a median time to CP failure of 3 months, 2 CRs and 3 PRs were noted and confirmed and 4 PRs not confirmed from 32 evaluable patients. The overall response rate was 15.6%. WHO graded toxicity: grade 3 and 4 anaemia occurred respectively in 3 pts (8%) and 1 pt (3%); grade 3 neutropenia and thrombocytopenia in 8 pts (21%) and 3 pts (8%); grade 3 and 4 pulmonary toxicity in 2 pts (5%); grade 3 CNS toxicity (consciousness) in 1 pt (3%); grade 3 alopecia in 1 pt (3%) and grade 3 vomiting in 1 pt (3%).

Conclusion: This study confirms the activity and low haematological toxicity of GEM in pretreated ovarian cancers, and a study is ongoing combining GEM and CP as a first line therapy in stage 3 or 4 disease.

539 POSTER

Dose response in primary ovarian cancer evaluated by an *ex vivo* ATP chemosensitivity assay

C.M. Kurbacher[1], S. Munsch[1], U. Brenne[1], T. Gilster[1], P. Mallmann[1], H.W. Bruckner[2] [1]*Dept. of Gynecology and Obstetrics, University of Cologne Medical Center;* [2]*Mt. Sinai School of Medicine, New York, NY, USA*

Purpose: High-dose chemotherapy (HDC) may be useful in primary epithelial ovarian cancer (EOC). Since the dose optimum of most drugs is still unknown, this study was initiated to evaluate dose response (DR) effects in primary EOC *ex vivo*.

Methods: 105 primary EOC were tested against cisplatin (DDP), carboplatin (CBDCA), 4-OOH-cyclophosphamide (4-HC), treosulfan (TREO), doxorubicin (DOX), mitoxantrone (MX), etoposide (VP-16), paclitaxel (PTX), cytarabine (ara-C), and gemcitabine (dFdC) using the ATP Tumor Chemosensitivity Assay (ATP-TCA). Drugs were tested at 6 test drug concentrations (TDC). For DR analyses, the cumulative number of tumors showing a 50 (IC_{50}) or 90 percent inhibition (IC_{90}) was plotted against increasing TDC.

Results: The highest *ex vivo* response rates were produced by PTX (48%), 4-HC (47%), and DDP (41%). Ara-C, dFdC, and MX showed little cross-activity with other drugs. Only PTX and 4-HC produced an IC_{90} response in the majority of tumors tested. IC_{50} DR effects over the whole TDC range were observed for all agents except ara-C and dFdC. For all drugs except VP-16 and DOX, IC_{50} DR curves were flattened at high concentrations.

Conclusion: Our study provides several new leads for the design of optimized HDC protocols for EOC. (1) Single agents are unlikely to cure patients with EOC. (2) Extreme dose escalation appears unnecessary due to non-linear DR plots at high concentrations. (3) Platinum compounds, cyclophosphamide, PTX, and MX appear to be the most suitable drugs in this setting.

540 POSTER

Adjuvant cisplatin and treosulfan chemotherapy in epithelial ovarian cancer stage I–III after complete surgical resection

E.M. Grischke, R. Felderbaum, G.P. Breitbach, G. Bastert. *For the GTOC Study Group; Department of Obstetrics and Gynecology, University of Heidelberg, Voss-Str. 9, 69115 Heidelberg, Germany*

Purpose: In the treatment of ovarian cancer, surgical tumor resection and primary stage are of prognostic value. In a phase II trial the effect of an adjuvant chemotherapy with cisplatin (CIS) and treosulfan (TREO) in patients (pts) with epithelial ovarian cancer stage I–III after complete surgical resection (R_0) was evaluated.

Methods: 125 pts with ovarian cancer were treated under study conditions with 70 mg/m^2 CIS and 5000 mg/m^2 TREO every 28 days, for 4 cycles. The data of 88 pts are available up to now. Response was assessed at second-look-laparoscopy/laparotomy or by imaging techniques.

Results: 39 pts were staged at second look (44%) the others by imaging techniques. After 4 cycles tumor progression was found in 2 pts (2.4%). After a median follow-up of 308 days, tumor progression was noted in 12 pts (14%), and 6 pts died (7%) during a median interval of 474 days. There was no significant hematologic, neurologic, or renal toxicity in any patient.

Conclusions: The combination chemotherapy examined proved an effective modality for adjuvant treatment with a low risk of toxicity, also in stage III ovarian cancer.

541 POSTER

High lysolipid activity in malignant effusions in ovarian cancer patients

A.M. Westermann[1], E. Havik[1], F.R. Postma[2], J.H. Beijnen[1], O. Dalesio[1], W.H. Moolenaar[2], S. Rodenhuis[1]. [1]*Department of Medical Oncology;* [2]*Division of Cellular Biochemistry, The Netherlands Cancer Institute, Amsterdam, The Netherlands*

Purpose: Lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P) are lysolipids with mitogenic and growth factor-like activities that act via specific cell-surface receptors present in many normal and transformed cell types. LPA has recently been implicated as a growth factor present in ascites of ovarian cancer patients. The hypothesis that lysolipid levels in effusions of ovarian cancer patients are higher than those in effusions of other cancer patients was studied.

Methods: A neurite retraction bioassay previously developed for *in vitro* detection of LPA activity on cell lines was used to determine LPA-equivalent levels in effusions of 62 patients with a range of malignancies, including 13 ovarian cancer patients. Biochemical and clinical parameters were evaluated for correlations with LPA-equivalent levels.

Results: Average LPA-equivalent levels were 50.2 μM [5 4–200] for all patients, and 94.5 μM [15–200] for ovarian cancer patients ($p = 0.004$). There were no additional independent significant correlations between LPA-equivalent levels in effusions and a range of other biochemical and clinical characteristics.

Conclusions: These data suggest a role for LPA in the peritoneal spread of ovarian cancer and possibly that of other predominantly intraperitoneal malignancies.

542 POSTER

Treatment of advanced ovarian cancer (AOC) with cisplatin (P), epirubicin (E) and cyclophosphamide (C)

J. Casal, M. Caeiro, A. de la Orden, C. Grande, C. Obispo, G. Bravo. *Servicios de Oncología y Ginecología, Hospital Meixoeiro, Vigo, Spain*

The aim of phase II study was to evaluate the pathological response rate after six courses of first line chemotherapy, given after radical cytoreductive surgery. From July 1991 to June 1996, 29 pts, median age 60 y (24–76), FIGO stage IIC/III/IV (2/16/11), with epithelial AOC were treated with PEC combination: P 100 mg/m2, E 60 mg/m2 and C 500 mg/m2 i.v. every 3 weeks. Tumor size after initial surgery was <2 cm in 13 pts of whom 4 pts were macroscopically tumor free and >2 cm in 16 pts. Following chemotherapy, overall clinical response was observed in 15 pts (55.5%, CI 95%: 37–72) and cCR in 9 pts. Second-look laparamoty was performed in 24 pts. Complete pathological response was assesed in 10 pts (37%, CI 95%: 19–55) and 8 pts (29.6%) had surgical CR. Median time for disease progression was 19 months and median overall survival 30 months. After 165 cycles, the major toxicities observed were: 26% g 3–4 nausea and vomiting; anemia 48 g 1–2; 37.5% neutropenia g 1–2 and 10.4% g 3–4. 3 pts developed febrile neutropenia and 1 toxic death ocurred. In conclusion, this PEC combination is active regimen against epithelial AOC, well tolerated with mild side effects.

543 POSTER

Phase 1 study to investigate alternate sequencing of the combination of gemcitabine and paclitaxel in ovarian carcinoma

C.J. Poole[1], T. Perren[2], T. Hogberg[3], J. Cook[1], A.H. Jenkins[2], M. Ridderheim[3], K. Anderson[4]. [1]*QE Hospital, Birmingham;* [2]*St James's University Hospital, Leeds, UK;* [3]*University of Lund, Sweden;* [4]*Lilly Industries Ltd.,*

Purpose: A phase 1 study, (Ann. Onc., 1996, vol 7, Supp. 5, 341P) utilising a 28 day cycle of gemcitabine (given days 1, 8 & 15) and paclitaxel (day 8) identified dose limiting thrombocytopenia & neutropenia at 1000 mg/m^2 of gemcitabine & 135 mg/m^2 paclitaxel. Encouraging antitumour activity was seen, despite dose omissions being required on day 15. In view of these results, a dose escalating study is now underway, to evaluate a 21 day cycle. Starting dose, gemcitabine 1000 mg/m^2 days 1 & 8 and paclitaxel 135 mg/m^2 day 8.

Methods: The first 6 patients were randomised at dose level 1 to receive either paclitaxel, or paclitaxel-then-gemcitabine on day 8, to identify sequence-specific toxicities, in parallel with pharmacokinetic (PK) measure-

ments. The optimal sequence at the starting dose formed the basis for subsequent dose escalations.

Results: 15 patients have been enrolled over 10 months; median age 56, range 46–68; PS median 1, range 0–2; 2 FIGO stage Ic, 8 stage III, & 5 stage IV; 8 with grade 3 histology, 5 grade 2 & 2 grade 1. 2 patients had clear cell morphology. All had undergone 1 previous platinum-based regimen, with a median treatment-free interval of 5 mths, range 6 wks to 29 mths. Dose-limiting neutropenia (CTC IV) & ALT rise (CTC III) was encountered at gemcitabine 1000 mg/m^2 and paclitaxel 175 mg/m^2. 2 patients who received gemcitabine prior to paclitaxel on day 8 at dose level 1 (1000/135) developed grade 3 transaminase rise. No other sequence-specific toxicities have been identified, and no significant PK differences defined. Four out of 10 evaluable patients have so far achieved a partial response (UICC).

Conclusion: Gemcitabine MTD is being explored at paclitaxel 150 mg/m^2. Further work will be presented utilising paclitaxel day 1, gemcitabine day 1 and 8.

544 POSTER

Ifosfamide and Hexamethilmelamine as rescue treatment for cisplatin refractory ovarian cancer

L. Torrecillas, G. Cervantes, A. Erazo. *Medical Oncology Department 20 de Noviembre ISSSTE hospital, Mexico*

Purpose: Before the taxane clinical introduction, the drugs with >30% response rate used as second line treatment were Ifosfamide (*I*) and Hexamethilmelamine (*H*). No experience has been published yet with the *IH* combination. We describe the results of 21 patients (pts) with cisplatin refractory ovarian cancer.

Methods: pts received *I* 2.5 g/m^2 days 1–2, mesna 500 mg/m^2 iv hours 0 + 4 and 1000 mg/m^2 po hours 8 + 12 on days 1–2 and *H* 150 mg/m^2/day on days 3–16 every 28 days, on an ambulatory setting. Pts median age was 52 years (range 35–70); previous cisplatin/carboplatin based cycle number 4–10 (median 7).

Results: the overall response was 38% (8 pts) with 2 complete responses (9.5%), 5 pts with stable disease (23.8%) and 8 pts with progression (38%). Toxicity for 77 delivered cycles (3.6 median cycles/pt): neutropenia G0 = 39.5%, G1 = 27.6%, G2 = 17%, G3 = 12%, G4 = 3.9%; two episodes of trombocythopenia and anemia G1; other mild side effects: abdominal cramps, muscular pain, nausea, astenia. The DFS for CR was 14–19 months, the free-progression interval for PR was 4, 6, 7, 8, 8 and 9 months respectively. The median overall survival for the entire group was 13.3 months (range 3–31 months). The observed median dose intensity: *I* 1.14 g/m^2/week (91.2%) and *H* 481.55 mg/m^2/week (91.72%).

Conclusions: 1. the low toxicity profile allowed a 91% dose intensity in a heavily pretreated group of pts with poor known prognosis; 2. *IH* can be safely delivered in an ambulatory setting; 3. *IH* can be considered a good option for rescue treatment in cisplatin refactory OC due to a high response rate, a good palliative effect and survival impact. This combination deserves more experience in larger population.

545 POSTER

Paclitaxel (PX) – Carboplatin (CBP) versus cyclophosphamide (CTX)-carboplatin supported by G-CSF as first line chemotherapy in figo III–IV ovarian carcinoma (O.C.)

A. Polyzos, N. Tsavaris, L. Giannikos, N. Kalahanis, K. Christodoulou, K. Giannakopoulos, G. Nikou, A. Toskas, J. Papargyriou, N. Katsilambros. *1st Dept of Propedeutic Medicine LAIKON Hospital, Goudi, Athens, Greece*

Purpose: To evaluate and compare the efficacy and toxicity of the combination of PX-plus-CBP versus CTX-plus-CBP as first line treatment in advanced O.C.

Method: Sixty patients (pts) – so far – with measurable or evaluable disease, aged 55 (40–70), stage III 48 pts, stage IV 12 pts, were randomized to receive: PX 175 mg/m2 over 3 h and CBP 7 (AUC) or CTX 600 mg/m2 plus CBP 7 (AUC). Both arms were supported by G-CSF 5 μg/kg/day × 5 days.

Results: Thirty pts for each arm were eligible and evaluable for response and toxicity. In PX-CBP arm 27/30 pts (90%) (95% CL 74–98) responded with 3PCR, 15 CCR and 9 PR. In CTX-CBP 22/30 pts (73%) (95% C.L. 54–88) responded with 3 PCR, 10 CCR and 9 PR ($p < 0.18$). Peripheral neuropathy (100%) and alopecia were the main toxicities of the PX-CBP arm. Apart from 20% grade 2 thrombocytopenia in both arms there was no other hematologic toxicity. Disease progression during treatment was recorded in 3/30 and 8/30 of the two arms respectively.

Conclusion: PX-CBL combinations is highly active. Both regimen supported by G-CSF are very well tolerated. Survival is pending. Patient's accrual continues.

546 POSTER

Chemotherapy in advanced ovarian cancer (AOC)

S. Ionescu Goga[1], N. Gutulescu[1], M. Ionescu-Goga[2]. [1]*Oncological Institute Bucharest;* [2]*University Paris VII, Romania*

The study designs an optimising therapy strategy with platinum derivatives in the aim to obtain surgical reconversion and consolidation of the results in AOC. The data presented, were from 86 cases of epithelial AOC, stage III and IV followed up between jan. 1993–dec. 1996. Features of the cases: age 29–69, diagnosis by citology of ascites (36% of cases), or histopathology after laparotomy or anexectomy. All had locally-advanced disease. We performed: a) neoadjuvant chemotherapy with 3–4 CAP schedules (CDDP 75 mg/m^2 or carboplatinum 450 mg + cyclophosphamide 500 mg/m^2 + farmorubicine 75 mg/m^2); b) debulking or radical surgery and c) 6 CAP schedules q 3 weeks. In 65% of cases radical histerectomy, bilateral anexectomy and omentectomy was possible; 35% of cases underwent citoreduction. Correct hydratation and antiemetic treatment realized good tolerance. Disease free survival (DFS) obtained was 6–11 months with good quality of life (QOL). After 12–24 months 35% of patients were submitted to second look: 55% had CR, 30% had restant tumors <2 cm and 15% progressive disease. For the last two categories we repeated chemotherapy with 3–4 CP courses (cyclophosphamide 500 mg/m^2 + CDDP 100 mg/m^2 or carboplatinum AUC 6). Overall response was 76% with good QOL. The 4 years follow-up underlines the value of platinum based regimens in the treatment strategy of AOC, realizing better DFS and good QOL.

547 POSTER

Serum concentrations of soluble interleucin-2 receptors (sIL-2R) in patients with benign and malignant ovarian tumors

G. Gebauer, M. Rieger, W. Jaeger, N. Lang. *Department of Obstetrics and Gynaecology, University of Erlangen-Nuremberg, Germany*

Purpose: In sera of patients with several benign and malignant diseases soluble interleucin-2 receptors (sIL-2R) are found in sometimes very high concentrations. We wanted to investigate if measurement of sIL-2R in serum could be useful for differentiation between benign and malignant ovarian tumors.

Methods: In sera of 130 patients with benign ovarian tumors and 112 ovarian cancer patients at different FIGO-stages concentration of sIL-2R was measured preoperatively with a chemolumineszenz assay.

Results: sIL-2R serum concentrations in patients with benign diseases were between 197 and 3236 U/ml (median 573 U/ml), in those with ovarian cancer between 237 and 6230 U/ml (median 807 U/ml). An upper normal level of sIL-2R serum concentration in patients with benign ovarian tumors was defined at the 95th percentile (1200 U/ml) of the distribution of sIL-2R concentrations in these patients (cut-off). 33% of the ovarian cancer patients had sIL-2R concentrations above these cut-off. sIL-2R concentrations increased with FIGO-stage

Conclusion: We conclude that sIL-2R could become a new interesting tumor marker in ovarian cancer. Further studies should clarify the possibility of therapy monitoring by serial sIL-2R measurement.

548 PUBLICATION

Evidence of p*53*-independent activation of bcl-2 in advanced ovarian and endometrium carcinomas

T.J. Gilster, C.M. Kurbacher, A. Goor, M. Janat, M. Becker, H. Engel, P. Mallmann. *Department of Gynecology and Obstetrics, University of Cologne Medical Center,*

Purpose: p*53* and bcl-2 are important determinants of apoptosis. Inactivation of p*53* by mutation often results in high expression of bcl-2 that is known to block apoptotic pathways and may thus lead to chemo- or radioresistance. However, bcl-2 may also be activated by p*53*-independent mechanisms which are not fully understood. This study was initiated to evaluate the coexpression of p*53* and bcl-2 in advanced human epithelial ovarian (EOC) and endometrium carcinomas (ENC).

Methods: A total of 24 samples derived from patients advanced EOC (n = 18) or ENC (n = 6) were studied by immunohistochemistry. Antigen recovery