20 O

OXALIPLATIN (L-OHP) IN FLUOROURACIL (FU) REFRACTORY PATIENTS WITH METASTATIC COLORECTAL CANCER.

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FU remains the standard treatment in advanced colorectal cancer. An increasing number of recurring patients (pts), however, has received FU as adjuvant treatment and there is no second-line therapy for pts with metastatic colorectal cancer who progress on FU ± Leucovorin (LV). L-OHP is a new platinum derivate with activity in pretreated advanced colorectal cancer. In association with 5-FU + LV response rate increases from 10% to L-OHP alone to 30-50 % in combination. To evaluate the activity of L-OHP in FU refractory patients, we performed a phase II study in which L-OHP was started as second-line treatment or added to previous regimen. In this study we administered L-OHP at 130 mg/ m^2 day 1 iv, over 2 hours q 3 weeks, carrying on with FU ± LV at the dose and schedule administered as first-line therapy. To date 20 pts have been enrolled: 16 are evaluable for toxicity and 14 for response (5 too early) ; all patients showed progressive disease during FU treatment, 3 on FU given in adjuvant setting and 13 for metastatic disease. **Patient characteristics:** median age = 60 years, (45-76) , M/F 7/9 PS O/1/2 in 11/4/1 pts. All pts had measurable metastatic disease: liver was involved in 13 pts, lung in 10 pts, lymph-nodes in 2 pts, other sites included pelvis, peritoneum, pleura and bone. Of 14 pts evaluable for response according to the NCI - CTCG criteria, 3 had a PR, 5 SD and 6 PD. No CR were observed. No grade IV toxicity has been observed and only 3 pts developed a grade 3 diarrhea. Nausea and vomiting occurred in 42% of the cycles as a grade 1, and in 27% as a grade 2. Grade 2 hematological toxicity has been reported in 15% and 4% of the cycles for neutrophils and platelets respectively. The most common toxicity was neurological (grade 1 and 2 in 56% and 12 % of the cycles respectively) as hand-foot paresthesias or hypersensivity to cold. Pts were treated for a median of 3 cycles (1-9) and for a median period of 3 months (1-8). Dose reduction was performed in 2 pts (2 cycles). The results of this study confirm the antitumour activity of L-OHP in pts with metastatic colorectal cancer refractory to FU, without enhanced toxicity of FU.

22 O

TAURINE ENHANCES MACROPHAGE-MEDIATED CYTOTOXICITY VIA INCREASED ARGINASE RELEASE.

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Taurine is the most abundant intracellular free amino acid present in inflammatory cells. Preliminary experiments have demonstrated that Taurine abrogates IL-2-mediated endothelial cell injury by NK and LAK cells while enhancing NK and LAK anti-tumour function, therefore the aim of this study was to investigate the tumouricidal potential of Taurine-stimulated murine peritoneal macrophages (MØs). CD-1 mice were randomised into two study groups. Group A received an i.p. injection of Taurine (200mg/kg) and group B received a saline control. Peritoneal cells were harvested after 24hrs and the MØs were isolated by adherence. Cytotoxicity ± lysine [(L) a known arginase inhibitor] was assessed using Cr^{51} against the Wehi (W) and P815 (P) tumour targets. Nitric oxide (NO) and arginase release were also assessed as markers of cytotoxic activity.

	CONTROL	TAURINE
Cytotoxicity Vs W (%)	35.0 ± 17.2@	75.1±15.4*@
Cytotoxicity + L Vs W (%)	4.9 ± 2.5	6.1 ±1.0
Cytotoxicity Vs P (%)	28.5 ± 8.9@	68.3 ± 14.3*@
Cytotoxicity + L Vs P (%)	9.5 ± 6.3	20.1 ± 10.6
NO umols/ug prot.	1.8 ± 0.7	1.4 ± 0.6
Arginase umols/ug prot./hr	118.6± 31.9	180.6 ±32.8*

Stats.=Students t-test, *p<.05 Vs control, @p<.05 Vs cytotoxicity + L
MØs stimulated by Taurine have enhanced tumouricidal activity against both tumour targets and this effect is abrogated when arginase release is blocked by the competitive inhibitor L-lysine. NO levels are decreased, however, arginase release is increased indicating a preferential uptake of L-arginine for the enhancement of MØ tumouricidal activity. Modulation of this anti-tumour pathway may play an important role in host anti-tumour defense.

24 O

ECTEINASCIDIN-743 (ET743) : IN VITRO (IVT) AND IN VIVO (INV) RESULTS IN SOLID TUMOR MODELS. G. Faircloth (#), L. Cameron (*), M. D'Incalci, H. Hendricks (@), J. Jimeno (*). #* Pharma Mar R&D (Boston, Madrid), I. M Negri (Milano), @EORTC/NDDO (Amsterdam).

ET-743 is a novel quinoline alkaloid isolated from a caribbean tunicate. IVT studies identifies activity (A) in A549 lung, HT29colon, and Melmelanoma (MEL) cell lines with IC50s=034,0.60 and 0.66nM rescepctivily. The NCI IVT panel confirmed A particularly in MEL,NSCLC, breast (B) and Ovarian (O) lines. This A has been validated in the IVT-HTCFU assay: 100 % and 50% IVT responses for B and O exposed to 1.0uM and 0.01uM respectivily. ET-743 binds to DNA and affects the microtubule network, moreover ET-743 bloks cell cycle progression in late S and G2/M. Initial INV studies confirmed A in early and advanced (MX-1) B xenografts (X) with a complete response (CR) rate=100% and 90% the respectivily. Further INV studies in HOC22 (O), MEXF514 (mel) and LX529 (NSCLC) show impressive A with %T/C<1 and %T/C<25% at the MTD and ½ of the MTD respectivily. Liver toxicity (TOX) is the DLT but is, at the range of active doses, reversible and no cummulative. An assay method has been developed and a clinical phase I program is being implemented.

21 O

TREATMENT OF PIG EXPERIMENTAL CHOLANGIOCARCINOMA BY 5-FLUORO-2-DEOXYURIDINE CONJUGATES: A COMPARATIVE STUDY

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Human cholangiocarcinoma (CHC) is one of the most dismal biliary tree cancers to cure. We describe the effects of conventional HIA chemotherapy (FUDR) to experimental pig CHC in comparison with those by FUDR con-jugates (FUDR-CEA, FUDR-Cathepsin B).
Methods: In 21 male pigs (Long white landrase) -weight 23 Kg, a CHC was induced by intraportal application of aflatoxin B, and 4-methylcholantren. After the end of cancerogenesis (affected 40% of the liver in US), a regional chemotherapy (HIA) has began.
Results: In the FUDR group, the median survival was 86,6 days; no tumour regression was seen during the autopsy. In the FUDR-CEA group, the median survival was 139,3 days. In the course of autopsy, some reduction of the tumour mass could be observed. In the FUDR-Cathepsin B group, the results of HIA chemotherapy were quite expressive. The median survival reached 210,7 days. Autopsy revealed a significant reduction of the tumour tissue according to US.
Conclusions: FUDR-conjugates seems to be much more potent drugs in the pig CHC palliation as FUDR alone. The same is possible to expect in human biliary tree cancers.

23 O

THE ANTI-TUMOUR EFFICACY OF TAURINE AND RECOMBINANT INTERLEUKIN-2 *IN VIVO*

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The administration of recombinant interleukin-2 (rIL-2) is limited by the induction of increased microvascular permeability. The *in vivo* antineoplastic effects of taurine in combination with rIL-2 were investigated and its impact on the associated vascular leak was examined. Lung metastases were established in mice via tail vein injection. Ten days after injection mice were randomized into groups for 5 days of treatment. On day 18 the mice were sacrificed; lungs were removed, weighed and metastases counted.
Treatment of tumour-bearing mice with rIL-2 alone resulted in a significant reduction in tumour nodule incidence compared to a control group, while the group receiving rIL-2 + taurine showed an even further reduction in the incidence of lung nodules. Animals receiving rIL-2 showed a significant increase in mean wet lung weight compared to control lung weight, while mean wet lung weight of the rIL-2 + taurine group was significantly less than that of the rIL-2 group and comparable to control values. Animals receiving rIL-2 + taurine *in vivo* demonstrated significantly enhanced splenocyte-mediated antimelanoma activity *ex vivo* compared to animals receiving rIL-2 alone. Thus taurine may have an important role in modulating both metastatic growth and the associated toxicity of rIL-2 immunotherapy.

25 P

THE ROLE OF A CYTOREDUCTIVE SURGERY IN NONSEMINOMATUS GERM CELL TUMOR PATIENTS WITH SMALL RETROPERITONEAL MASS AFTER INDUCTION CEMOTERAPY

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We identify 64 nonseminomatos germ cell tumor pts, received 4 cycles of the induction chemoterapy with VAB-6, BEP or EP, who presented a residual retroperitoneal mass (RRM) < 2 cm (med. 1.0, range 0.4-2.0), measured by an abdomen CT scan and ultrasound. All pts were marker negative and underwent a retroperitoneal dissection. The correlation of pathologic findings with a size of RRM are presented in the table.

Histology	Number	Tumor size of pts (cm)		
		<1.0	1.1-1.5	1.5-2.0
Fibrosis/necrosis	47	33	5	9
Mature teratoma	16	-	3	13
Malignancy	1	-	0	1
Relapse	3	1(14 mo)	1(6mo)	21(25mo)

Fibrosis/necrosis was observed in all resected RRM < 1.0cm. Pts with RRM > 1.0cm frequetly had teratoma and 1 pt hed a malignacy. Retroperitoneal relapses occurred in 3 pts. Our data suggests that surgery could be safely avoid in a marker negative pts who presented RRM < 1.0cm.