of vasoactive agents including serotonin (from platelets aggregating to damaged vasculature) and tumour necrosis factor (TNFá). The study objective was to determine whether plasma levels of the serotonin metabolite, 5HIAA, correlated with DMXAA induced blood flow changes, first in preclinical mouse and rat tumour models and then in cancer patients.
Methods: 5HIAA levels from blood were determined by HPLC. Mice, bearing syngeneic colon 38 subcutaneous tumors, were given single doses of DMXAA (up to ~150 mg/m^2). Rats bearing GH3 prolactinomas were dosed with DMXAA at up to ~2200 mg/m^2. In a completed Phase I double-blind randomised study in refractory tumors; DART) plasma 5HIAA was measured in patients receiving 20 minute intravenous infusions of DMXAA at 300 to 3000 mg/m^2.
Results: 5HIAA levels in mice measured 4hr post DMXAA showed a significant linear correlation with increased extravasation of the albumin binding Evans Blue from tumours ($r = 0.82$; $P < 0.05$); extravasation significantly correlated with reduced tumour blood flow ($r = 0.88$; $P < 0.01$). Notably, in the same mice, no change in extravasation was seen in normal skin. In rats, there was a significant increase in plasma 5HIAA concentration 24hr post treatment with doses of ~1300 mg/m^2 and above. In patients, peak 5HIAA plasma levels occurred at 4hr post dosing at dose levels >600 mg/m^2. Notably, there was a positive correlation between 5HIAA plasma levels and DMXAA dose up to 1200 mg/m^2 but thereafter a plateau was observed (even though plasma levels of free DMXAA increased linearly with dose up to 3000 mg/m^2).
Conclusions: Increased plasma levels of 5HIAA appear to represent a sensitive biological marker of blood flow changes induced by the VDA, DMXAA. Dose-response data from Phase I trial patients show that the optimum biological dose of DMXAA to cause tumour blood flow/5HIAA changes is in the range of 1200 mg/m^2, that is, around only 30% of the maximum tolerated dose. This is the same dose-range at which significant changes in plasma 5HIAA were seen in tumour bearing rats. Doses in this range are being studied in Phase II combination trials with taxanes (where marked synergy was seen in various preclinical tumour models); with docetaxel in patients with prostate cancer and with paclitaxel, and carboplatin, in non small cell lung and ovarian cancer.

1458 POSTER

Weekday on – weekend off oral capecitabine: a Phase I study of a continuous schedule better simulating protracted fluoropyrimidine therapy

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Background: Although management of solid tumours with protracted 5-Fluorouracil infusion is superior to bolus regimens in terms of pharmacokinetic considerations, activity, radiosensitization and toxicity, the equivalent oral fluoropyrimidine capecitabine is administered at 2510 mg/m^2 daily for two weeks followed by a 7-day break. As attempts at continuous capecitabine dosing were offset by cumulative toxicity and low administered dose (1331 mg/m^2/day), we investigated an alternative regimen that avoided long breaks.
Materials and Methods: Oral capecitabine was administered twice daily continuously with weekend breaks (5 days on, 2 days off) until disease progression or unacceptable toxicity. Eligible patients had advanced solid tumours refractory to standard therapy, adequate organ function and performance status of 0–2. Dose escalation proceeded in levels of 1331, 1665, 2000, 2250, 2500 mg/m^2 of daily oral capecitabine according to appearance of dose-limiting toxicity (DLT) during the first six weeks. DLT consisted of any grade 3 or 4 adverse event except for alopecia and skin toxicity resolving within 7 days.
Results: Twenty heavily pretreated patients with a median age of 67 and advanced, refractory breast (7), gastric (5), colorectal (2), bile duct (2) and other cancers entered the study. Among 5, 4 and 3 patients treated in cohorts 1331, 1665 and 2000 mg/m^2 respectively, no DLT occurred. The additional patients were recruited to replace patients quitting treatment before 6 weeks due to rapid disease progression. No DLT was seen in any of the 3 and 4 patients treated at 2000 and 2250 mg/m^2 either. Four patients were recruited at 2500 mg/m^2 and 2 developed grade III diarrhoea in weeks 3–4 of therapy (DLT), resolving uneventfully in 3 days. The most common toxic episodes during all cycles of treatment in all patients were grade 1–2 fatigue (8), nausea (4), constipation (4), abdominal pain (4), skin erythema (3) and anemia (3). In this pretreated population with refractory tumours, disease stabilization with clinical benefit was seen in 10 patients. Among the 7 women with breast cancer who were treated at a dose of 2000 mg/m^2 of continuous capecitabine or higher, 3 partial responses and a disease stabilization/clinical benefit rate of 86% were seen. Pharmacokinetic studies of capecitabine and metabolites are under way in additional 6 patients at the recommended dose of 2250 mg/m^2 and will be presented.
Conclusions: Weekday on-weekend off continuous oral capecitabine better simulates protracted fluoropyrimidine therapy at a recommended dose (2250 mg/m^2) close to that of the intermittent schedule and clearly higher than the continuous one (1331 mg/m^2), with lack of severe toxicity from mucous membranes, skin or bone marrow. The regimen offers promise for activity in advanced disease as well as for incorporation in radiotherapy and adjuvant programs.

1459 POSTER

A Phase I clinical study of weekly heptaplatin and paclitaxel in previously treated patients with advanced solid tumor

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Background: On a 4-week schedule, the maximal tolerated dose (MTD) for single heptaplatin (H), a less toxic platinum analog, was 480 mg/m^2 with recommended dose at 360 mg/m^2 (Kim NK et al. Cancer 2001; 91: 1549–56). This study was carried out to establish the MTD and dose-limiting toxicity (DLT) of weekly administration of H in combination with weekly paclitaxel (P) in previously treated patients (pts) with advanced solid tumor.
Material and Methods: Patients with advanced solid tumor, age 20–65, ECOG PS 0–1, adequate organ function, and 1 or more prior chemotherapy regimen without prior exposure to platinum or taxanes, were eligible. P 60 mg/m^2 was given first i.v. over 1 hr followed by H i.v. over 1 hr on days 1, 8, and 15, every 4 weeks. Each cohort of 3 pts were treated with escalating doses of H at 120, 150, 200, 250, 300, 350, 400 and up to 450 mg/m^2. The DLT and MTD pertaining to first cycle only were obtained and serial blood samples were drawn for H and P pharmacokinetics (PK) during first cycle.
Results: of 30 pts enrolled, 27 pts were evaluable for toxicity. The DLT, which was noted in 2 of 6 pts, was G3 proteinuria at dose level of H 450 mg/m^2. The MTD was H 400mg/m^{2}in combination with P 60 mg/m^2. Other grade 3/4 toxicities were (no. of patients); G3/4 neutropenia (11), G3 thrombocytopenia (3), G3 constipation (1), G3 anorexia (1) and G3 elevated liver enzyme (1). Objective tumor responses (PR) were noted in 6 of 18 non-small cell lung cancers (NSCLC), 1 of 4 breast cancers and 2 of 2 gastric cancers. PK data is in progress.
Conclusion: The recommended dose of weekly H is 400 mg/m^2 combined with weekly P 60 mg/m^2. Further phase II studies of this combination regimen are warranted, particularly in NSCLC and gastric cancer.
(Supported in part by SK Pharma and NCC grant 0210140)

1460 POSTER

Metronomic oral vinorelbine (MOVIN): a dose establishing translational and pharmacokinetic study in patients with metastatic refractory cancer

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Background: Preclinical research and clinical observations evidence that continuous administration of small dose chemotherapy (metronomic dosing scheme) may effectively target activated endothelial cells in the tumor vasculature; yet metronomic chemotherapy remains to be validated in the clinical setting and several issues such as the identification of most appropriate agents and optimal doses and schedules should be addressed. In this clinical trial we studied metronomic dosing of the oral formulation of microtubule poison vinorelbine with the aim to establish a biologically optimal metronomic dose (OMD), investigate feasibility of protracted continuous administration and describe antitumor activity.
Methods: Fixed doses of oral vinorelbine were given three times a week (TIW) non-stop until disease progression or unacceptable toxicity. The trial deployed in two phases. In phase-alpha successive cohorts of patients received escalated doses of vinorelbine (20 mg base-dose, 10 mg