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