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PHASE I TRIAL AND PHARMACOKINETIC STUDY OF A NEW ORALLY ADMINISTERED PLATINUM ANTICANCER DRUG JM 216

[AF-*bis*(acetato)-B-ammine-CD-dichloro-E-cyclohexylamine platinum(IV)].
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JM 216 was developed as an orally available platinum anticancer drug with good bioavailability, low emetogenicity and equivalent antitumour activity to carboplatin. A phase I trial began at the Royal Marsden Hospital in Aug 1992 using a single dose every 3 week schedule, escalating from 60-540 mg/m^2. A total of 20 patients have been treated with a wide variety of tumour types, median age: 53 yr, median PS: 1. Without prophylactic antiemetics nausea and vomiting, median CTC grade 1, occurred in 25/47 courses and diarrhoea, median CTC grade 1, in 15/47 courses. Vomiting responded well to antiemetics and was significantly less severe and frequent with prior antiemetics. No neuro-, oto- or nephrotoxicity has been observed. Myelosuppression has so far been limited to 1 episode of grade 1 thrombocytopenia at 200 mg/m^2. A sustained partial response occurred in a patient with recurrent ovarian cancer treated at 120 mg/m^2. Median time to maximum ultrafilterable (free) platinum (Pt) plasma concentration was 1-2 h. Mean free Pt AUC values were:- 60 mg/m^2: 390 (± 120)ng/ml.h; 120 mg/m^2: 614 (± 397)ng/ml.h; 200 mg/m^2: 648 (± 256)ng/ml.h; 300 mg/m^2: 743 (± 208)ng/ml.h. In view of the limited increase in absorption with increased dose above 200 mg/m^2, a daily x 5 every 3 week schedule will now be investigated at a starting dose of 30 mg/m^2/day.

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NOVEL SCHEDULE FOR ADMINISTRATION OF TOPOTECAN (TPT): 21 DAY LOW DOSE CONTINUOUS INFUSION (CI).

Hochster H, Speyer J, Oratz R, Meyers M, Wernz J, Chachoua A, Raphael B, Lee R, Sorich J, Taubes B, Liebes L, Fry D, Blum R. NYU Med Ct, NY, NY 10016.

TPT is a water soluble analog of camptothecin (CPT) which functions by inhibition of topoisomerase-1. Our previous studies showed elevated topo-1 levels in colon cancer and curability of human xenografts by prolonged administration of CPT analogs. To replicate this pharmacology we performed a Phase I study of CI TPT beginning at a dose of 0.2mg/m^2 x 7 d and escalating the time duration to 21 d, q 28 d. After reaching a 21 d CI without toxicity, we further escalated dosage groups to 0.3, 0.4, 0.53 and 0.7mg/m^2/d. 41 pts were entered for >1500 pt days of CI. Minor toxicities include mild fatigue and alopecia, seen only at higher doses. Dose limiting toxicity is leukopenia and thrombocytopenia; 2 Grade 3 at 0.53 and 2 of 3 Grade 4 at 0.7. All pts have been heavily pretreated with at least 2 chemotherapy regimens and 11/41 have had prior radiation. Activity has been seen: 3 PRs (breast, NSCLC, ovary) and 2 minor responses (breast, ovary). Dose intensity exceeds the conventional dx5 schedule by 50%. This schedule is well tolerated and active in these heavily pretreated pts.

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A PHASE I PHARMACOKINETIC TRIAL OF ZILASCORB(2H) IN PATIENTS WITH ADVANCED MALIGNANCIES

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Zilascorb(2H), (5,6-benzylidene-d$_1$-ascorbic acid), has shown antitumour activety in human cell lines and in human xenografts. A previous phase I study showed the bioavailability of zilascorb(2H) 250 mg capsules to be 56±13% (mean±SD). The capsules were tolerated well and one patient with ca recti had a partial remission and is still on treatment after 14 months+ (Aamdal et.al, ESMO symp. 1992).
In this trial 13 patients were entered to determine the bioavailability and toxicity of zilascorb(2H) 500 mg tablets. The intravenous (iv) and oral doses were 2.8g x 1 and 3.0g x 2 respectively. The bioavailability of the tablets was 32±12% which was lower compared to the capsules. This may be explained by a shorter dissolution time of the tablets and increased zilascorb(2H) hydrolysis in the stomach. In 3 patients the plasma steady state level increased 34%, range 26-47%, after concomitant administration of ranitidine. This suggested increased bioavailability of zilascorb(2H) possibly due to reduced hydrolysis in the stomach. No bonemarrow-, nephro-, neuro-, or gastrointestinal toxicity was reported. Two patients reported febrile reactions, grade II-III, probably related to treatment. Otherwise zilascorb(2H) treatment was tolerated well.

Preliminary pharmacokinetic parameters, mean±SD, n=7-13

	Bioavail. (%)	t1/2-α (hr)	t1/2-β (hr)	Tmax (hr)	Excreted zil *	Excreted hip *
iv	100±0	1.0±0.3	57±16	-	78±12	21±26
oral	32±12	1.6±1.2	115±70	1.1±0.5	26±12	33±21

** % of dose excreted in the urine as zilascorb(2H) and as hippuric acid (metabolite)*

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A PHASE I AND PHARMACOKINETIC TRIAL OF KW-2149, A MITOMYCIN C ANALOGUE,IN PATIENTS WITH SOLID TUMOURS.

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KW-2149 is a new, water soluble MMC analogue with a C-7-N substituted, disulfide containing, side-chain. This compound has shown to have similar or superior activity as compared to MMC, against variours cell lines, in murine tumours and in human tumor xenografts. KW-2149 also showed major antitumor activity against MMC-resistant murine leukemias. Animal toxicology studies showed reduced myelotoxicity in comparison with MMC.
A phase I study was initiated in which the drug was administered as bolus injection every three weeks with a starting dose of 5 mg/m^2. Dosages were escalated to respectively 10, 17,25,35,47,60,75,90 and 100 mg/m^2. At present 37 patients have been treated in this trial. At the highest dose step grade IV hematological toxicity occurred in 1/3 patients. Other toxicities are moderate nausea and vomiting and in several patients dyspnea. We have seen some antitumour effect in 4 patients.
Pharmacokinetic analysis shows rapid clearance of KW-2149, and seems mainly to be due to intensive metabolism into M-16 and M-18, the major metabolites. The short residence time could explain the considerable dose escalation before toxicity was observed.

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PHASE I CLINICAL STUDY AND PHARMACOLOGICAL EVALUATION OF ORAL ETOPOSIDE PHOSPHATE (BMY-40481)

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The toxicity and pharmacokinetic of Etoposide phosphate (EP), a water soluble prodrug of Etoposide (E) which is converted to E by phosphatases, was investigated in a phase I in which the drug was given orally for 5 consecutive daily doses. A total of 36 pts with solid tumors or lymphomas entered the study. The doses were escalated from 50 to 220 mg/m^2. The dose limiting toxicity was neutropenia. The recommended doses for Phase II studies are 175 and 220 mg/m^2 for previously treated or untreated pts respectively. EP was never detectable in plasma after oral administration. The mean bioavailability of E±SD was 85±23% after 50 mg/m^2 (n=5), 91±35% after 100 mg/m^2 (n=9) and 72±28% after 200 mg/m^2 (n=6). E peak was reached within 2 h after the administration. A very good correlation between dose and peak or AUC of E was found. A larger number of pts is under investigation at both recommended doses to confirm the MTD, bioavailability data and possibly to establish if a correlation exists between pharmacokinetic parameters and neutropenia.

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HIGH DOSE INTENSITY OF CPT-11 ADMINISTERED AS SINGLE DOSE EVERY 3 WEEKS : THE INSTITUT GUSTAVE ROUSSY EXPERIENCE.

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CPT-11, a novel semi-synthetic DNA topoisomerase I-inhibitor, showed antitumor activity in preclinical and early clinical studies. Twenty five patients (pts) received 80 courses of CPT11 (30mn IV q 3 weeks) at high doses ≥ 350mg/m² (350-600mg/m² dose levels -DL-) at the Institut Gustave Roussy.
Major toxicities included : granulocytopenia gr 3-4 at 350 (1/5pts) 400 (3/6 pts), 450 (2/5pts) and 500 mg/m² (3/6 pts), anemia gr 3 in 3 heavily-pretreated (hpt) pts at 400 mg/m², thrombocytopenia gr 3 in 2 hpt pts at 350 and 400 mg/m², gr 4 in 1pt at 500mg/m², ondansetron-requiring vomiting in 1 pt at 450 mg/m². Transient asymptomatic increase in transaminases gr 2-3 was present at different DL but was infrequently observed upon rechallenge. An easily controlled cholinergic syndrome of variable intensity was observed in nearly all pts during and/or shortly after CPT-11 infusion. Other toxicities included alopecia and moderate asthenia. Most pts developed non-dose related diarrhea between treatments which was sucessfully controlled with early administration of high-dose loperamide 2 mg q2h resulting in only 1 hospitalization with a serious grade 4 toxicity. One biopsy proven drug-related skin allergic reaction was cumulative and treatment-limiting at the 6th cycle. Pharmacokinetic analysis showed a triphasic CPT11 plasma disposition with a terminal half-life ranging from 10 to 16H. Five partial responses (PR) were noted : 4 in refractory colon cancer (2 at 450, 2 at 500 mg/m²) and 1 in metastatic squamous carcinoma of the cervix at 450 mg/m². More pts and dose levels have to be explored to confirm a dose effect relationship and a safe dose for routine administration. Patients accrual is still on going at 600 mg/m² with 3 evaluable pts already treated with acceptable toxicity over a total of 7 cycles.