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

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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

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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

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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.

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

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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.

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

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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-