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