1473 POSTER

Tocosol® paclitaxel and cremophorel®-paclitaxel: the pharmacokinetic comparison shows that a new paclitaxel formulation leads to increased drug exposure

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Background: TOCOSOL® Paclitaxel (TP) is a novel tocopherol-based cremaphor-free formulation that allows a 15 minute infusion time. Phase II clinical trials have demonstrated antitumor activity in bladder, ovarian, and non-small cell lung cancers. The pharmacokinetic (PK) comparison of TP and CremophorEL®-formulated paclitaxel (P) is important for further development of TP.
Methods: 36 patients with solid tumors without proven treatment option were enrolled. Each patient was randomized to receive as first course either a single infusion of 175 mg/m^{2}of TP given over 15 minutes q 21 days or 175 mg/m^2 of P given over 3 hours q 21 days. In a second cycle the other formulation was administered so that each patient served as his/her own control. Blood samples for PK of free and total paclitaxel were obtained up to 120 hours after each dose; non-compartmental and compartmental PK analyses were performed. Adverse events and complete blood counts were assessed every 3 days.
Results: TP given over 15 minutes produced a mean 67% higher exposure to free paclitaxel and a mean 108% higher exposure to total paclitaxel compared to P administered over 3 hours. The geometric mean ratio of free paclitaxel AUC values after equal 175 mg/m^2 doses of TP and P was 1.67 (90% CI 1.56–1.79, $p < 0.0001$) and that for total paclitaxel AUC values was 2.08 (90% CI 1.97–2.20, $p < 0.0001$). Mean values for paclitaxel terminal elimination t2 were similar for TP and P. TP produced more neutropenia than P, but without causing clinical complications. Grade 1–3 non-hematologic adverse events were comparable between the two drugs.
Conclusions: TP offers a significant increase of drug exposure with similar tolerability. The differences in exposure may reflect differences in rate and/or extent of dissociation of paclitaxel from the tocopherol emulsion formulation compared to cremaphor-ethanol micelles. TOCOSOL® Paclitaxel is easily administered and may provide a profoundly higher drug exposure if given on a weekly basis. Since this may result in improved clinical activity compared to P further development is warranted.

1474 POSTER

A Phase I, open-label study with escalating doses of intravenous PTK787/ZK 222584, a multi-VEGF receptor inhibitor, followed by multiple oral daily dosing to assess the absolute bioavailability of PTK787/ZK 222584 after single and multiple doses in advanced cancer patients

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Background: PTK/ZK is a novel oral small molecule that blocks the tyrosine kinase activity of all known VEGF receptors and inhibits tumor angiogenesis and lymphangiogenesis, slowing tumor growth and spread.
Material and Methods: This Phase I study was performed to evaluate the safety and pharmacokinetics (PK) of single intravenous (IV) doses of PTK/ZK and the absolute bioavailability of the oral (PO) PTK/ZK after single (SD) and multiple doses (MD). Patients had histologically confirmed advanced cancer, adequate organ function and WHO PS of 0–2. The study was done in two parts. In Part 1 cohorts of 3 pts received single IV PTK/ZK doses of 22.5 mg, 45 mg and 90 mg on day 1 and PK samples were taken. Pts were monitored for safety until day 8. In Part 2 pts received a single IV dose of PTK/ZK 90 mg on day 1, and 1250 mg/d PO from days 8 to 22 and second IV dose of PTK/ZK 90 mg on day 23. PK was taken on days 1, 8, 22 and 23. Levels of PTK/ZK and it's metabolites were measured by HPLC/UV. Pts could continue with PO PTK/ZK until disease progression or unacceptable toxicity. The results of follow-up will be reported later.
Results: 26 pts were enrolled (9 to Part 1 and 17 to Part 2). PTK/ZK was the major active analyte in plasma. PK profiles of PTK/ZK following SD and MD oral administration with a dose of 1250 mg/d were similar to those observed in previous studies. Average PK parameters following PTK/ZK IV dose of 90 mg and PO dose of 1250 mg is shown in table 1:

Parameters (Unit)	Day 1 SD IV N = 20	Day 23 MD IV N = 12	Day 8 SD PO N = 17	Day 22 MD PO N = 12
Cmax (ng/mL)	2074	2462	9146	6457
AUC0-t (ng*h/mL)	5579	5018	63334	25307
Clearance(L/h)	18.5	25.2	31.6	71.5
Vz (L)	65.5	104	229	509
$t_{\frac{1}{2}}$ el.(h)	2.90	3.28	7.00	5.31

The mean (CV%) absolute bioavailability of PTK/ZK was 0.58 (55%) after SD and 0.37 (53%) after MD and was significantly lower after MD as compared to SD [Geo. mean ratios (90% CI); 1.6 (2.22 –2.10)]. PTK/ZK was well tolerated. No significant toxicities were reported in any of IV dose cohorts. The most frequent AEs with IV administration were nausea and fatigue and with PO administration dizziness, nausea and vomiting. Most of AEs were grade 1/2. No grade 4 AEs were observed. Two pts had grade 3 PTK/ZK related SAEs. Five pts discontinued Part 2 of the study because of AEs.
Conclusions: Both IV and PO PTK/ZK were well tolerated. The absolute bioavailability of PTK/ZK was 0.58 after SD, and declined to 0.37 after MD due to increase in oral clearance following multiple oral doses of PTK/ZK.

1475 POSTER

ErbB3 expression predicts tumor cell radiosensitization induced by Hsp90 inhibition

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The ability to identify tumors that are susceptible to a given molecularly targeted radiosensitizer would be of clinical benefit. Towards this end, we have investigated the effects of a representative Hsp90 inhibitor, 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (17DMAG), on the radiosensitivity of a panel of human tumor cell lines. 17DMAG was previously shown to enhance the radiosensitivity of a number of human cell lines, which correlated with the loss of ErbB2. We now report on cell lines in which 17DMAG induced the degradation of ErbB2, yet had no effect on radiosensitivity. In a comparison of ErbB family members, ErbB3 protein was only detectable in cells resistant to 17DMAG-induced radiosensitization. To determine whether ErbB3 plays a casual role in this resistance, siRNA was used to knock down ErbB3 in the resistant cell line AsPC1. Whereas individual treatments with siRNA to ErbB3 or 17DMAG had no effect on radiosensitivity, the combination, which reduced both ErbB2 and ErbB3, resulted in a significant enhancement in AsPC1 radiosensitivity. In contrast to siRNA to ErbB3 or 17DMAG treatments only, AsPC1 cell exposure to the combination also resulted in a decrease in ErbB1 kinase activity. These results indicate that ErbB3 expression predicts for tumor cell susceptibility to and suggest that the loss of ErbB1 signaling activity is necessary for 17DMAG-induced radiosensitization. However, for cell lines sensitized by 17DMAG, treatment with siRNA to ErbB2, which reduced ErbB1 activity, had no effect on radiosensitivity. These results suggest that, whereas the loss of ErbB1 signaling may be necessary for 17DMAG-induced radiosensitization, it is not sufficient.

1476 POSTER

Phase I study of S-1 plus cisplatin (CDDP) in patients with advanced non-small-cell lung cancer (NSCLC): a 2-week course of S-1

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Background: A combination of S-1 (tegafur, oxonic acid, and CDHP), an oral drug active against advanced NSCLC, plus CDDP resulted in a 47% response rate in our previous study, which used a relatively low dose intensity (DI) of CDDP (12 mg/m^2/week) [Clin Cancer Res 10: 7860, 2004]. This study examined the maximum tolerated dose (MTD) and recommended dose (RD) of CDDP when combined with a 2-week course of S-1 to increase the DI of CDDP in patients with advanced NSCLC.