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