Conclusion: The MTD of the schedule is 10 mg/d and the DLTs are neutropenia and diarrhea. Tolerance was good and the treatment is feasible as home therapy.

1172 PUBLICATION

A phase I study of the multitargeted antifolate (MTA) (LY 231514) in combination with oxaliplatin (LOHP) in metastatic solid tumors

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MTA is a novel multitargeted antifolate which inhibits the enzymes thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT). LOPH is an oxalato-diaminocyclohexane platinum analogous. Previous in vitro and in vivo studies reported synergistic effects of LOPH and 5-FU a well known TS inhibitor suggesting that there may be an advantage in combining MTA and LOPH. This phase I trial aimed to determine the maximum tolerated doses (MTD) of MTA given as a 10 mn IV infusion followed 30 mn after by LOPH administered by IV infusion over 2 hours q 21 days. DLTs were assessed at first cycle and defined as grade 4 neutropenia of more than 7 days, febrile neutropenia, grade 4 trombocytopenia or grade $\geq$3 non hematologic toxicity (excluding alopecia, nausea and vomiting). To date, 9 patients (pts) median age 51, median PS 1 have received 24 courses of therapy at 3 dose levels: MTA/LOPH level 1: 300/85 (3 pts); level 2: 400/85 (4 pts); level 3: 400/100 (2 pts). Drug related toxicities include leukopenia grade 3 (1 pt), anemia grade 3 (1 pt) and transaminase grade 3 (1 pt) but no DLT is observed so far. Accrual is continuing at following levels.

1173 PUBLICATION

Gemzar® (G) and epirubicin (E) in patients (pts) with metastatic breast cancer (MBC): Final results of a phase I dose finding study

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G, a new cytidine analog has shown activity as first or second line in the treatment of MBC. E is among the most active agent with different toxicity profile. We combined G and E in a phase I dose finding trial to determine the maximum tolerated dose (MTD) and the toxicity profile of the combination. Pts with MBC, adequate organ functions and WHO performance status (PS) $\leq$ 2 were eligible. Up to one previous regimen was allowed. G was given as 30 mn IV infusion on days 1 and 8; and E as 15 min IV infusion on day 1 q 21 days. 43 pts enrolled, median age: 54 years, median WHO PS: 0.

No DLTs appeared on the 4th first levels: (G/E)
(level 1: 800/50; level 2: 800/50; level 3: 1200/50; level 4: 1200/60).

No. Level (G/E)	DLT/total pts	Dose Limiting Toxicity (pt)
5 – (1200/75)	2/6	prolonged grade 4 neutropenia (1) febrile neutropenia (1)
6 – (1300/75)	2/7	prolonged grade 4 neutropenia (1) febrile neutropenia (1)
7 – (1400/75)	0/3	
8 – (1500/75)	2/8	prolonged grade 4 neutropenia (2)
9 – (1500/90)	2/6	prolonged grade 4 neutropenia (1) febrile neutropenia (1)

A phase II trial is now opened with the recommended dose as follow: G: 1500 mg/m^2 day 1 & day 8 and E 90 mg/m^2 day 1, q 21 days

1174 PUBLICATION

Phase I study of docetaxel epirubicin and cyclophosphamide (TEC) in patients with advanced cancer (AC)

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Purpose: Docetaxel (T) has considerable activity as a single agent and epirubicin and cyclophosphamide (EC) are commonly used in breast cancer. The aim of this study is to establish the maximum tolerated dose (MTD) of TEC ± lenograstim.

Methods: Pts with AC, normal organ function, ECOG PS 0–2 and 0–1 prior chemotherapy (<300 mg/m^2 doxorubicin or equiv.) were treated every 3 weeks with E, then C 600 mg/m^2 followed 1 hr later by T (E/T doses are described below). Stepwise use of ciprofloxacin (Ci) 500 mg bid from day 5 until neutrophils $\geq$1.0 $\times$ 10^9/l or lenograstim (L) 263 μg daily from day 2 until neutrophils $\geq$1.0 $\times$ 10^9/l was used to prevent febrile neutropenia (FN).

Results: 36 pts entered to identify the MTD, median age 55 years (range: 25 to 73), prior chemo 18/36, median 6 cycles received (range 1 to 10).

Grade 3–4 Toxicity = Dose Limiting Toxicities (DLTs) experienced

E/T mg/m^2 Dose Level	60/60 1	60/60 1 + Ci	60/60 1 + L	60/75 2 + L	75/75 3 + L	90/75 4 + L	90/85 5 + L	105/85 6 + L
Total Pts	3	5	3	5	6	6	3	6
FN	2	2		1	1	2	0	2
Infection		1						
Diarrhea	2							
Vomiting								1

The MTD was defined as the dose causing DLT in 3/3 or >3/6 pts. There were 13 PR's and 3 CR's in 28 evaluable pts. (8/12 in Ca breast).

Conclusion: The MTD was reached at dose level 1 ± Ci. Lenograstim allowed escalation of TEC to dose level 6. The recommended dose for phase II/III is E 90, C 600 and T 85 mg/m^2, with lenograstim support.

1175 PUBLICATION

Synergistic effects of ZD9331 a non-polyglutamatable thymidylate synthase inhibitor in combination with SN38 in human colon cancer cells

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ZD9331, a recent quinazoline, showed potent cytotoxic effects in vitro and in vivo and manageable toxicity in phase-I/II trials. This study aims (1) to identify new drug combinations against human colon cancer, (2) to define optimal sequences combining ZD9331, and (3) to investigate the cellular and molecular mechanisms involved in drug interactions in cancer cells. Cytotoxicity and drugs interactions were studied in human HT29 colon cancer cells at both non-constant and constant ratios using the Chou and Talalay analysis based on the median-effect principle. In HT29 cells, the IC50s of ZD9331, 5-FU, SN38 and oxaliplatin were 1.3 10-8 M [range 0.7–2.3], 9.4 10-7 M [4.8–18.0], 5.6 10-9 M [3.2–9.8], and 1.1 10-6 M [0.8–1.6], respectively. The concomitant exposure to ZD9331 and SN38 (the active metabolite of CPT-11) yielded synergistic effects at low concentrations and additive effects at higher concentrations. Additive effects were observed with 5-FU but antagonism was seen with oxaliplatin. Preliminary results suggest that SN38 should be given prior to ZD9331. Our data support clinical trials combining ZD9931 with CPT-11, the prodrug of SN38, in patients with colon cancer.

1176 PUBLICATION

Single and multiple dose pharmacokinetics of letrozole (®Femara) in elderly and younger postmenopausal patients (pts) with advanced breast cancer

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A multicenter, open-label, non-randomized phase II trial was designed to compare single and multiple dose pharmacokinetic data of letrozole (2.5 mg, given orally once daily) in two age groups of postmenopausal women with advanced breast cancer: younger, aged 50–65 years (group A) and elderly, aged $\geq$70 years (group B). Pharmacokinetic profiles were collected after a single dose (dy 19) and at steady state (day 66). Sixteen pts were enrolled in group A (mean age 61 yrs, range 52–66) and 12 in group B (mean age 72, range 70–76).

Results: the mean Cmax (nmol/L ± SD) at day 1 and day 66 was 117 ± 45 and 423 ± 185 in group A and 111 ± 12 and 541 ± 319 in group B. The half-life (h ± SD) at day 1 and day 66 was 69 ± 33 and 111 ± 53 in group A

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