partial response was demonstrated after 6 cycles of OGT 719 at 250 mg/m^2 on days 1 to 5 (renal cell carcinoma with liver metastases). Two patients had stable disease after 6 cycles of OGT 719 at 1000 mg/m^2 on days 1, 3 and 5 (metastatic adenocarcinoma) and 1750 mg/m^2 on days 1 to 5 (melanoma with lung metastases). Pharmacokinetic data show no accumulation with daily dosing and dose linearity for AUC and Cmax up to 10000 mg/m^2 is apparent.

Conclusions: These data indicate that OGT 719 has predictable pharmacokinetics with more variability at the higher doses. Structural modification of 5-FU with a carbohydrate ligand significantly affects potency on a mg/m^2 basis.

1155 POSTER

Phase I and pharmacokinetic study of BBR 2778

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BBR 2778, a novel anthracenedione, induces DNA intercalation and inhibition of the topoisomerase-II enzyme. In this study BBR 2778 was given as a 1 h intravenous infusion weekly for 3 weeks (w) every 4 w. The aims were (1) to study the pharmacokinetics (PKs), (2) to determine the maximum tolerated dose (MTD), (3) to define dose-limiting toxicities (DLT), and (4) to recommend a dose for phase II studies. Dose escalation proceed according to the following weekly dose-levels (mg/m^2): 5 (4 pts, 9 cycles), 10 (3 pts, 3 cycles), 16.5 (3 pts, 5 cycles) 25 (6 pts, 9 cycles), 37.5 (1 pt, 1 cycle), 75 (4 pts, 5 cycles), 112.5 (6 pts, 10 cycles), 150 (3 pts, 4 cycles). Plasma PKs followed a multiexponential profile with a rapid distribution phase followed by a prolonged elimination phase. BBR 2778 had a large volume of distribution and was efficiently cleared from the plasma compartment. DLT was neutropenia. Other toxicities were mild to moderate including lymphopenia, thrombocytopenia, alopecia, and moderate nausea/vomiting. No cardiac toxicity was reported. The MTD was 150 mg/m^2/w for 3w, q4w (2/3 DLT) and the recommended dose for phase II studies was 112.5 mg/m^2/w for 3w, q4w.

1156 POSTER

Biweekly docetaxel (DOC), gemcitabine (GEM), oxaliplatin (LOHP) in heavily pretreated patients with solid tumors – Preliminary results of a phase I study

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Purpose: In vitro data suggests a schedule-dependend synergistic antineoplastic activity of Doc/Gem/LOHP. To evaluate the toxicity of this novel triple combination, a pilot trial with 10 pts with refractory tumors was conducted with a biweekly application of this combination. Protocol (dose-level 0): Doc 35 mg/m^2 1 hr-infusion d1 (with standard premedication), followed after 1 hr rest by Gem 800 mg/m^2 30 min-infusion, followed by LOHP 65 mg/m^2 2 hrs infusion on d2; q d15 until progression. Based on the results of this 10 pts, a dose-escalation study was initiated. At time of this interim analysis 17 pts are evaluable for toxicity, 13 for response.

Patient characteristics: 12 male/5 female, median age 58 yrs, median ECOG-Status 1, median prior chemotherapies 2. Type of treated tumors: Squamous cell carcinoma of head and neck (10 pts), sarcoma (2 pts), CUP, gastric cancer, adrenal-, nasopharyngeal- and ovarial-carcinoma 1 pt.

Results: Toxicity (CTC-NCI-criteria): To date, 90 cycles are evaluable, median 5 cycles/pt (range: 3–10). Diarrhea II°: 1 pt, mucositis II° 1 pt, nausea/vomiting I/II° 4 pts, neurotoxicity I° 3 pt, IV° 1 pt (this patient has received 10 applications), no hematologic toxicity >2°; alopecia II° 5 pts, no other toxicity occurred.

Response: 3 (23%) objective remissions (sarcoma, head and neck, CUP) were seen. 8 pts (62%) showed disease stabilisation, 4 of them with clinical benefit (decrease of clinical symptoms or tumor markers). 2 pts (15%) progressed under therapy.

Conclusion: The application of Doc/Gem/LOHP is feasible in an outpatient setting and shows promising activity. One pt was taken of study due to neurotoxicity IV° after 10 applications. The patient cohort of this dose level was escalated to 6 pts. No further neurotoxity >II° occurred in this cohort in pts with a nearly similar number of applications. Dose-escalation continues further. Updated results of the dose-escalation study will be presented at the meeting in September 1999.

1157 POSTER

Escalated dose docetaxel (TXT) with G-CSF support in patients (PTS) with solid tumours

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Patients received TXT with G-CSF (lenograstim) support in a phase I dose escalation study, aiming to reduce dose limiting toxicities (DLTs) of neutropenia and sepsis. A 3 day steroid prophylaxis was given and pts received G-CSF 5 (ug/kg/d sc) from day 2 until neutrophils >1 × 10 9/l. 35 pts with various solid tumours were entered. Median age was 59 yrs (29–76) and 16 pts had previously received chemotherapy. TXT dosing was escalated by 10 mg/m^2 for cohorts of 3–6 pts, commencing at 110 mg/m^2 q21 days. At TXT170 mg/m^2, 2/3 pts experienced DLTs: grade III neuropathy and grade III skin toxicity respectively. Only two pts had DLTs at lower dose levels (130 mg/m^2). Twelve pts have now been treated at the recommended dose of 160 mg/m^2 without DLTs. The median neutrophil nadir occurred prior to day 8 with day 8 being the median day of cessation of lenograstim. Grade IV neutropenia was observed in 10/29 pts (35%). Only 3 pts developed febrile neutropenia which was not prolonged. Mobilisation of progenitor cells has been examined during cycle one for patients at all dose levels. Median CD34+ cell levels rose to 2.2 × 10 6/l on day 8 and 60% of pts had peak levels >1 × 10 6/l. A Phase II trial of TXT 160 mg/m^2 and lenograstim is currently being undertaken of pts with breast cancer who have not previously received chemotherapy for advanced disease.

1158 POSTER

A dose finding and pharmacokinetic study of docetaxel (TXT) and methotrexate (MTX) in patients with epithelial cancer

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TXT and MTX, very active drugs in epithelial cancer, were associated and evaluated in a phase I study. TXT was given on day 8 as 1 hour infusion with dose escalation and MTX on d1 and 8 at fixed dose (40 mg/m^2). DLT was defined as NCI-CTC >2 toxicity, vomiting, diarrhea and stomatitis gr. >3 or a prolonged (>7 d) or febrile gr. 4 neutropenia (FN). 28 pts have been treated. Pts characteristics are: median age 55 [44–71], 5 females/23 males, PS 0:8 pts, 1:15 pts, 2:5 pts, tumor type: urothelial: 12, head and neck: 12, lung: 3, cervix: 1. All 28 patients are evaluable for toxicity. PK data were analyzed using NONEM, according to a 3 compartment model for both drugs. Co-variables were mainly age, body weight and surface area, sex, renal and hepatic parameters, α 1-acid glycoprotein. Major DLTs on cycle 1 were: FN (4), thrombocytopenia (3), cytolysis (3), stomatitis (2). Combination of TXT and MTX is feasible without severe toxicity and has notable activity. Adjunction of cisplatinum will be evaluated in a new phase I study

Dose Level		Toxicities (Nb of pts)		Obj.	PK Data (mg l^{-1}·h)	
TXT mg/m^2	MTX mg/m^2	Entered/ Evaluable	with cy 1 DLT	Resp.	AUC TXT 16 pts/28	AUC MTX 19 pts/28
60	40	3/3	0	1/3	2.32 ± 0.34	7.54 ± 1.71
70	40	6/6	0	1/6	3.48 ± 1.19	7.59 ± 1.63
80	40	7/6	2	2/7	4.27 ± 1.47	7.37 ± 1.97
90	40	6/6	3	1/6	4.59 ± 1.07	7.97 ± 1.44
100	40	6/6	2	–	–	–

1159 POSTER

Phase I trial and pharmacokinetic (PK) study of S16020 according to a weekly and every 2 week (W) schedule in cancer patients (PT)

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In a previous phase I study carried out with the new Olivacine derivative S16020 according to a single dose schedule (1 or 3 hour infusion) every