patients) has been observed. Pralatrexate has achieved a remarkably high CR rate among patients with select forms of NHL. The goals of this ongoing trial are to identify the ORR in patents with B- and TCL, and to initiate an international registration study for patients with TCL.

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Research and identification of the polymorphisms of the thymidylate synthase gene in the human tumor cell lines panel of the National Cancer Institute (NCI)

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Background: Thymidylate synthase (TYMS) is the target enzyme for 5-fluorouracil (5-FU). It has been shown that TYMS expression is inversely correlated with the activity and/or toxicity of 5-FU in cancer patients. On the other hand, TYMS expression is dependent on TYMS gene polymorphisms (PM). Three distinct PMs have been identified: the 2R/3R PM, consisting of the presence of 2 or 3 tandem repeats of a 28 bp sequence in the gene promoter; the 3C/3G PM, consisting of a C>G SNP in the second repeat of 3R alleles; and the 6ins/6del PM, consisting of the deletion of a 6 bp sequence in the 3′ untranslated part of the gene.
Methods: DNA was extracted from the cell lines of the NCI panel and TYMS PMs were identified using PCR-RFLP techniques. TYMS catalytic activity was evaluated in cell cytosols using a radioactive substrate.
Results: In the NCI panel, the allele frequency of the 2R allele is 53% (19 3R/3R, 17 2R/3R and 23 2R/2R cell lines). Among the 3R allele-containing cell lines, 7 with 2R/3R and 10 with 3R/3R genotype present at least one copy of the 3G allele (allele frequency: 18%). Finally, the allele frequency of the 6del variant is 32% (32 6ins/6ins, 16 6ins/6del and 11 6del/6del cell lines). We have looked for relationships between 5-FU cytotoxicity, as extracted from the NCI database, TYMS expression and catalytic activity in the cell lines of the NCI panel, and the presence of TYMS gene PMs. 5-FU cytotoxicity is significantly related to none of the PMs, and is not related either with TYMS expression or activity. However, the presence of 3G alleles is significantly associated to high enzyme expression and activity ($P = 0.03$), especially in cell lines with mutated p53 ($P = 5 \times 10^{-5}$). There is a linkage disequilibrium between the PMs, the 3G allele being significantly associated with the 6del allele and the 2R allele with the 6ins allele. In addition, there is a deviation from the Hardy-Weinberg distribution, with a smaller than expected proportion of heterozygous cell lines for any PM. This can be attributed to loss of heterozygosity occurring in tumor cell lines.
Conclusion: The NCI panel offers an interesting model for the establishment of relationships between gene PMs and pharmacological data. The absence of relationship between in vitro 5-FU cytotoxicity and TYMS gene expression, activity and polymorphisms could be due to the fact that 5-FU cytotoxicity was measured in the absence of optimal amounts of the cofactor of TYMS.

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Phase I study of sapacitabine, an oral nucleoside analogue, in patients with refractory solid tumors or lymphomas

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Background: Sapacitabine (CYC682, CS-682) is a rationally designed 2'-deoxycytidine-type nucleoside analogue that can be administered orally. Compared with other nucleoside analogues, sapacitabine is unique in its ability to induce G2 cell cycle arrest and cause single-strand DNA breaks that are irreparable by ligation. Following oral administration, sapacitabine is converted by amidases and esterases in the gut, plasma, and liver to its major active metabolite (CNDAC). Sapacitabine had potent anti-tumor activity in animal studies and was superior to gemcitabine or 5-FU in a mouse liver metastasis model. Previous phase I studies had evaluated once daily dosing (qD) × 3 or 5 days/week for 4 weeks every 6 weeks. To maximize drug exposure, this phase I study evaluates twice daily dosing (b.i.d.) × 7 or 14 days every 21 days, using body surface area (BSA)-based or fixed dosing.
Methods: Eligible patients had incurable advanced solid tumors or lymphomas and adequate organ function. At least 3 patients were enrolled at each dose level. Maximum tolerated dose (MTD) was the dose level at which at least 2/3 or 3/6 patients experienced DLT in the first cycle. The recommended phase II dose (RD) was the dose level immediately below MTD. Pharmacokinetic (PK) sampling was performed after administration of sapacitabine with and without food.
Results: 37 patients were treated, 28 on the b.i.d. × 14 days schedule and 9 on the b.i.d. × 7 days schedule. The most common tumor types were non-small cell lung (n = 7), colon (n = 5), breast (n = 5) and ovary (n = 4). The MTD for the14 day-schedule is 40 mg/m^2 b.i.d. (RD = 33 mg/m^2 or 50 mg b.i.d.). The MTD for the 7 day-schedule is 100 mg b.i.d. (RD =75 mg b.i.d.). DLTs were reversible myelosuppression. One patient treated at the MTD of 40 mg/m^2 b.i.d. died of candida sepsis in the setting of grade 4 neutropenia and thrombocytopenia. Non-hematological adverse events (all grades, regardless of causality) were mostly mild to moderate and included nausea, vomiting, fatigue, diarrhea, constipation and anorexia. PK data are being analyzed. The best response to sapacitabine was stable disease in non-small cell lung (n = 3), ovary (n = 3), colon (n = 2), breast, gastrointestinal stromal tumor and parotid adenocarcinoma (n = 1 for each).
Conclusion: The RD of sapacitabine for the b.i.d. × 14 days schedule is 33 mg/m^2 b.i.d. or 50 mg b.i.d. and that for the b.i.d. × 7 days schedule is 75 mg b.i.d. The DLT was myelosuppression.

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Pharmacokinetics of talotrexin (PT-523), a novel aminopterin analogue, in patients with non-small cell lung cancer

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Background: Talotrexin, N^{α}-(4-Amino-4-deoxypteroyl)-N^5-hemiphthaloyl)-L-ornithine (PT-523) is a nonpolyglutamatable antifolate which has demonstrated improved antitumor activity in a broad spectrum of cancer models by targeting DHFR to inhibit tumor growth. Talotrexin binds more tightly (15-fold, Ki 0.35 pM) to DHFR than methotrexate (MTX). In lung cancer cell lines, talotrexin inhibits tumor cell proliferation at sub- to low-nanomolar concentrations and is more potent than MTX in all cell lines tested. We conducted a dose escalation study of talotrexin administered as a 5–10 minute infusion on Days 1, 8, on a 21-day cycle in non-small cell lung cancer (NSCLC). The primary objectives of this study were to determine the maximum tolerated dose (MTD), pharmacokinetic (PK) profile, as well as the safety and efficacy. This report describes the PK behavior of talotrexin in NSCLC patients.
Methods: Plasma samples were obtained prior to infusion, at the completion of the infusion, at 15 and 30 minutes, then at 1, 2, 3, 4, 6, 8, 10, 16, 24 and 48 hrs after completion of the infusion. A validated LC/MS/MS assay was used to measure talotrexin in plasma. PK parameters were estimated by standard noncompartmental methods.
Results: The PK of talotrexin was characterized in 25 patients with normal renal and hepatic function, and a median age of 59 years (range, 48–76 years). Data was obtained from groups of at least three patients receiving doses of 13.5, 27, 54, 90, and 135 mg/m^2. The talotrexin concentration in plasma decreased in a mono-exponential manner following a rapid distribution phase. In the 6 patients who received the MTD dose of 54 mg/m^2, the mean peak drug concentration in plasma (C_{max}) was 17.42 ng/L (13.7−22.3) and the mean plasma concentration 48 hr after dosing was 17.3 ng/ml (range, 17.8−36.7 ng/mL). The apparent biological half-life ($t_{1/2,z}$), total body clearance (CL) and apparent volume of distribution at steady-state (V_{ss}) were all independent of the dose. Mean (range) values of PK parameters for the entire cohort of 25 patients were: CL, 1.4 L/hr/m^2 (3.6−10.3), $t_{1/2,z}$, 6.6 hr (4.7−6.8) and Vd_{ss}, 8.1 L/m^2 (7.4−13.0).
Conclusions: Talotrexin exhibits linear PK with moderate interpatient variability when administered as a short IV infusion at doses of 13.5−135 mg/m^2. In future PK studies, talotrexin major route of elimination will be examined and an evaluation of whether diminished renal or hepatic function warrants dose modification will be conducted.

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Phase I/II study of oxaliplatin (L-OHP) in combination with S-1 (SOX) as first-line therapy for metastatic colorectal cancer (MCRC)

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Background: FOLFOXs are one of the world's established standard therapies for MCRC. S-1 is an oral dihydropyrimidine dehydrogenase (DPD)-inhibitory fluoropyrimidine consisting of tegafur which is a 5-FU prodrug activated by CYP2A6 in the liver, 5-chloro-2,4-dihydroxypyridine of the DPD inhibitor, and potassium oxonate of the orotate phosphoribosyltransferase (OPRT) inhibitor. The response rate of S-1 monotherapy for chemo-naïve MCRC was 35.7%. SOX may provide a new alternative to FOLFOX. This study was designed to determine the recommended dose (RD), to assess the pharmacokinetics (PK), and to evaluate the efficacy and safety of this combination therapy.
Methods: Patients were eligible as follows: unresectable MCRC with no prior chemotherapy, PS (ECOG) 0–1, age 20−75, measurable