a model-independent analysis from 13 pts-15 cy, showed a high increase in systemic exposure to CPT-11 (≈ 80–100%) and SN-38 (≈ 180–300%) in pts with liver dysfunction, even for slight hyperbilirubinemia as observed in gr B and could explain DLTs observed in gr C at 240 mg/m^2 as well as in gr B. Intermediate dose level for gr C (200 mg/m^2) and a new gr of pts with Tbili >3.0 NL with 100 rag/m^2 starting dose are now investigated (1 pt already included in each gr). Updated clinical and PK results will be presented.

1139 ORAL

Phase I and pharmacokinetic (PK) study of troxacitabine (b-L-dioxolan-cytidine;BCH-4556) on a daily × 5 day every 4-week schedule

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Purpose: Troxacitabine, the first of a new class of dioxolane analogs, has broad activity against solid tumors in preclinical studies. Troxacitabine is resistant to cytidine deaminase. The objectives of this study are to define the toxicities and MTD for troxacitabine given as a 30 min infusion daily × 5 days

Methods: 30 patients have received 76 courses. At 1.2 mg/m^2/day, delayed marrow recovery required a change in dosing interval to every 4 weeks. At 1.5 mg/m^2/day, DLT consisting of grade 4 neutropenia + fever was observed in 2 heavily pretreated patients (heavily pretreated = >6 prior cx of alkylators; Xrt to pelvis or >25% marrow; >2 cycles mitomycin C), Dose escalation was then stratified for both minimally and heavily pretreated pts. Heavily pretreated and minimally pretreated pts are currently accruing at the 1.2 and 1.8 mg/m^2/d dose levels, respectively. A patient with metastatic melanoma had a PR.

The PKs appear linear and fit a 3-compartment model. The fractionary urinary excretion (0–24 hr) of parent compound is 66 ± 22% and clearance is slow (mean clearance, 129 ± 44 ml/min/m^2).

Conclusion: The recommended doses for heavily and minimally pretreated pts are projected to be 1.2 and 1.5–1.8 mg/m^2/day, respectively. The PK profiles of troxacitabine are clearly distinctive relative to other nucleoside analogs.

1140 ORAL

NCIC CTG IND 103: A Phase I and pharmacokinetic (PK) study of the novel L-nucleoside analog troxacitabine (BCH-4556) given every 21 days

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Aims: Troxacitabine is a dioxolane L-nucleoside analog with broad cytotoxic activity in preclinical models. This study sought to define the safety and PK profile of troxacitabine given as a single 30-minute infusion every 3 weeks.

Methods: Starting dose was 0.025 mg/m^2. Doses were doubled until grade 1 or 2 toxicity seen; thereafter a modified Fibonacci schema was used up to the maximum tolerated dose (MTD) at dose level (DL) 13 (12.5 mg/m^2).

Results: 42 patients (pts) who had had no more than 2 prior chemotherapy (CT) regimens and with acceptable organ and marrow function were entered to 13 DL,s and received 120 cycles of troxacitabine. Median age was 52 yrs (34–75 yrs); 31 pts were male; performance status was 0 (13 pts), 1 (22 pts), or 2 (7 pts); the most common tumor types were renal cell (11 pts), colon (4 pts), rectal (3 pts) and head and neck (3 pts); the most common sites of disease were lung (24 pts), nodes (23 pts) and liver (12 pts); 25 pts had had prior CT and 21 pts prior radiation therapy. 20 pts were treated at 3.2 mg/m^2 without dose limiting toxicity (DLT); 3 pts received 8 mg/m^2 (1 DLT – gr 3 rash); 6 pts received 6.4 mg/m^2 (1 DLT – neutropenia); 3 pts received 8 mg/m^2; 7 pts received 10 mg/m^2 (2 DLT,s- rash); and 3 pts received 12.5 mg/m^2 (2 DLT,s – neutropenia). Hand-foot syndrome was reported in 2 pts. Rash was ameliorated by the introduction of prophylactic steroids in DL12. The most common toxicities reported were rash (43%), fatigue (29%), nausea (19%), grade 3/4 granulocytopenia (19%) and dry skin (14%). 1 pt with renal cell carcinoma achieved a confirmed partial response, and 13 patients had stable disease with median duration of 4.4 months (range 2.2–11.9 mths). PK,s were linear and at 10 mg/m^2 AUC was 1886 ng*h/ml; Cmax 882 ng/ml; clearance 159 mL/min, and T1/2 12 hrs.

Conclusions: The MTD of troxacitabine when given in this schedule is 12.5 mg/m^2 and the recommended doses for further study 10 mg/m^2. The DLT is granulocytopenia when prophylactic steroids are used.

1141 ORAL

Phase I studies with antimetabolites (A-M): Should dose escalation be driven by considerations other than body surface area (BSA)?

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Aim: The clinical development of A-Ms often seems confounded by the occurrence of dose limiting toxicities (DLT) at doses well below those ultimately recommended (RD) for further study, necessitating frequent expansion of dose levels and usually a change to more conservative dose escalation. This not only slows development but exposes more patients to ineffective doses of the drug, and raises questions about current methodology of including a single patient per dose level. Christian et al described results from the NCI phase I database showing first DLT occurred at 80% of the maximum tolerated dose (MTD).

Methods: Starting dose, number of dose levels, dose at first DLT, MTD and RD was extracted from the NCI-Canada phase I trial database, and from a literature survey of phase I studies published between 1991–1998. Combination phase I studies were excluded.

Results: 11 trials with A-M and 18 with other cytotoxic agents were reviewed. The median dose at first DLT/MTD was 44% ± 0.21 for A-Ms and 76% ± 0.20 for other cytotoxic agents ($p < 0.05$). Patients included in phase I trials are strictly controlled for adequate liver, renal and bone marrow function and dose is guided by BSA. Not controlled are gender, lean body mass, age, subclinical differences in renal or liver function, prior exposure to chemotherapy agents (usually), nutritional status nor pharmacodynamic aspects for e.g. intracellular polyglutamation.

Conclusions: For A-Ms toxicity appears to be incompletely predicted by dose alone. DLT may occur in certain patients at doses well below RD. Current phase I design may not be ideal for development of this class of compound.

1142 POSTER DISCUSSION

Phase I study of BMS-184476, a new taxane analog, given weekly in patients with advanced malignancies

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BMS-184476 is a new taxane analog with superior activity in a number of experimental tumor models and has a much reduced purified polyoxyethylated castor oil content as compared to paclitaxel. The main objectives of this study were to establish the maximum tolerated dose (MTD), the dose-limiting toxicities (DLTs), and the pharmacokinetics of BMS-184476 given weekly on day (d) 1, 8 and 15 by a 1-hour infusion in patients (pts) with advanced malignancies. Courses (crs) were repeated every 28 d. No pre-medication was given. An accelerated Phase I design using single pt cohorts, rapid (100%) dose escalation and intra-patient dose escalation (IPDE) was used. When pre-defined toxicity was observed, a standard Phase I design (3–6 pts cohort) with IPDE was to be used. 36 pts (9 breast, 8 NSCLC, 4 colon, 2 sarcomas, 2 ovary, 2 SCLC, 9 others) -14 males and 21 females- with a median age of 55 years (range: 32–72) and a median performance status of 1 (range: 0–2) were enrolled. All pts but 2 had received prior chemotherapy (median 2, range 1–5 regimens). Dosing/toxicity data is available for 22 patients. No drug-related severe toxicity was reported at 7, 14 and 28 mg/m^2 in 1, 2 and 8 pts respectively. At 40 mg/m^2, 1/14 pt developed a DLT (Grade (Gr) III diarrhea) and GrIII neutropenia with fever. At 50 mg/m^2, no DLT were observed in 4 pts. At 60 mg/m^2, 1/1 pt developed a GrIV febrile neutropenia and GrIII diarrhea (DLT). Additional non-hematological drug-related toxicities reported include GrII diarrhea (6 pts), GrII asthenia (6 pts), GrII nausea/vomiting (6 pts), GrII arthralgia/myalgia (5 pts), GrII anorexia (4 pts), GrII peripheral neuropathy (2 pts), and GrII mucositis (2 pts). No hypersensitivity reaction was reported. Activity has been documented in patients with breast cancer, NSCLC and colon cancer. MTD has not been reached and the study is enrolling patients at 60 mg/m^2.