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NEUROTOXICITE (NTX) OF LONG TERM OXALIPLATIN (L-OHP) THERAPY. S. Brienza*, J. Gastiaburu*, A. Fandi, F. Hugret*, M. Itzhaki, S. Lecouturier*, P. Déprès-Brummer, J.L. Misset and F. Lévi. SMST - Hôp P.-Brousse, Villejuif - France. *Debiopharm, Lausanne - Switzerland

Recomended phase II dose of L-OHP is 125-150mg/m2 q 3 weeks. Cumulative neurotoxicity, its duration and reversibility are presented on 193 consecutive pts (111 men/82 women) from 12/88 till 10/92 ; 160 with colon ca, liver 11, biliary tract 8, stomach 8, pancreas 3, misc. 3. 154 had liver involvement, 10 pts had renal insufficency, 7 diabetic, and 15 had prior CDDP. They had 1874 cycles (cy) of chronomodulated L-OHP-containing chemo (Cancer 02.92, vol 69, 893-900) (49pts: 100mg/m2 q 2 w and 144 pts: 125mg/m2 q 3 w). L-OHP total dose (median) was 900mg/m2 (100-2735mg/m2). Nb of cy/pt: 9.7, with 151 having ≥ 6 cy, 76 with ≥ 1000mg/m2, 20% had ≥ 1300mg/m2. Median follow up: 340 days (30-1390 d).

| NTX | N pts (%) | L-OHP med | Comp. Regr | Part Reg | No improv |
|---|---|---|---|---|---|
| GrII WHO | 58/193 (30) | 900mg/ m2 | 47/58 (5 mos) | 7/58 | 4/58 m F.up |
| GrIII WHO | 27/193 (14) | 900mg/ m2 | 16/27 (3 mos) | 4/27 | 6/27 3month s |

L-OHP given at the dose intensity rate of 30mg/m2/w with 120mg/m2 single dose allows prolonged administration with less than 4% persisting grade III NTX after a median of 8 months treatment. Unlike other neurotoxic platinum compounds L-OHP's NTX is completely reversible in 70% of pts/5 months after its discontinuation.

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## EFFECT OF VINBLASTINE (BOLUS VERSUS SPLIT DOSE) ON SA-1 ASCITIC TUMOR CELLS IN MICE

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To determine the dependence of antitumor effect of vinblastine (VLB) on the mode of administration (bolus vs split dose treatment) an animal tumor model was used. SA-1 ascitic tumor cells growing in syngeneic A/J mice were treated with VLB in different doses (2.5μg, 5.0μg, 10.0μg and 20.0μg VLB per animal). Survival of cells was determined after bolus or split dose treatment simulating continuous infusion (doses were split into 4 fractions and injected in 8-hour intervals). The effect of bolus treatment was dose dependent; 2.5μg VLB/animal reduced cell number to 84%, and the highest dose (20.0μg VLB/animal) to 47% of the untreated controls. The split dose significantly increased VLB cytotoxicity, which was reflected in reduced cell number to 20% at 2.5μg and 19% at 5.0μg VLB/animal of the untreated controls. According to these preliminary results, split dose treatment was much more effective than bolus at the same dosage. This corresponds to our clinical observations in thyroid tumors. Also, SA-1 tumor model seems to be suitable for further studies on drug administration and underlying mechanisms.

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FATTY ACID AND ANTIOXIDANT STATUS IN PLASMA DETERIORATES DURING HIGH DOSE CHEMOTHERAPY M. Dürken[1], J. Agbenu[1], C. Hübner[1], B. Finckh[1], P. Kapaun[1], K. Winkler[1], A. Zander[2], A. Kohlschütter[1]. Dept. of Paediatrics[1] and Bone Marrow Transplantation[2], University of Hamburg, Germany.

Targets of free radical attack under high dose chemotherapy (HDC) include polyunsaturated fatty acids in membrane lipids and lipoproteins. In 17 patients undergoing bone marrow transplantation (BMT), polyunsaturated fatty acids were monitored three times weekly. Individual antioxidants, vitamin E, C, uric acid and bilirubin as well as the total radical antioxidant parameter (TRAP) of plasma were measured in 7 of these patients, who received allogeneic BMT. Linoleic acid decreased from normal concentrations of 28.1±1.3 wt% at day -7 (day of BMT=0) to 13.5+4.6 wt% at day +3 (p<0.01). Eicosatrienoic acid increased from normal concentrations (0.15±0.06 wt%; day -7) to 0.71 + 0.35 wt% (day +3; p< 0.01), indicating essential fatty acid deficiency. TRAP-values in patients prior to HDC were similar to those of healthy controls (pts: 1064±189 μmol/l, contr.: 909± 167), decreased during HDC (day +5: 602±132 μmol/l; p< 0.001) and increased slowly thereafter, reaching normal values at day +35 following BMT. Uric acid levels during HDC paralleled TRAP-values, whereas vitamin E, C and bilirubin did not. Serum iron levels were inversely correlated to TRAP-values. This study demonstrates the deterioration of the antioxidant status during HDC and raises the question of pharmacological and nutritional intervention.

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## ISOLATION PERFUSION WITH RTNFα + RIFNγ + MELPHALAN FOR IN TRANSIT METASTASES OF MALIGNANT MELANOMA. UPDATE OF A PILOT STUDY.

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This is an update of the pilot study on melanoma previously reported (J. Clin. Oncol, 1 : 52-60, 1992). 55 patients were accrued between Oct. 88 and June 92. There were 44 F and 11 M aged 64 (22-84); 36 had stage IIIA, 15 stage IIIAB and 4 stage IV. 21 presented 10 to > 100 in transit nodules. 30 had been previously treated mainly by regional chemotherapy. Protocol included 90 min. Isolation Perfusion at 40 °C with 3-4 mg rTNFα (Boehringer Ingelheim), 0,2 mg rIFNγ (Boehringer Ingelheim), 10-13 mg/l melphalan (Wellcome) (for 60'). Septic shock like syndrome was prevented with dopamine and fluid overloading. Toxicity remained acceptable with 7 hypotension, 7 ARDS, 1 grade III kidney toxicity. There has been no toxic death.

Response rate remained very high with 49/55 (91.5 %) CR, including 2/49 after 2 perfusions, 6/55 PR (8.5 %) and no failure. With a median follow-up time of 18 months (in 54 patients), there were 12 (22 %) regional recurrences, 19 (34 %) distant metastases and 6 (11 %) local + distant recurrences. Median DFI has been 9.04 months and median overall survival 24.02 months. Limb salvage was achieved in 52/55 patients (95 %).

We conclude that high dose rTNFα associated to melphalan in isolation perfusion is the therapy of choice for in transit melanoma metastases of the limbs. However, the risk of septic shock like syndrome limits its application to specialized centers.

# Phase I Studies

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## PHASE I STUDY OF TAXOL PLUS DOXORUBICIN PLUS GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF) IN PATIENTS WITH METASTATIC BREAST CANCER

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We conducted a Phase I study of escalating doses of taxol and doxorubicin by 72-hour continuous intravenous infusion with G-CSF in metastatic breast cancer patients. The 42 patients treated on study were previously untreated with chemotherapy for metastatic disease, had not received doxorubicin in the adjuvant setting, and had measurable disease. The maximally tolerated doses were taxol 180mg/m² and doxorubicin 60mg/M² over 72 hours with G-CSF, 10μg/kg, administered subcutaneously days 4-18. The dose-limiting toxicity of this combination (taxol 180mg/m² and doxorubicin 75mg/m²) was reversible grade 3/4 diarrhea and abdominal pain. Cecal thickening suggestive of typhlitis was seen on CT scan in 3/3 patients. All patients developed grade 4 neutropenia , 7% grade 4 thrombocytopenia; in 47% of cycles hospitalization was required for treatment of fever and neutropenia. No significant allergic, cardiac, or neurologic toxicity was seen. The overall response rate was 72% (28/39) with 10% complete responses. The median duration of response was 7 months. There was no difference in taxol (0.12 μM) or doxorubicin (24nM) steady state plasma concentrations when the drugs were given alone over 72 hours versus in combination. Taxol and doxorubicin by 72 hour continuous infusion with G-CSF is associated with high overall response rates and significant gastrointestinal and hematologic toxicity.

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## PHASE I STUDY ON EO9 GIVEN EVERY 3 WEEKS.

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EO9 [3-hydroxy-5-aziridinyl-1-methyl-2 (1H-indole-4,7-indione)-propenol] is a synthetic indoloquinone. The $LD_{10}$ in mice was 27 mg/m². We performed a phase I study with EO9 given as a 5 minutes i.v infusion once every 3 weeks. Twenty-six patients (pts) entered the study, age 45-73, median WHO performance score 1 (range 0-2). Twelve pts had colorectal cancer, 4 pancreatic cancer and 10 miscellaneous tumor types. Doses studied were 2.7, 5.4, 10.8, 18.0 and 27 mg/m² in at least 3 patients each. Major toxicity occurred at the dose of 27 mg/m² consisting of proteinuria (CTC grade 4 in 3/11 courses, grade 1-2 in 4/11 courses) coincided by moderate edema (5/6 pts), temporary hypertension (2 pts), and grade 1-2 creatinine increase (2 pts). At the subsequent dose of 22.0 mg/m² (6 pts/11 courses), proteinuria without the other symptoms was found in 5/6 pts. It ranged from 1.7-14 gr/24 hrs (median 4.6) and was accompanied by sodium and water retention. The IgG/Albumin clearance ratio (range 0.02-0.12, median 0.06) and the pancreas/saliva amylase clearance ratio (range 1.33-1.71, median 1.49), pointed to a loss of glomerular negative charge, consistent with a minimal change nephropathy. All changes were reversible on day 15. In 64 evaluable cycles other side effects were: mild headache (13 cycles, 20%), dose-dependent transient nausea (21 cycles, 33%) and vomiting (24 cycles, 38%). Pharmacokinetics revealed a $t_{1/2}\beta$ of 2.5-19 minutes and AUC linearly related to dose ranging from 1.0-1.21 μg.min/ml at 5.4 mg/m² to 4.6-12.8 μg.min/ml at 27.0 mg/m2. Objective responses were 1 PR and 1 PR in lung metastases with coinciding stable disease in liver metastases, both in ACUP and an ongoing 45% tumorregression in a pt with bile-duct cancer. The MTD of EO9 at this schedule is 27 mg/m², the recommended dose for phase II studies is 22 mg/m².