644

COMBINATION OF HYPERTHERMIA (HT) AND CHEMOTHERAPY (CT) FOR HEPATIC TUMORS (HT) A PHASE I STUDY.

A.Tsamas,M.diPalma,R.Adam,M.Ionescu-Goga,M.Nagi,M.Rotarski,J.Sidi,J.M.Vannetzel,H. Bismuth,C.Jasmin. SMST HT U. and Hep. Bil Surg.-Liver Transplant. U. Hôp. Paul-Brousse-Villejuif-France.

In order to assess feasability and usefulness of HT in hT 9 patients (pts) with primary (3) or metastatic disease (6) were treated by HT and CT. All heavily pretreated with polyCT; Karnofsky Index > 70 and good hepatic function (Child A or B). All gave informed consent. HT was performed using an electromagnetic external capacitive device (Jasmin 3 x1000-Bruker-France). 1 hour HT sessions (S) were given on day (D) 1,3 and 5 of 5D cycle (C) repeated after 2 or 3 weeks rest, for a total of 101 S (3 to 18, med. : 12). Various CT were associated depending on pts background, given daily on D1 to D5. For each pts 2-4 close ended catheters (KT) were inserted percutaneously into liver (L) under local anesthesia with echographic control allowing monitoring temperatures (θ) in hT, normal L surrounding hT and subcutaneous fat by an optic fiber system (Luxtron-USA). Table 1 shows it was possible to reach high θ levels in hT (mean 41,15;med 41,2;range38,1-44,5) without change for normal L nor general θ. There was no procedure related morbidity Tolerance was good no change in hepatic function. The current phase I faisability study with good tolerance and differential θ distribution in hT and normal L allows further studies. T max :

T	Norm.L	δ θ	T	Norm.L	δ θ	T	Norm.L	δ θ
39	37	2	38,3	37	1,3	44,5	37	7,5
38,1	37,1	1	43,9	37,3	6,6	39,3	37	2,3
44	37	7	41,2	38	3,2	42,1	38	4,2

645

PHASE I STUDIES OF GEMCITABINE (G). Fossella FV, Abbruzzese J, Pang A, Gravel D, Tarassoff P*, Lippman S, Raber M, Hong WK. University of Texas MD Anderson Cancer Center, Houston, TX; *Eli Lilly Co., Indianapolis, IN. USA

Gemcitabine, a novel pyrimidine analogue, has activity in a wide range of solid tumors. In 2 phase I trials we studied different approaches to dose escalation of iv G given weekly X 3 wks Q 4 wks. STUDY 1: G dose was escalated and given over a fixed time of 30 mins. 22 chemo-naive pts with advanced non-small cell lung cancer (NSCLC) received G at 1000 to 1750 mg/m²/wk/30 mins. 4/21 pts (19%) had partial response (PR) and these responses were seen at all dose levels. At 1750 mg/m²/wk/30 mins (6 pts), dose-limiting toxicity (DLT) is reversible hepatotoxicity (reversible rises in transaminase values) (HT) and myelosuppression (MS): grade 4 neutropenia (NP) in 1 pt, gr 3 platelets (TP) in 1 pt, and gr 3 HT in 2 pts. STUDY 2: Based on pharmacologic data showing that infusion at 10 mg/m²/min results in maximum intracellular accumulation of difluorodeoxycytidine triphosphate, G dose was escalated while also increasing the infusion duration such that the infusion rate was constant at 10 mg/m²/min. 21 solid tumor pts (14 with prior chemo) received G at 1200 mg/m²/wk/120 mins to 2800 mg/m²/wk/280 mins. 2/8 pts (25%) with pancreatic cancer and 1 with cholangiocarcinoma had PR. DLT is MS. At 2250 mg/m²/wk/225 mins (5 pts), we saw gr 4 NP in 2 pts and gr 3 TP in 2 pts; at 2800 mg/m²/wk/280 mins (2 pts), we saw gr 4 NP in 2 pts and gr 3 TP in 1 pt. CONCLUSIONS: G has activity against pancreatic cancer and NSCLC. As a 30-min infusion, 1750 mg/m²/wk in chemo-naive pts is nearing maximum tolerated dose (MTD); DLT is HT and MS. By prolonged infusion, 2250 mg/m²/wk/225 mins is MTD; DLT is MS but not HT.

646

PHASE I STUDY ON 4-WEEKLY 6 HOUR INFUSION OF BMY-25067 IN PATIENTS (PTS) WITH SOLID TUMORS.

Verweij J., Planting A., van der Burg M., Stoter G., de Boer-Dennert M., Dewji R., Santabarbara P., Kolkers H and Schellens J..
Rotterdam Cancer Institute, P.O. Box 5201, 3008 AE Rotterdam, The Netherlands.

BMY-25067 is a semi-synthetic analog of mitomycin-C created by substitution of the aminogroup on C6 by a nitrophenyl disulfide radical. In vitro and in murine tumors BMY-25067 was active in a wide variety of tumors. Preclinical toxicology showed myelosuppression and proteinuria as well as dose-related cardiac-toxicity in rats. The LD_{10} in mice was 25 mg/m², while in toxicology studies the dog was more susceptible. For this reason the starting dose for the first phase I study was 1/30 of the mouse LD_{10}. We are performing a phase I study with BMY-25067 given as a 6-hours i.v infusion once every 4 weeks. Because another phase I study, applying a bolus schedule, was initiated before, starting dose and dose-escalation steps in our study were partly based on the already available clinical information from that study.
At least 3 patients (pts) with 4 evaluable courses were observed, before any dose-escalation was made. Thirteen pts, 10 males and 3 females, median age 59 years (range 36-73), median WHO performance score 1 (range 0-2), entered the study. Six pts had colorectal cancer, 3 had CUP and 4 miscellaneous tumor types. All pts had had prior chemotherapy. The starting dose was 3.2 mg/m², which was escalated subsequently to 6.4, 11.5, and 19 mg/m² in at least 3 patients each. A total of 20 treatment cycles are evaluable. Major toxicity did not yet occur, observed side effects are mild stomatitis, nausea and phlebitis each in 1 course only.
Pharmacokinetics (HPLC method) in 2 pts revealed a $t^{1}/_{2}\beta$ of 12 and 18 h. and a total plasma clearance of 60 and 150 ml/min. Objective responses were not yet observed. The MTD of BMY-25067 at this schedule is not reached at 19 mg/m².

647

PHASE I TRIAL OF BUTHIONINE SULFOXIMINE (BSO) IN COMBINATION WITH MELPHALAN

PJ O'Dwyer, TC Hamilton, FP LaCreta, D Kilpatrick, JM Brennan, RC Young, RL Comis, RF Ozols
Fox Chase Cancer Center, Philadelphia, PA 19111 USA.

Resistance to alkylating agents and platinum compounds is associated with elevated levels of glutathione (GSH). Depletion of GSH by BSO restores the sensitivity of resistant tumors to melphalan *in vitro* and *in vivo*. In a Phase I trial each patient receives two cycles: BSO alone i.v. q12h x 6 doses, and one week later the same BSO as cycle 1 with melphalan 15 mg/m² i.v. 1h after the fifth dose. BSO doses have been escalated from 1.5 to 17 g/m² in 34 pts. The only toxicity attributable to BSO is grade I or II nausea/vomiting in 50%. Dose-related neutropenia required a melphalan dose reduction to 10 mg/m² at BSO 7.5 g/m². Peripheral mononuclear cell GSH nadirs were about 10% of control from 7.5 g/m²; at 13 and 17 g/m² all patients had nadir values in this range. In sequential tumor biopsies findings were similar. The pharmacokinetics of the active S-BSO diastereoisomer were linear over the dose range 5 to 10.5 g/m². The terminal half life was 1.78 ± 0.39 hours (SD), Cl_{tot} 143 ml/min of which 64% was renal, and the V_{ss} 17.0 ± 6.9 liters. Disposition of the BSO isomers was stereoselective, most strikingly in non-renal clearance. The Phase II dose will be based on further tumor biopsy sampling for biochemical endpoints.

648

CLINICAL EXPERIENCE WITH TEGAFUR AND LOW DOSE ORAL LEUCOVORIN: A PHASE I STUDY.

Noguè M., Saigi E. and Segui M.A.
Medical Oncology Unit. Hospital de Sabadell.

Background : Oral protracted administration of Tegafur (FT) and Leucovorin (LV) is an attractive schedule of modulation that pretends to simulate a 5-Fluorouracil and LV continuous infusion with the advantages of outpatient administration. A dose finding study was performed involving FT and LV.

Patients and methods : 33 patients with advanced adenocarcinoma (19 M, 14 F, median age 57.3) were included. The treatment consists of FT, 0.75 gr/m²/day, for 21 days, with oral continuous LV at different dose levels: 15, 30, 45, 60 and 90 mg/day in a 28 day cycles.

Results : A correlation between the LV dose and an increase of grade III/IV toxicity (diarrhea, oral mucositis and fatigue) was established in the non linear regression model, reaching a plateau at 60 mg/day of LV.

LV dose (mg)	Patients/ cycles	Grade III/IV toxicity (episodes) Fatigue	Mucositis	Diarrhea	Patients with toxicity (%)
15	7/21	-	1	2	2/7 (28.5)
30	6/20	1	2	1	2/6 (33.3)
45	6/13	1	1	2	3/6 (50)
60	7/14	-	2	4	5/7 (71.4)
90	7/11	1	2	2	5/7 (71.4)

Conclusions : With this schedule it is possible to obtain a modulation of 5-FU, with a dose-dependent toxicity . For the FT dose used, recomended dose of LV is in the range of 45-60 mg/day.

649

INTRAPERITONEAL (I.P.) INFUSION OF TUMOR NECROSIS FACTOR (TNF) AND MITOXANTRONE IN PATIENTS WITH NEOPLASTIC ASCITES: A PHASE I STUDY.

Garrone O, Addamo G, Oliva C, Carnino F, Conte PF, Del Mastro L, Galletti P, Vigani A, Russo P, Venturini M, Rosso R.
Dept. Medical Oncology Genoa IST, Dept. Med Oncol Pisa, La Spezia, Torino, Knoll Italia.

Our previous laboratory study on ovary carcinoma cell lines demonstrated an increase of cytotoxic activity between TNF (Knoll Italia) and some Topoisomerase II inhibitors, such as Mitoxantrone (Mito) (Gynecol Oncol 1991). On this basis, a phase I study in pretreated patients (pts) with neoplastic ascites or peritoneal carcinosis has been started. Treatment plan provided simultaneous administration of TNF plus Mito by weekly i.p. infusion for at least 4 cycles. Mito has been administered at 6 mg/m² fixed dose, while TNF dosage has been progressively increased by cohort of pts: 0.060, 0.110, 0.160, 0.200, 0.240 mg/m². Pts received premedication with Paracetamol 500 mg os t.i.d. Six pts entered the 1st cohort: main toxicities were nausea and vomiting (N-V) gI 1 pt; fever gII 2 pts; chills gII 2 pts; abdominal pain gII 1 pt; anemia gII 2 pts; fatigue and malaise gIII 1 pt. In the 2nd cohort 3 pts were treated: N-V gIII 1 pt; chills gII 2 pts; abdominal pain gII 1 pt; anemia gII 1 pt; platelet increase 1 pt. Three pts entered the 3rd cohort: N-V gII 2 pts; fever gI 1 pt; chills gI 1 pt; fatigue gII 1 pt; pain at injection site gII 1 pt; progressive platelet increase 1 pt. One pt entered the 4th cohort, and he is still on therapy. An ascites decrease was observed in 5 out of 12 evaluable pts: 2 CR, 3 PR. Since Maximum Tolerated Dose has not been reached, the study is ongoing.

Partially supported by AIRC.