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

increments) to define a maximum non-toxic metronomic dose (MNMD). In phase-beta, patients allocated randomly to one of three dose levels (low-medium-MNMD) and underwent blood sampling throughout the treatment to analyze for kinetics of surrogate biomarkers of angiogenesis (soluble VEGF, VEGFr2, TSP1, bFGF and circulating progenitor endothelial cells) and twice for pharmacokinetics. OMD will be defined by considering kinetic profile of biomarkers in association with antitumor activity and pharmacokinetics.
Results: Forty six patients [21 female and 25 male; median age 58 range 38–85 years; median PS 1, median prior treatments 2 range 0–7] were enrolled between June 2004 and May 2005. They had a variety of progressive refractory solid cancers and were treated at the dose range of 20 to 50 mg. All patients received continuous non-stop therapy without overt clinical toxicity. Median time of treatment failure was 17 weeks (range 6 to 44+ weeks) that also corresponded to time to progression, since no withdrawals from therapy were due to toxicity. MNMD has not been reached and dose is presently escalated to 60 mg. Objective tumor response (confirmed partial remission) was documented in four cases (renal cancer, NSCLC, unknown primary and sarcoma Kaposi) and 32% of treated patients had stable disease for more than 6 smonths. The trial is ongoing to define the OMD.
Conclusions: Continuous administration of metronomic oral vinorelbine, given TIW is feasible and exceptionally well tolerated at doses up to 50 mg. Early results show activity against refractory tumors and provide evidence towards clinical proof of principle for metronomic chemotherapy. Data on biomarker analysis and pharmacokinetics will be presented at the meeting.

1461 POSTER

Circulating endothelial cells and monocytes as markers of sunitinib malate (SU11248) activity in patients with imatinib mesylate-resistant GIST

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Background: This study evaluated circulating endothelial cells (CECs), monocytes (MCs), circulating VEGF and soluble VEGFR-2 (sVEGFR-2) as potential pharmacodynamic markers of sunitinib malate (SU) activity in GIST patients (pts).
Materials and methods: SU is an oral multitargeted tyrosine kinase inhibitor of VEGFR, PDGFR, KIT, RET and FLT3 with antiangiogenic and antitumor activities. The majority of pts enrolled in a phase I/II trial of SU for metastatic GIST resistant to imatinib mesylate (IM) therapy received repeating cycles of 50 mg SU daily for 4 wks followed by 2 wks off treatment. CBC and differential WBC counts were taken pre- and post-treatment in 73 pts enrolled in the study. In 16 pts, CECs were assessed serially by 4-color flow cytometry. Changes in mature CEC and MC counts were correlated with clinical outcome, classified as either clinical benefit (CB: PFS >6 mos) or PD. Plasma levels of soluble proteins were analyzed using validated sandwich ELISA assays.
Results: MC levels decreased 54% after 2 wks of SU therapy ($P < 0.001$) and rebounded (96%) after 2 wks off therapy ($P < 0.001$). This pattern of decrease and increase in MC levels during periods on and off SU therapy was observed across multiple drug cycles, while no such pattern was observed with lymphocytes. After 2 wks of SU therapy, mean MC count decreased 59% in the PD group, but only 48% in the CB group ($P = 0.03$). CEC counts increased significantly early after initiation of SU therapy (first follow-up: 6–20 d), but not at subsequent timepoints. Changes in CEC count following therapy distinguished pts based on clinical outcome: all 7 pts with SU-related CB also exhibited a rise in CEC count between baseline and first follow-up, while only 3 of 9 pts with PD had a rise in CEC count. The rate of change per day in CECs was significantly different between pts with CB and PD (median: 0.52 vs. –0.01 cells/μL; $P = 0.03$). After active treatment in each cycle, mean plasma VEGF levels increased by an average of 2.9-fold, while mean sVEGFR-2 levels decreased by an average of 1.7-fold, with both returning to near-baseline levels during treatment breaks. These changes did not strongly correlate with clinical outcome.
Conclusions: Percent drop in MC counts and rate of change per day in mature CECs distinguished pts with metastatic IM-resistant GIST who experienced CB during SU therapy from those who did not. CEC and MC counts may be useful markers for identifying pts who may ultimately benefit from SU therapy.

1462 POSTER

A multicenter Phase II trial of gefitinib 500 mg/day in 192 patients with advanced epidermal growth factor receptor-positive solid tumors who had failed previous chemotherapy.

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Background: 15 Belgian oncology centers participated in an open-label Phase II trial of gefitinib (IRESSA) 500 mg/day in patients (pts) with advanced epidermal growth factor receptor-positive solid tumors who had failed >1 previous chemotherapy regimen and had no further chemotherapy treatment options.
Methods: EGFR expression was assessed using DakoCytomation's EGFR pharmDx™ kit. Pts with EGFR expression of >1 received gefitinib 500 mg/day until disease progression. Objective tumor assessments, by RECIST, were made every 8 weeks and confirmed by repeat assessments >4 weeks later. Disease control rate (DCR) was defined as objective response (confirmed complete response or partial response [PR]) plus stable disease (SD) for >8 weeks. All adverse events (AEs) were reported and assessed by NCI-CTC version 2.0.
Results: 192 pts have been enrolled with the following tumors: pancreatic cancer (PC) [n = 39], cervical cancer (CC) [n = 36], ovarian cancer (OC) [n = 33], sarcoma (S) [n = 23], cancer of unknown primary origin (U) [n = 19], hepatocellular carcinoma (HC) [n = 18], bladder cancer (BC) [n = 14], and endometrial cancer (EC) [n = 10]. Mean time between first tumor diagnosis and the start of gefitinib treatment was 33.5 months (±44.8). 18 pts (HC only) had received no previous chemotherapy, 74 pts 1 line, 58 pts 2 lines and 42 pts >3 lines. DCR was 34%: 7 pts had a PR (3 CC, 3 OC, 1 PC) and 58 pts had SD at 8 weeks (16 CC, 9 OC, 8 S, 6 PC, 9 HC, 4 EC, 3 BC, 3 U). Mean duration of disease control was 27.2 weeks (±2.2). 84% of pts had at least one drug-related AE. In 16% of patients (n = 31), this drug-related AE was CTC grade 3, in 0.5% (n = 1) of patients CTC grade 4. Most of these grade 3–4 adverse events were of cutaneous or gastrointestinal origin. Gefitinib dose reduction to 250 mg/day was required in 21% of pts. In 7% of patients gefitinib treatment was withdrawn because of drug-related AEs.
Conclusions: Gefitinib showed promising activity and acceptable tolerability in patients with EGFR-positive pancreatic cancer, cervical cancer and ovarian cancer. Our data support findings from previous gefitinib Phase I/II trials in patients with advanced cervical cancer[1] and ovarian cancer [2].
IRESSA is a trademark of the AstraZeneca group of companies

References

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1463 POSTER

The urinary excretion of l-carnitine and its short-chain ester acetyl-l-carnitine in patients undergoing carboplatin treatment

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Background: During chemo- and radio-therapy cancer patients experience fatigue symptoms. Dietary and nutritional factors are among postulated to be involved in the multifactorial aetiology of fatigue. In fact, when L-carnitine (LC), a compound necessary for energy production through mitocondrial fatty acid oxidation, is reduced in the body or its endogenous system is altered, fatigue symptoms appear and are improved after its administration. Some anticancer drugs, such as cisplatin, cause excessive urinary LC elimination through a possible inhibition of its renal reabsorption. Other platinum-derivatives, such as carboplatin, could have a similar effect. This study investigated the influence of carboplatin treatment on plasma concentration and urinary excretion of LC and its main ester, acetyl-L-carnitine (ALC) in tumoral patients.