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PHASE I STUDY OF THE DISTAMYCIN DERIVATIVE FCE 24517.

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FCE 24517 is a Distamycin A derivative having a benzoyl mustard moiety instead of the formyl group at the N-terminal. It can bind to T-A rich sequences in beta-DNA minor groove. Forty two patients (pts) with advanced pretreated cancer were enrolled in this phase I study : Male=25, Female=17, median age 55years (30-73), PS(WHO) =1, tumor type = 12 head and neck, 11 lung, 6 ovary, 3 ethmoid, 3 colon, 1 Hodgkin, 1 mesothelioma, 1 unknown primary, 1 pancreas, 1 somach, 1 gall bladder, 1 cervix. Doses ranged from 200 ug/m²IV over 10mn q4 wks. Three received 200 ug/m², 6 = 300 ug/m², 14 = 500 ug/m², 7 = 600 ug/m², 9 = 750 ug/m² and 3 = 1000 ug/m². The maximal tolerated dose (MTD) is the dose that produces a neutropenia (N) < 100/mm3 lasting ≥ 7 days in 3/6 pts in absence of febrile neutropenia (FN) or the dose that produces FN in 3/6 pts or occurence of hepatic and/or renal toxicity ≥ grade (Gr) 2 (CTC) or other toxicity Gr ≥ 3 in 3/6 pts. Major toxicities included : Neutropenia (Gr 4) 8/14 pts at 500 ug/m², 4/7 at 600, 8/9 at 750 and 3/3 at 1000 ug/m². Nadir of N : Day 15. Thrombopenia (Gr 3) 2/3pts at 1000ug/m². Three objective partial response : 2 in ethmoid adenocarcinoma (>70% at 500ug/m² and 55% at 750ug/m² respectively) and the 3rd in ovarian cystadenocarcinoma (>70% at 600ug/m²). FCE 24517 would be an interesting active antineoplastic drug to b evaluated in phase II studies. Accrual of pts continues to define the recommanded dose and the MTD.

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WHOLE BODY HYPERTHERMIA COMBINED WITH HIGH DOSE CHEMOTHERAPY IN THE TREATMENT OF PATIENTS SUFFERING FROM SOFT TISSUE SARCOMA

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In previous studies on nude mice carrying xenotransplanted human (MX1) tumors we applied whole body hyperthermia in combination with high doses of ifosfamide (IFO). Combined with hyperthermia the therapeutic efficacy of a given dose of IFO was significantly enhanced without a concomittant rise of myelotoxicity. This encouraged us to start a clinical pilot study thus far on 5 patients (11 treatments) who suffered from end stage soft tissue sarcoma, and for whom no alternative effective treatment exists. The patients were treated with a combination of whole body hyperthermia (41.8°C for 1 hr), IFO (5 - 7.5 g/m²) and actinomycin D (1 - 2 mg/m²). After 2 sessions with thermochemotherapy a partial remission of the tumors occurred in 2 out of the 5 patients. Under the high dose thermochemotherapy neither the number of blood leucocytes nor the number of thrombocytes decreased more than under normothermic chemotherapy with equally high doses of drugs. All severely ill patients survived the physically demanding treatment. Thus, since the results so far obtained are promising, we feel justified to continue the clinical study.

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PHASE I STUDY OF THE MITOMYCIN C ANALOGUE BMY 25067

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BMY 25067 is a semi-synthetic analogue of mitomycin C having pre-clinical activity in a variety of solid tumours. The objectives of this ongoing study were to determine the maximum tolerated dose (MTD), toxicity and pharmacokinetic parameters of the drug following iv bolus injection every 28 days.

Forty patients (21 F, 19 M; median age 60, range 37 - 74 yrs; median PS 1, range 0-3) representing 13 solid tumour types (colorectal 12, NSCLC 7, ovarian 7, other sites 14) have been treated so far at eight dose levels (0.8-32 mg/m²) without intrapatient dose escalation for a total of 83 courses, ranging from 1 to 6 (median 2) per patient.

The MTD has not yet been reached. Worst WHO grade toxicity per patient: anaemia, (versus normal base line) 0 54%, I 26%, II 15%, III 5%; leucopenia, 0 97%, I 3%; thrombocytopenia 0 100%; liver function tests elevations, usually associated with disease progression, were seen in the lower and intermediate dose levels: I 24%, II 26%, III 2%, IV 2%; phlebitis 10% (Grade III in one patient); mucositis 5%; fatigue 5%; fever 2%. There have been no adverse cardiac events; left ventricular ejection fraction (LVEF) reduced by more than 25% in 2/29 patients but there was no correlation with dose level. Average reduction in LVEF was 4% (+10% to -32%). 39/40 patients are evaluable for response (1 patient too early): PD 30/39 (77%), SD 8/39 (21%), PR 1/39 (2%, previously treated colorectal cancer). Disease stabilisations and objective response occured at intermediate dose levels.

We conclude that BMY 25067 caused minimal myelotoxicity up to 32 mg/m², and non dose-related phlebitis. Reduction in LVEF and elevation of liver function tests occurred in some patients.

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A PHASE I AND PHARMACOKINETIC STUDY OF RP 60475F ADMINISTERED AS A ONE HOUR IV INFUSION EVERY 3 WEEKS IN SOLID TUMORS

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RP 60475F is a benzo-pyrido-indole derivative which inhibits both DNA topoisomerase I and II. This phase I trial explored a single IV dose of RP 60475F administered over 1 hour, every 3 weeks, to 30 patients (pts). Pts characteristics were as follows : male : 21, female : 9 ; mean age 57 (32-72) ; WHO P.S. 0-1 : 27, 2 : 3. All but 1 pt had received prior chemotherapy . Tumor types were : head and neck : 10, colo-rectal : 5, other : 15. 60 cycles of RP 60475F were administered at 8 dose levels (12, 24, 48, 80, 120, 180, 270, 360 mg/m²). Drug-related toxicities included hepatic toxicity which was dose limiting at 360 mg/m². Elevations in serum transaminases occured in 1/4 pt at 180 mg/m² (grade 4), and 3/3 pts at 360 mg/m² (1 gr 4, 1 gr 3, 1 gr 2). 1 pt died at day (D) 4 of course (C) 1 due to a potentiation of the side effects of the concomitant medications with gr 4 hepatic toxicity. 2 pts suddenly died on C1 at 12 and 48 mg/m² (D4 and D15) from unknown cause. Only minor hematologic toxicity and nausea were observed. Pharmacokinetics (PK) were obtained in 23 pts so far. A pharmacokinetically guided dose escalation was attempted but not pursued as serious adverse events occured at the first dose-level. PK were performed in plasma (PL) and whole blood (WB). In PL, t 1/2 was 19.8 ± 16.9 h ; total body clearance (CL) : 49.8 ± 22.5 L/h/m². In WB t 1/2 was : 53.9 ± 36.6 h ; CL : 7.8 ± 4.7 L/h/m². Both peak PL concentrations and PL AUC increased linearly with dose.

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SEQUENTIAL PHASE I STUDIES OF MODULATING PROLONGED INFUSION 5FLUOROURACIL(5-FU) WITH FOLINIC ACID (FA) AND ALPHA INTERFERON (IFN)

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Sequential studies aimed to establish the maximum dosing schedules for phase II studies in colorectal cancer when combining prolonged ambulatory infusions of at least 14 days of 5FU with the modulators FA then IFN. 5FU was commenced at 300mg/m²/day and could be delivered continuously for 12 weeks. When a cohort of 3 patients had FA added at an initial dose of 15mg orally every 6 hours, severe diarrhoea and stomatitis limited the infusion to 14 days or less. In 6 further patients it was shown that longer infusions could only be safely given with FA if the 5FU was reduced to 200mg/m²/day. In a second study cohorts of 3 patients received 5FU 300mg/m²/day with escalating doses of IFN at first 5mu tiw then 10mu tiw subcutaneously. No such dose limiting toxicities occured and further dose escalation to 15mu tiw is proceeding to establish a maximum dose of prolonged 5FU and IFN for studies of efficacy.