and 74 ± 42 and 131 ± 94 group B. The AUC (h*nmol/L) at day 1 and day 66 was 7238 ± 4530 and 8478 ± 4081 in group A and 7244 ± 4276 and 9734 ± 6111 in group B. The mean urinary excretion (expressed as % of dose ± SD) of letrozole and its main metabolite (CGP44645) during a dose interval at steady state was 71.19 ± 19.95 in group A and 75.83 ± 21.78 in group B. Four pts in group B had partial response; nine pts in group A and three in group B showed no changes.

Conclusions: there were no large differences between the younger and elderly pts in the pharmacokinetics parameters as well as in the urinary excretion of unchanged letrozole and major metabolite. Compared to the first dose, the half-life and AUC increased slightly at steady state and consequently the clearance/F decreased. This confirms the slight non-linearity in the pharmacokinetics of letrozole on 2.5 mg daily dosing.

1177 PUBLICATION

Combination of cisplatin with the degramont regime in advanced GI cancer: A phase I study

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The prognosis of inoperable GI carcinomas is poor and chemotherapy has no significant impact on survival. Recently, the combination of Cisplatin with continuous infusion of 5-FU has been used with promising results. Long-term infusion is associated with problems due to the constant need of an electric pump. We studied a combination of Cisplatin with the DeGramont regime, a combination of bolus and two-day continuous 5-FU (Leucovorin 200 mg/m^2, 5-FU 400 mg/m^2 bolus, 5-FU 600 mg/m^2 continuous infusion, days 1 + 2), which is effective in colorectal cancer. This combination was administered every 2 weeks, using disposable pumps. Since dose intensity seems to be important for maximal efficacy, we conducted a phase I study in order to define the MTD of Cisplatin.

Fifteen patients with advanced GI malignancies (10 gastric Ca, 2 hepatocellular Ca, 3 cholangiocarcinomas) have entered this study. Cisplatin was given on day 1, at 40 mg/m^2 (4 patients), 50 mg/m^2 (6 patients) and 60 mg/m^2 (5 patients). GCSF was used to achieve maximal dose intensity. DLT was defined as grade IV neutropenia or thrombocytopenia, any grade III non-haematological toxicity and >1 week delay in GCSF supported patients. 73 cycles (range 1–9) have been administered so far. 3 patients had Grade III and IV toxicities, all haematological: 1 grade III neutropenia at 40 mg/m^2, 1 grade IV neutropenia at 50 mg/m^2 and 1 grade IV neutropenia and thrombocytopenia at 50 mg/m^2. Other toxicities included stomatitis (2 grade I) and diarrhoea (1 grade I). There was 1 death due to neutropenic sepsis. Nine patients were evaluable for anti-tumour response. PR was achieved in 5 cases, SD in 2 and PD in 2. The study is ongoing, since MTD has not been reached yet. Since neither Cisplatin, at the doses used so far, nor the DeGramont regime are particularly myelotoxic, a pharmacokinetic study comparing our combination with the DeGramont regime alone has been initiated and the results will be presented.

In conclusion, the combination of Cisplatin with the DeGramont regime is well tolerated and increased Cisplatin dose intensity can be achieved. Our preliminary results also show interesting anti-tumour activity in patients with advanced GI malignancies and it could be used in future phase II trials.

1178 PUBLICATION

Phase I study of liposomal daunorubicin (Daunoxome) in the treatment of metastatic breast cancer

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Purpose: To establish the maximum tolerated dose (MTD) of daunoXome (NeXstar Pharmaceuticals) in breast cancer without growth factor support.

Methods: DaunoXome is administered as a 2 hour infusion every 3 weeks to a maximum of 8 cycles. Patients (pts) have been treated at 3 dose levels: 80, 100 and 120 mg/m^2. Pt evaluation: weekly full blood count; biochemistry prior to each cycle; echocardiography pretreatment and after cycles 4, 6 and 8; disease assessment after every 2 cycles and subsequently every 3 months until disease progression. Dose limiting toxicities (DLTs): grade ≥3 non-haematological toxicity (apart from alopecia, nausea and vomiting and hypersensitivity reactions), febrile neutropenia and thrombocytopenic bleeding.

Results: 12 pts, 4 to each dose level, age range 34–77 years, have been enrolled. Pt 4 at level 3 has had febrile neutropenia. One pt, previously treated with a cumulative dose of doxorubicin 300 mg/m^2, developed grade 2 cardiomyopathy after 600 mg/m^2 daunoXome. One CR, 1 MR and 2 SDs >4 months were seen in 10 pts evaluable for response. Three pts had tumour biopsies performed 24 h after treatment in cycle 1. Uptake of daunoXome into tumour cells was verified using confocal and electron microscopy.

Conclusions: DaunoXome has anti-tumour activity and is well tolerated in breast cancer patients, significant alopecia and nausea and vomiting being rare. The MTD, although not yet established, is likely to be 100 or 120 mg/m^2 the DLT being febrile neutropenia

1179 PUBLICATION

Phase I-study of bendamustine-HCl in patients with solid tumors

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Purpose: Bendamustine-HCl (BM) combines a purine-like benzimidazol and bifunctionally alkylating nitrogen mustard group. *In vitro* data indicate only partial cross-resistance to cyclophosphamide, CDDP, L-PAMM or BCNU, and activity in doxorubicin-resistant breast cancer cell lines. BM has antitumor acitivity in lymphoma, myeloma, small-cell lung and breast cancer. In earlier observations, the maximum tolerated dose (MTD) for single bolus BM was 215 mg/m^2, for fractionated therapy days 1–4 85 mg/m^2. Anticholinergic symptoms and myelosupression were dose-limiting, cardiac arrythmia did occur. Our trial was designed to define the MTD of a short infusion schedule and establish a recommended dose (RD) for phase II.

Methods: Patients with refractory tumors qualified for the trial after written informed consent. BM was given as a 30 min iv. infusion on days 1 + 8 of a 4 week cycle, with a starting dose of 100 mg/m^2 and increment per group of 20 mg/m^2.

Results: 19 patients (13 male, 6 female, mean age 58 years, range 38–74) were treated for 1–2 cycles with up to 180 mg/m^2 BM. At 160 mg/m^2, fatigue °3 (NCI Common Toxicity Criteria) and mouth dryness °3 occurred in two, diarrhea °3 in one patient; another patient with a history of myocardial infarction and arrythmia developed a reversible total atrioventricular block after first administration of 160 mg/m^2 BM. Other events such as nausea/vomiting, appetite loss, fever or chills were not dose-limiting. Haematologic toxicity was mild except for lymphopenia, which was cumulative and seen on all dose levels.

Conclusion: The MTD of 30 min. iv. infusions of BM is 160 mg/m^2, mouth dryness and fatigue are dose-limiting; the RD for phase II is 140 mg/m^2.

1180 PUBLICATION

A phase I study of docetaxel (D) and oxaliplatin (L-OHP) as front line treatment in metastatic breast and non-small lung cancer (NSCLC): Preliminary results

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Objectives: To determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT) of D in combination with L-OHP in patients with metastatic breast cancer (MBC) and NSCLC.

Patients and Treatment: Eighteen chemotherapy-naive patients (11 with NSCLC and 7 with (MBC) were enrolled onto the study. D was given as 1-hour infusion after standard premedication on day 1 (at escalated doses starting from 60 mg/m^2 with increments of 5 mg/m^2); L-OHP was given as 2 hour infusion on day 2 (at escalated doses starting from 60 mg/m^2 with increments of 10 mg/m^2). Cycles were repeated every 3 weeks. Patients' median age was 67, 13 (72%) had a PS (WHO) 0–1 and 16 (88%) had visceral disease. Cohorts of at least 3 pts were included at each dose level. DLT was defined as: grade 4 neutropenia or thrombocytopenia or grade 3 febrile neutropenia, or any non-hematologic toxicity of grade 3 and more, or any treatment delay due to toxicity and lasting more than 3 days.

Results: DLTs was exceeded at dose level 3 with two patients presenting neutropenia grade 4 and one patients febrile neutropenia grade 4. The recommended doses for further phase II studies are D: 75 mg/m^2 on day 1 and L-OHP: 80 mg/m^2 on day 2. Grade 3/4 neutropenia was observed in 7/62 cycles with 2 febrile neutropenic episodes; there was one septic death. No grade 3 or 4 anemia or thrombocytopenia was observed. Non-hematologic

toxicity was mild; only 1 pt developed neurotoxicity grade 2 while 4 pts fatigue grade 2. The study is now ongoing at the DLT level with G-CSF support.

1181 PUBLICATION

Phase I clinical trials of intravenous 2′-deoxycytidine-2′-fluoromethylene (FMdC) in patients with advanced solid tumors

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Purpose: To assess the clinical safety, tolerability, and pharmacokinetics of the nucleoside analogue, FMdC, a ribonucleotide reductase inhibitor and DNA chain terminator shown to have potent activity against a broad range of murine and human tumor cell lines in preclinical studies.

Methods: Four open-label, dose-escalation trials were conducted in patients with a variety of advanced solid malignancies. Dose levels: 16 to 670 mg/m^2; dosing schedules: 2×/wk × 3 wk + 1–2 wk rest to 1×/3 wk.

Results: 70 patients were evaluable. Pharmacokinetics were generally linear over a wide dose range. 86% of the dose was recovered in the urine within 24 h of administration; 23% of this amount was parent compound, and 64% was uridine metabolite. C_{max} occurred 4 h after dosing; then drug disappeared monophasically. The most common treatment-related adverse events (AEs) included transient fever (96%, 67/70), leukopenia (71%, 50/70), neutropenia (69%, 48/70), nausea (40%, 28/70), asthenia (39%, 27/70), and vomiting (27%, 19/70). Duration of leukopenia and neutropenia was brief (grade 4, 1–2 d and 1–8 d, respectively), and recovery was prompt. 27 patients accounted for 49 serious treatment-related AEs, of which 9 prompted discontinuation of the drug. One patient (metastatic colon cancer, 200 mg/m^2, 2×/mo) had a partial response after 4 cycles (4 mo) which was maintained for 5 mo. One patient with metastatic cholangiocarcinoma (32 mg/m^2, 2×/mo) had stable disease for 18 treatment cycles and progressed after 20 cycles (19 mo).

Conclusion: FMdC was generally well tolerated and showed objective anticancer activity. Phase II studies will be initiated in non-small-cell lung carcinoma, colorectal cancer, and ovarian cancer.

1182 PUBLICATION

A phase I study of weekly one hour escalating dose of paclitaxel infusion in conjunction with amifostine in patients with advanced cancer

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Background: Weekly infusion of paclitaxel is an active, well tolerated treatment under extensive investigation. Using standard premedications for the control of hypersensitivity reaction and colony stimulating factors to prevent myelosupression, neurotoxicity is the principal non-hematological toxicity of paclitaxel. Much higher doses of paclitaxel have been given using weekly instead of three week schedule. Dose limiting toxicities are noted between 80–100 mg/m^2 for previously treated patients. Amifostine protect normal tissue against ionizing radiation and chemotherapeutic agents without affecting the anti tumor effect. Many clinical trials have shown the decrease incidence of chemotherapy related toxicities including neuropathy, nephrotoxicity and myelotoxicity. Limited published data is available assessing its use in combination with paclitaxel.

Objective: To ascertain the maximum tolerated dose of weekly one hour paclitaxel infusion in conjunction with amifostine.

Methods: Phase I non randomized non-comparative, prospective study. Patients received granisetron 2 mg orally and dexamethasone 20 mg orally 2 hours before and cimetidine 300 mg with diphenhydramine 50 mg IVSS in 50 cc of NS 30 minutes before the chemotherapy and NS 250 cc over 1/2 hour. Each cohort has fixed amifostine dose of 740 mg/m^2 infused over 3–5 minutes immediately after hydration and escalating doses of paclitaxel infused over 60 minutes, 5 minutes after amifostine infusion, starting from 90 mg/m^2. In addition to routine evaluation, all patients have neurologic examination, nerve conduction studies, quantitative sensory testing with CASE IV and FACT neurotoxicity questioner.

Results: To date 9 patients with advanced metastatic cancers received 49 cycles of paclitaxel. Transient grade 2 neutropenia noted in 2/49 cycles in one patient. 5/49 cycles in 3 patients had grade 2 vomiting, after amifostine infusion. Although asymptomatic transient drop in blood pressure is common, only 1/49 cycles required hydration. Grade 3 neurotoxicity developed in 1/49 cycles in one patient after 11 doses of paclitaxel 100 mg/m^2, at the same time patient was noted to have multiple brain metastatic lesions from his small cell lung cancer.

Conclusion: Combination of amifostine and weekly paclitaxel in this current trial is tolerable with acceptable toxicities. Trial is ongoing with paclitaxel dose of 110 mg/m^2.

1183 PUBLICATION

In vitro concentration response studies of gemcitabine as experimental base for regional chemotherapeutic studies

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Purpose: To improve the theoretical background and to find out the potential benefit of gemcitabine for regional chemotherapy.

Methods: Dose- and time-dependent cytotoxicity of gemcitabine was analyzed in the human colorectal (HT29 and NMG 64/84) and pancreatic (PaCa-2 and PMH 2/89) cancer cell lines using the human tumor colony-forming assay (HTCA). Dose-dependent cytotoxicity was also generated in tumor cell suspensions, 1/99 and 3/99, isolated from colorectal liver metastases of 2 patients.

Results: Gemcitabine exerted a significant dose- and time-dependent cytotoxicity in all 4 cell lines with IC_{50} values of 100 μg/ml, 1.15 μg/ml, 18 μg/ml, and 1.5 μg/ml (2 h), 45 μg/ml, 0.5 μg/ml, 1.5 μg/ml, and 0.4 μg/ml (4 h), and 2 μg/ml, 0.1 μg/ml, 0.15 μg/ml, and 0.15 μg/ml (24 h) for HT29, NMG 64/84, PaCa-2, and PMH 2/89, respectively. Gemcitabine (2 h) resulted also in dose-dependent cytotoxic effects with an $IC_{50} > 100$ μg/ml and 2.5 μg/ml in 1/99 and 3/99, respectively.

Conclusions: Cytotoxicity varied more than 60-fold between the individual cell lines and tumor cell suspensions suggesting that response to gemcitabine is dependent on individual factors of each tumor. Dose- and time-dependent cytotoxicity *in vitro* moreover implies that gemcitabine may be qualified for regional chemotherapy.

1184 PUBLICATION

Inhibition of CYP3A4 does not influence Aromasin® (exemestane, EXE) pharmacokinetics (PK) in healthy postmenopausal volunteers (HPV)

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EXE is a novel oral irreversible aromatase inactivator effective in the treatment of advanced breast cancer and is extensively metabolised also by cytochrome P-450 3A4 (CYP3A4). The effect of the inhibition of CYP3A4 on the PK of EXE has been evaluated in five HPV following single doses of EXE (10 mg) before and after ketoconazole administration (200 mg daily for 6 days), a treatment known to selectively inhibit CYP3A4. The volunteers were phenotyped as extensive metabolisers of CYP2C19 and CYP2D6 substrates. To assess the inhibitory effect of ketoconazole, the ratio of urinary excretion of 6-β-hydroxicortisol/cortisol, a marker for CYP3A activity, was calculated. EXE in plasma was evaluated using HPLC-RIA; urinary mounts of 6-β-hydroxicortisol and cortisol using ELISA and RIA assay, respectively. No significant differences were observed in the pharmacokinetic parameters of EXE (mean ± SD) before and during ketoconazole repeated administration, being AUC 31.33 ± 8.95 and 28.37 ± 5.07 ng.h/mL, C_{max} 15.26 ± 10.17 and 9.16 ± 2.77 ng/mL, CL/F 351 ± 142 and 360 ± 53 L/h, V_z/F 12507 ± 6163 and 22258 ± 15312 L. The inhibition of CYP3A4 activity, confirmed by the significant decrease in the ratio of 6-β-hydroxicortisol/cortisol, does not affect the bioavailability and the metabolism of EXE. This suggests that the multiplicity of metabolic pathways for EXE might compensate *in vivo* for the inhibition of the CYP3A4 pathway.