cross resistance with cisplatin and carboplatin. We conducted a phase I study to evaluate the MTD and DLT of the GMB and L-OHP combination.

Patients and Treatment: GMB was administered on days 1 and 8 as a 30 min IV infusion at escalating doses of 1000–1600 mg/m^2 and L-OHP on day 8 as a 2-hour IV infusion at doses of 60-110 mg/m^2. Cycles were repeated every 3 weeks without growth factors. Thirty nine patients with histologically confirmed advanced stage carcinomas have been entered into the study. Median age 65 (30–76), PS (WHO) 0:11, 1:20, 2:8. Treatment was 1st line for 12 (31%), 2nd line for 9 (22%) and 3rd line for 18 (46%) pts. DLT was evaluated during the first cycle of treatment and included any grade 4 hematologic toxicity, neutropenia grade 3–4 with fever, non-hematologic toxicity grade 3–4 and any treatment delay due to toxicity.

Results: So far 8 dosing levels have been evaluated with 3 or 6 pts at each level and the DLT level (at least 50% of pts develop DLT) has not yet been reached. The evaluated doses for GMB/L-OHP in mg/m^2 have been: 1000/60, 1200/70, 1200/80, 1400/80, 1400/90, 1600/90, 1600/100, 1600/110. All patients were evaluable for toxicity. A total of 131 cycles have been administered (median 3 cycles/pt), with 11 (8%) cycles complicated with grade 3/4 neutropenia, 4 (3%) grade 3 thrombocytopenia, 5 (4%) grade 3 asthenia and 8 (6%) edema. Seventeen cycles (13%) have been delayed due to toxicity. No febrile neutropenia, cumulative hematologic or non-hematologic toxicity or toxic deaths have occurred. Among 27 pts evaluable for response we observed 3 (11%) PR and 10 (37%) SD.

Conclusion: The combination of GMB and L-OHP is well tolerated with acceptable toxicity. Whilst the study is ongoing to determine the MTD, pharmacokinetic studies are also underway.

1164 POSTER

NCIC CTG IND 98: A phase I dose escalation study of raltitrexed (Tomudex) Plus doxorubicin (DOX) in patients with advanced cancer

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Rationale: Raltitrexed (TOM), is a quinazoline antifol with good single agent activity in a range of tumor types, including gastrointestinal and is thus an interesting compound to study in combination with DOX.

Methods: A dose ranging phase I study of TOM in combination with escalating doses of DOX was performed. Patients (pts) with evaluable recurrent or metastatic inoperable solid tumors with acceptable cardiac, hematologic, renal and hepatic function were eligible. The starting dose level of TOM was 2.5 mg/m^2 followed immediately by DOX 30 mg/m^2. DOX was escalated by 10 mg/m^2 increments up to 60 mg/m^2 and thereafter TOM escalated by 0.5 mg/m^2 increments up to 3.5 mg/m^2. Cycles were repeated every 3 weeks. Dose limiting toxicity included grade 4 hematologic and grade 3/4 non-hematologic toxicity.

Results: 22 pts were accrued to 6 dose levels (DL). Median age was 59 yrs (37–76); 12 pts were male; performance status was 0 (2 pts), 1 (13 pts), or 2 (7 pts); 20 pts had gastric cancer; no pts had received chemotherapy for metastatic diseases; the most common sites of disease were stomach (10 pts), liver (10 pts), ascites (8 pts) and regional nodes (8 pts). The 22 pts have received 99 cycles with 9 pts receiving 6 or more cycles. The most common drug related toxicities included alopecia (91%), nausea (68%), fatigue (59%), vomiting (50%), anorexia (46%), stomatitis (32%), altered taste (32%) and diarrhea (23%), usually grade 1 or 2 in severity. There appeared to be no excess of cardiotoxicity. At DL 6 (TOM 3.5 mg/2 and DOX 60 mg/m^2 1 pt had febrile neutropenia while 2 pts had grade 4 myelosuppression and this dose was declared the maximum tolerated dose (MTD). Interestingly, 3 durable (7–12.8 months duration) confirmed partial responses have been seen in 13 evaluable patients at the first 4 dose levels, all in pts with gastric cancer.

Conclusions: The recommended dose for further study is TOM 3 mg/m^2 plus DOX 60 mg/m^2.

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1165 POSTER

Gemcitabine and Docetaxel in patients with advanced solid tumors. A GETICS phase I trial

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Gemcitabine (G) and Docetaxel (D) have a broad spectrum of clinical activity. This phase I trial was designed to identify the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of G administered days 1 and 8 plus D day 8 every 3 weeks. A minimum of 3 patients (pts) were entered per dose level.

Thirty three pts were entered in seven dose levels (G/D): I: 800/50, II: 1000/50, III: 1000/75, IV: 1000/90, V: 1000/100, VI: 1250/75, VII: 1500/75.

Demographics: 17 M/16 F, median age 59 years (range 37–77), median ECOG PS 1, prior chemotherapy: 31 pts (prior paclitaxel 19 pts, >1 regimen 24 pts). Tumor types included: NSCLC (14), breast (10), ovary (3), bladder (2), sarcoma (1), parotid (1), germ cell (1), unknown primary (1).

G was given as a 30 min. infusion on days 1 and 8, and D was given as a 1 hour infusion on day 8. Cycles were repeated every 3 weeks. All pts received oral dexamethasone for 5 days starting on day 8. Colony stimulating factors were not allowed.

DLT was leucopenia at dose level IV and V, with higher doses of G Leucopenia and Thrombocytopenia were DLTs. Non-hematologic toxicities were <grade 3 and included: nausea, fatigue, anorexia, dermatitis, myalgia and peripheral neurotoxicity. Mild to moderate peripheral edema was found in seven pts and two of them required diuretics. The suppression of G on day 15 maybe was the cause of this lower toxicity profile. Antitumor activity was observed.

We conclude that G1000 plus D90 and G1250 plus D75 are feasible to perform in this heavily pretreated population and deserve further studies.

1166 POSTER

Clinical pharmacokinetic comparative crossover study between three times a day and once a day-oral administration of etoposide

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Purpose: Based on previous studies, an etoposide concentration of approximately 1 μg/ml appears to be effective, while peak plasma levels greater than 2–3 μg/ml are thought to be associated with more severe myelosuppression. Since the drug's interpatient and intrapatient variability is large with oral dosing there are some different items in pharmacokinetic studies in the literature. This is the first study with a crossover design, to neglect the individual differences in comparing the pharmacokinetic results of three times a day and once a day-oral administration of etoposide capsule.

Methods: Two groups of four patients each received 75-mg/day oral etoposide for two days as either 75-mg once daily, or 25-mg three times daily for two days. On days 8 and 9, each group received the other form of treatment. On days 2 and 9 blood samples were collected during 24 hours to measure plasma etoposide levels. The etoposide concentrations were determined by high-performance liquid chromatography in Nippon Kayaku Co. Laboratory, in Japan.

Results: There was no significant difference between Cmean (Cmean = area under the curve/24 hr) in two treatments and no relationship between the daily dose per body surface area and Cmean. In one dose schedule peak was greater than 2 μg/ml in five (62.5%) patients (95% CI 24.5-91.5) and greater than 3 μg/ml in three (37.5%) patients (95% CI 8.5-75.5).

No patient in three-dose schedule had higher than 2 μg/ml level ($p = 0.038$). No such difference in time the concentration exceeded 1 μg/ml was observed between the mean values of the two different dosing schedules.

Conclusion: As the interpatient variability was neglected by crossover method, based on these data, the results favor fractionating a daily 75-mg etoposide dose.

1167 POSTER

Oral ZD9331, a non-polyglutamated thymidylate synthase (TS) inhibitor: A phase I and pharmacologic study

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ZD9331 is a novel selective TS-inhibitor, which does not undergo polyglutamation and therefore, might overcome resistance to other polyglutamated drugs that arise due to alterations in FPGS expression. We are performing a phase I study on the oral formulation of ZD9331. To date, 31 patients (pts), 24 male and 7 female, median age 59 years, with colorectal (17 pts), (A) CUP (2 pts), renal ca (2 pts) or miscellaneous tumours (10 pts) have

received 99 courses of ZD9331 over 8 dose levels: 2.5, 5, 10, 20, 30 and 40 mg once daily for 5 days, 10 mg twice daily for 5 days and 10 mg once daily for 10 days, respectively, repeated every 3 weeks. One pt treated at 40 mg/day, 2 pts treated at 20 mg/day (bid), and 1 pt at 10 mg for 10 days developed grade 3–4 neutropenia and/or thrombocytopenia. Non-haematological toxicity was usually mild and included nausea/vomiting, stomatitis, diarrhea, myalgia/arthralgia, fever, and alopecia. Transient asymptomatic rises in liver transaminases occurred at all dose levels. Skin rash occurred in 23% of cycles. Pharmacokinetics (PK) demonstrated a saturable absorption of ZD 9331 from doses of 20 mg once daily onward, precluding further dose escalation. Twice daily dosing did not significantly increase exposure compared with a once-daily administration. PK analysis at the 10 mg × 10 days schedule is still on going. Preliminary plasma deoxyuridine data indicate that they can be used as a marker for TS-inhibition.

1168 POSTER

Phase I trial with farnesyltransferase inhibitor R115777 in patients (pts) with advanced solid tumors

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Purpose: The critical modification needed for the ras protein to exert its function is farnesylation, which can be blocked by R115777, a potent and selective orally bioavailable non-peptidomimetic inhibitor of farnesyltransferase. This study was designed to determine the MTD of a 28-day bid oral regimen.

Methods: R115777 is given according to an intra- and inter-pt dose-escalation scheme with 1–6 pts per dose level depending on toxicity. Each 28-day cycle (C) is followed by a 7–14 d restperiod. Starting dose was 200 mg bid, increased with 100 mg bid with a maximum of 2 intra-pt dose escalations. DLT was defined as grade 3–4 toxicity or treatment delay >3 wks.

Results: Sofar 7 pts have been treated, median age 58 yrs, all had received previous chemotherapy. One pt had grade 4 leucopenia at 300 mg bid in C1, and this cohort was expanded to 6 pts. One pt in this cohort had grade 4 leucopenia at 500 mg bid. At 300 mg bid one pt had grade 3 diarrhea in C2 and one pt grade 3 fatigue in C1, possibly related to R115777. One pt with gastric cancer has an ongoing SD for 8 months. PK of R115777 was assessed in C1 for the 1st 12 h dosing interval on day 1 and 28 and was measured by a validated HPLC method. Peak concentrations ranged from 431–800 ng/ml and were obtained within 2–5 h. Trough levels ranged from 29.3–98.7 ng/ml. There was little accumulation, and steady-state concentrations were maintained throughout the dosing period.

Conclusion: Recruitment continues to determine MTD and to confirm whether leucopenia is dose-limiting.

1169 POSTER

Phase I trial of a three-day schedule of cisplatin plus topotecan

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Purpose: Topotecan (tpt) is emerging as a new chemotherapy option in the treatment of lung and ovarian cancer. Preclinical data suggest a sequence dependent synergy of tpt with cisplatin but a clinically acceptable sequence-schedule of these two agents has yet to be defined. We conducted a phase I study of a convenient and logistically feasible daily ×3 schedule. By splitting the dose of cisplatin over three days we aimed to a more favourable toxicity profile and a possibly better pharmacological inter-reaction of the two agents. Main objectives were to define the maximum-tolerated dose (MTD) and dose limiting toxicity (DLT) and to characterise the toxicity profile of this regimen.

Methods: The standard for phase I entry criteria and definitions for MTD and DLT were applied. Both agents were administered intravenously on a daily ×3 basis every 3 or 4 weeks with or without G-CSF. Cisplatin was given first with hydration followed by topotecan two hours later. At present 18 patients (4 F/14 M, median age 58, range 30–72) have been treated and a total of 49 courses have been given at four dose-levels: cisplatin/tpt: 25/0.75 – 25/0.9 -25/1- 25/1.15 mg/m^2/day.

Results: Myelossupression was the DLT as expected. With cisplatin at 25 mg.m−2 daily dose the MTD of the combination was 25/1.15 at which 2/2 patients developed febrile neutropenia and grade 4 thrombocytopenia each one respectively. Febrile neutropenia also occurred in 1/6 patients at dose levels 25/0.9 and 25/1. Both were carboplatin-pretreated pts and succeeded to continue treatment with G-CSF support. At these levels a short-lived grade 2 or 3 neutropenia was seen in half of the patients and grade 3 thrombocytopenia was infrequently observed but tended to be cumulative in pretreated patients. Non-haematological toxicity was unremarkable. Efficacy was documented in 3 lung and 1 ovarian case.

Conclusion: A three-day schedule of the cisplatin plus topotecan combination is well tolerated with mainly haematological toxicity. With cisplatin at 25 mg.m−2 daily dose the MTD of the combination is 25/1.15 and the optimal 25/1. The study is in progress investigating the combination at 20 mg.m−2 fixed daily dose of cisplatin.

1170 POSTER

Phase I pharmacokinetic study of MEN-10755 in solid tumors

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Purpose: In a phase I and pharmacokinetic study the safety profile of MEN-10755 (MEN) was evaluated. MEN is a novel anthracycline showing in the animal models an improved therapeutic efficacy over doxorubicin, especially in breast, ovarian and lung cancer.

Patients & methods: Eligible patients (pts) had incurable cancer, performance status ECOG ≤ 2, no prior anthracyclines and LVEF ≥50%. MEN was administered as 15 min iv infusion once weekly for 3 weeks, followed by 1 week rest. Starting dose was 15 mg/m^2 per infusion and was escalated to 30 mg/m^2 and up to 45 mg/m^2 per infusion. Plasma and urinary MEN levels were measured by HPLC with fluorescent detection.

Results: Until now, 8 pts were entered. Anemia grade (gr) 1–3 occurred in 7 pts, anemia gr 4 in 1 pt at 30 mg/m^2, thrombocytopenia gr 1 in 1 pt at 30 mg/m^2. Two pts had leukopenia gr 1 at 30 mg/m^2. At 45 mg/m^2, in 2 pts the third infusion day 15 was omitted because of ANC ≤1000/mm^3. These pts also had leukopenia gr 3. Nausea/vomiting gr 1–2 occurred in 4 pts, gr 3 in 1 pt at 45 mg/m^2. During infusion 2 pts had flushing gr 2. Most pts experienced alopecia gr 1. No significant LVEF reduction has been observed. AUC was correlated with dose. Mean $AUC_{0\rightarrow\infty}$ for 30 mg/m^2 = 6.0 mg/L.h. Mean values (all doses) were: $t_{\frac{1}{2}\beta}$ = 15.2 ± 3.6 h, CL = 5.6 ± 0.9 L/h/m^2, Vss = 81.2 ± 23.5 L/m^2. Mean renal clearance was 4.4 ± 2.1%.

Conclusion: Neutropenia day 15 was dose limiting at 45 mg/m^2/infusion. Currently 40 mg/m^2/infusion is evaluated.

1171 POSTER

Pharmacology study of chronic oral idarubicin for breast cancer

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Purpose: To investigate new modalities of IDA administration, we designed a phase I study of IDA given orally in hyperfractionated doses. The purpose was to determine the maximum-tolerated dose (MTD), toxicity profile, and pharmacokinetics of IDA with this schedule.

Methods: Patients with metastatic breast cancer relapsed after standard therapy (including anthracyclines). The initial dose of IDA was 2 mg/d given orally in two doses every 12 hrs for 21 days every 28 days. Subsequent dose escalations were in increments of 1 mg/day. Dose limiting toxicity (DLT) was defined as G4 hematologic toxicity or any other toxicity ≥G3. Pharmacokinetic parameters were calculated using a noncompartmental model.

Results: Thirty-one patients were enrolled. IDA was escalated from 2 mg/d to 10 mg/d and MTD was reached at this dose level; DLTs were neutropenia (G4) associated with leukopenia and piastrinopenia in 1 patient and diarrhea (G3, 1 patient) out of 5 patients. Both IDOL and IDA exhibited linear pharmacokinetics over the dose range studied. The median $AUC_{(0-24)}$ of IDA increased from 3.95 μg*h/L (range, <2.4 to 6.9 μg*h/L) to 15.2 μg*h/L (range, 14.2 to 18.4 μg*h/L) when the dose was increased from 2 to 10 mg/d. The median $t_{1/2}$ for IDA was 21.2 hours (range, 11.3 to 49.7 hours), whereas $t_{1/2}$ for IDOL was much longer (median, 50.0 hours; range, 22.7 to 85.3 hours). IDA/IDOL ratio in plasma (median, 8.3; range, 5.4 to 16.5) was not dose-dependent.