Experimental and Molecular Therapeutics 15: Novel Mechanisms to Enhance Chemotherapy Efficacy

PHY906 as a broad-spectrum enhancer in cancer therapy: Clinical and preclinical results in hepatocellular carcinoma

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Abstract

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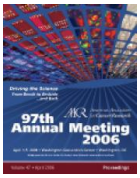
PHY906, a traditional Chinese botanical formulation, was first described 1800 years ago for common gastrointestinal distress. Currently, PHY906 is being developed for FDA approval as a botanical prescription medicine offering a new approach to cancer supportive care. The preclinical data indicates that PHY906 can reduce chemo-induced gastrointestinal toxicity while simultaneously enhancing the therapeutic efficacy of a broad-spectrum of common anticancer agents, including CPT-11, 5-FU, capecitabine, oxaliplatin, VP-16, taxol, and gemcitabine in a variety of tumor-implanted *in vivo* animal models. The mechanism of PHY906 antitumor activity is multifarious, including inhibitory activities of NF-κB, matrix metalloproteases (MMPs), multi-drug resistant protein (MDR), and CYP450 and modulation of numerous cytokines. Possible mechanisms of action for the reduction of gastrointestinal toxicity are the inhibition of Tachykinin NK-1 and Opiate δ receptors and modulation of inflammatory cytokines. A phase I/II, multicenter, open-label, dose-escalation, safety and efficacy study of PHY906 plus capecitabine in patients with unresectable hepatocellular carcinoma is presently underway. The main objective of phase I is to define the safety, tolerability, and effective dose of PHY906 when co-administered with capecitabine. Three doses have been



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studied. Cohort I: PHY906 (1000mg, bid, D1-4 and 8-11) plus capecitabine (1000 mg/m^2,bid, D1-14); cohort II: PHY906 (600mg, bid, D1-4 and 8-11) plus capecitabine (750 mg/m^2, bid, D1-14); and cohort III: PHY906 (800mg, bid, D1-4 and 8-11) plus capecitabine (750 mg/m^2, bid, D1-14). The cohort I dose regimen has resulted in unacceptable dose-limiting toxicities while the dosing in cohorts II and III were both well tolerated. Stable disease after two cycles of study-drug treatment for cohorts II (N=4) and III (N=6) are 75% and 67%, respectively. The median time to disease progression (TTP) is 26.5 weeks and the median survival time is greater than 44.5 weeks for Cohort II. The majority of the patients in Cohort III remain on study. The primary objective for the current phase II is determining the objective antitumor response rate while the secondary objectives are determining TTP, overall survival time, and quality of life (QoL). While clinical trials address efficacy and safety of the drug, chemical and biological analytic methods have been developed to address drug consistency and quality control. Comprehensive molecular resolution chemical fingerprints utilizing a three-dimensional LC/MS profile and a sensitive cellular bioresponse genomic profile to generate a quantitative signature pattern for comparing and confirming batch-to-batch similarity of study drug. These studies offer a modern approach to the study of ancient botanicals that may represent novel regimens for cancer treatment.

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