resulted in a significant tumor growth retardation in vivo. Moreover, when combined with radiation, a 25 mg/kg dose of OXI 4503 reduced tumor cell survival 20–50-fold lower than that seen with radiation alone.
In summary, the present findings suggest that OXI 4503 bears certain similarities to the parent compound CA4DP. However OXI 4503 demonstrated greater antiumor efficacy as noted by its reduction of the rim of viable tumor cells at the periphery as well as its ability to induce significant tumor growth delays. These data suggest that OXI 4503 may hold greater therapeutic significance.

520 POSTER

Modulation of N,N-dimethylamino-benzoylphenylurea (BPU) absorption by the CYP3A and ABCG2 inhibitor ritonavir

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Background: BPU is a poorly water-soluble benzoylphenylurea derivative with significant cytotoxic activity that acts through inhibition of tubulin polymerization. A previous study has indicated that BPU is metabolized *in vitro* to the cytotoxic compounds desmethylBPU (mBPU) and aminoBPU (aBPU) and to several minor metabolites. The successive demethylation is mediated by cytochrome P450 (CYP) 3A4>CYP3A5>CYP3A7=CYP2D6 (Rudek et al, Clin Cancer Res 2003;9:6197s). A preliminary report also suggested that BPU is a substrate for the transporter protein ABCG2 (BCRP), but not for P-glycoprotein, which combined with CYP3A-mediated metabolism, may explain why the oral bioavailability of BPU in animals is low and highly variable (4.4 to 29%). Oral BPU is currently being evaluated in phase I clinical trials, and pharmacokinetic data have revealed that BPU is very extensively metabolized to mBPU and aBPU. The unpredictable extent of metabolic conversion has been linked to drug-induced neutropenia in patients and presents a major obstacle to further development of this agent. It was hypothesized that temporary, simultaneous inhibition of intestinal and hepatic activity of total CYP3A and ABCG2 would improve the low and variable oral absorption characteristics of BPU.
Materials and methods: To test this hypothesis, female C57BL/6 mice were treated with oral BPU at a dose of 10 mg/kg in the presence and absence of the HIV protease inhibitor ritonavir, a potent inhibitor of both CYP3A and ABCG2, administered orally 30 min prior to BPU at a dose of 12.5 mg/kg. Samples for pharmacokinetic studies were drawn from 3 animals per time point at 5, 15, and 30 min, and at 1, 2, 4, 6, and 24 h following administration of BPU. Samples were analyzed for the parent drug and its metabolites using solvent extraction followed by liquid chromatography with tandem mass spectrometric detection.
Results: Ritonavir co-treatment resulted in an approximately 10-fold increase in BPU area under the curve (AUC) [180 (BPU) vs 1744 nM.h (BPU+ritonavir); $P<0.05$] and a simultaneous decrease in aBPU AUC (5347 vs 2477 nM.h; $P<0.05$) and increase in time to peak concentration (2 vs 24 h). Surprisingly, there was no significant difference in exposure to mBPU (2436 vs 2217 nM.h), although the mBPU peak concentration was decreased by 1.7-fold. The combined exposure to BPU and the metabolites was affected to a lesser extent by ritonavir (8263 vs 6438 nM.h) than each of the compounds individually, suggesting that metabolism rather than transport is the major factor involved in the observed interaction.
Conclusions: These data show that oral BPU pharmacokinetics are significantly influenced by ritonavir. Based on these encouraging findings, a clinical trial is currently being planned to study the concept of intentional pharmacokinetic biomodulation in cancer patients to better control the extensive and variable first-pass metabolism of BPU.

521 POSTER

New synthetic Epothilone Derivative ZKEPO inhibits the proliferation of a human glioma implanted orthotopically in nude mice

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Drugs interfering with cellular microtubules, i.e. paclitaxel and vinca alkaloids are one mainstay of anti-tumor chemotherapy. Human Gliomas, however, have been rather resistant to a treatment with paclitaxel by two reasons, limited delivery of paclitaxel to the glioma cells due to the existence of the blood-brain-barrier (although in tumors often leaky) and because of the development of multidrug resistance.
Epothilones represent a novel class of natural products which also stabilize microtubules. Based on a broad fully synthetic drug optimization program with more than 350 synthesized analogs, we have developed ZK-EPO, a new derivative with outstanding preclinical efficacy.
ZK-EPO is taken up rapidly by tumor cells, preferentially accumulates in the cell nucleus, is not recognized by cellular efflux mechanisms which lead to the development of multidrug resistance, and it diffuses into the brain.
The ability of ZK-EPO to cross the blood-brain-barrier was shown after i.v. application to scid mice. Similar concentrations of ZK-EPO in the brain (0.9 μg/g) and in the plasma (1.2 μg/ml) were detected 10 min after i.v. application. When comparing the partial areas under the plasma level/brain level time curves (0–40 min), a ratio AUC_{brain}/AUC_{plasma} of approx. 0.8 was found, indicating a free access to the brain.
The paclitaxel concentration was below the limit of quantitation in all brain samples (ratio AUC_{brain}/AUC_{plasma} of zero).
Based on these characteristics, we concluded that ZK-EPO should be effective in gliomas and tested ZK-EPO in an orthotopic human glioma model to proof this hypothesis.
In vivo, ZK-EPO produced strong antiproliferative activity in the human glioma model U373 in nude mice. These results suggest that ZK-EPO might also be suited for the treatment of human brain tumors.

522 POSTER

Oral taxane BMS-275183 demonstrates therapeutic synergy in human tumor xenografts when combined with cetuximab

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Combination therapy consisting of an oral taxane, BMS-275183, and the anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody, cetuximab, was assessed for enhanced therapeutic benefit in preclinical tumor models. Athymic mice bearing human tumor xenografts, either L2987 lung or GEO colon carcinoma, were administered the aforementioned treatments singly or in combination regimens. Delays in tumor growth, and tumor-free status, were evaluated and combination treatments were assessed relative to optimal solo treatments. Combinations of cetuximab plus BMS-275183 were tolerated, and synergistic outcomes were obtained at doses ranging from half to full solo maximum tolerated dose (MTD) levels of the oral taxane. The extent of the therapeutic enhancement was reproducibly more than one log cell kill greater than the antitumor effect caused by either solo agent applied optimally. For example, at the MTD of BMS-275183, 60 mg/kg/administration, given orally (po) once every three days for a total of six administrations (q3dx6), 1.0 gross log cell kill (LCK) was achieved in mice bearing well established (100–200 mg) L2987 tumors. Cetuximab, at an optimal dose of 1 mg/mouse, given intraperitoneally (ip) q3dx6, produced 1.3 LCK. When cetuximab, 1 mg/mouse, ip, plus BMS-275183, 25 mg/kg/administration, po, were both given q3dx6, the result was 2.6 LCK with 3 of 8 mice cured. Similar efficacy benefits were obtained in the GEO tumor model. In summary, the combination of oral taxane, BMS-275183, plus anti-EGFR monoclonal antibody, cetuximab, provided therapeutically synergistic antitumor activity in two different human tumor xenograft models. Synergies were observed at doses below MTD levels, but the combination was tolerated even at doses combining solo drug MTD or optimal dose levels. Clinical evaluation of this combination is recommended.

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Selective targeting of cancer cell tubulin with anti-tumor drugs

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Neuronal tubulin, isolated from bovine or porcine brain tissue, is the standard in the field for performing microtubule polymerization assays. One use of neuronal tubulin concerns screening for tubulin ligands which have anti-tumor activity. Neuronal tubulin is ideal for preliminary screens where a large number of compounds have to be screened for initial tubulin binding activity. However there has been poor correlation between IC50 values determined from dose response curves on neuronal tubulin versus tissue culture or patient studies. This is due to several reasons including blood brain barrier diffusion, neurotoxicity, resistant phenotypes and possibly differential tubulin isotype expression. Here we explore the latter by polymerizing neuronal and cancer cell tubulins in the prescence of paclitaxel, vinblastine and their derivatives and also compounds that failed drug approval via the FDA process. Bovine neuronal tubulin has mainly beta II (58%) and beta III (25%) tubulins (Banjeree and Luduena, 1992) in combination with alpha I to make the typical heterodimer, this is in contrast to HeLa cells which have mainly beta I (90%) and beta IV