 Liu SH, Jiang Z and Cheng YC: A Chinese medicine formulation, PHY-906, can enhance the therapeutic index of CPT-11 and other anticancer drugs against cancer in mice. Proc Am Assoc Cancer Res *42*: (abstr 458), 2001.

35 Liu SH, Jiang Z, Gao W: PHY906, a Chinese herbal formulation enhances the therapeutic effect of cancer chemotherapy in human colorectal and liver cancer. Proc Am Soc Clin Oncol *22*: 864 (abstr 864), 2003.

36 Liu SH, Foo A, Jiang Z *et al*: PHY906 as a broad-spectrum enhancer in therapy: clinical and preclinical results in hepatocellular carcinoma. Proc Am Assoc Cancer Res *47*: (abstr 2142), 2006.

37 Liu SH, Jiang Z, Su TM *et al*: Developing PHY906 as a broad-spectrum modulator of chemotherapeutic agents in cancer therapy. Proc Am Assoc Cancer Res *45*: (abstr 557), 2004.

38 Llovet JM, Ricci S, Mazzaferro V *et al*: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med *359*: 378-390, 2008.

39 Cheng A, Kang Y, Chen Z *et al*: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomized, double-blind, placebo-controlled trial. Lancet Oncol *10(1)*: 25-34, 2009.

40 O'Neil BH and Venook AP: Hepatocellular carcinoma: the role of the North American GI Steering Committee Hepatobiliary Task Force and the advent of effective drug therapy. Oncologist *12*: 1425-1432, 2007.

41 Abou-Alfa GK and Venook AP: The impact of new data in the treatment of advanced hepatocellular carcinoma. Curr Oncol Rep *10*: 199-205, 2008.

42 Farrell MP and Kummar S: Phase I/IIA randomized study of PHY906, a novel herbal agent, as a modulator of chemotherapy in patients with advanced colorectal cancer. Clin Colorectal Cancer *2*: 253-256, 2003.

43 Liu, SH, Jiang Z, Foo A *et al*: PHY906 in hepatocellular carcinoma. Proc Am Assoc Cancer Res 48 (abstr 1841), 2007.

44 Hoimes CJ, Lamb L, Ruta S *et al*: A phase I/II study of PHY906 plus capecitabine (CAP) in patients (pts) with advanced pancreatic cancer. J Clin Oncol *26*: (May 20 suppl abstr 15538), 2008