499 POSTER

PROGNOSTIC FACTORS IN OVARIAN CARCINOMA IN PATHOLOGIC COMPLETE REMISSION (PCR) AT SECOND LOOK SURGERY (SL)

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Prognosis of ovarian carcinoma in pCR at SL is still controversial. In a series of 83 patients in pCR at SL, we retrospectively studied several prognostic factors (age, stage, histologic grade, histologic type, initial residual disease after first surgery, time to CA 125 normalization). Median age was 55 years (20–80), there were 5 Stage IC, 17 Stage II, 53 Stage III and 7 Stage IV. All patients underwent an initial maximal debulking surgery followed by 6 platinum based chemotherapy cycles and SL. Consolidation treatment was variable and consisted of intraperitoneal mitoxantrone in 52 pts, intensive chemotherapy in 17 pts or others in 14 pts. Stage (I + II vs III + IV), histologic grade (1 + 2 vs 3), histologic type (serous vs non-serous) were of no prognostic value for relapse. Age < or > 55 years (Disease Free Survival (DFS) 71% vs 55%), initial tumoral residue < or > 2 cm (DFS 85 vs 41%) and time to CA 125 normalization < or > 8 weeks (DFS 80.5% vs 44.4%) are statistically significant for relapse at 2 years ($P < 0.05$). The combination of CA 125 normalization < 8 weeks with absence of macroscopic tumoral residue permits to define a group with a very good prognosis, while patients with CA 125 normalization > 8 weeks and an initial macroscopic residual tumor display a poorer prognosis (DFS at 2 years 100 vs 47%, $P < 0.05$).

500 POSTER

AMIFOSTINE (AMI) SELECTIVELY PROTECTS AGAINST CUMULATIVE TOXICITIES OF CYCLOPHOSPHAMIDE (C) AND CISPLATIN (P)

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Two hundred and forty-two advanced ovarian cancer pts were randomized to receive 6 cycles of 1 gm/m^2 C and 100 mg/m^2 P ± 910 mg/m^2 Ami every 3 weeks. Ami significantly reduced the incidence of cumulative nephrotoxicity. Protracted elevations of serum creatinine were reduced from 13.3% with CP to 1.6% with Ami + CP, $P = 0.001$. Following the last cycle of chemotherapy, 32% CP patients vs 10% Ami + CP had ≥40% decrease in creatinine clearance, $P < 0.001$. Ami also reduced the overall incidence of treatment limiting renal, neuro-, or ototoxicity by 62% (26% to 10%, $P = 0.001$). Additionally, 7% of CP patients compared to 1% of Ami + CP discontinued therapy due to hematologic toxicity, $P = 0.016$. Fever and/or infection associated with grade 4 neutropenia was reduced by 52% (21% to 10%) in the Ami + CP arm, $P = 0.019$ with a consequent 60% reduction in days in hospital, $P = 0.019$ and days on antibiotics, $P = 0.031$. The incidence of grade 4 neutropenia was also significantly reduced in the Ami + CP arm at the last cycle, $P = 0.001$. Antitumor efficacy as assessed by pathologic tumor response rates and survival was preserved. With a median follow-up of 41 months, survival curves are identical; median survivals: 31 months. Ami selectively protects normal tissues from the hematologic and non-hematologic toxicities from CP without any loss of antitumor activity.

501 POSTER

COLOR-DOPPLER ULTRASOUND IN RADIOLOGICAL EVALUATION OF OVARIAN LESIONS

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32 patients with 37 ovarian expansive lesions (18 cystic, 19 solid or mixed) were evaluated by color-Doppler examination and the RI (resistive index) was calculated. If the RI was >0.40 the lesion was considered benign, if it was <0.40 malignant. All lesions were confirmed at surgery or laparoscopy. The technique showed a high sensitivity (75%) and specificity (92%) with 3 false negatives due to borderline carcinomas and 2 false positives due to thecomas. The method is anyway a very reliable tool for the diagnosis of malignancy based on the characteristics of the vascular pattern.

502 POSTER

LONG TERM OUTLOOK IN 421 OVARIAN CANCER PATIENTS FROM A SINGLE INSTITUTION

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This retrospective study analysed 421 patients with epithelial ovarian cancer referred to a U.K. cancer centre between 1984–1991 for clinico-pathological factors, management procedures and survival. Median follow up was 34 months. The actuarial survivals were FIGO stage I >10 yrs, stage II 34.5 m, stage III 17 m, stage IV 10.5 m ($P = 0.00001$). Other tumour related factors with a significant effect on survival were ascites ($P = 0.0006$), and differentiation ($P = 0.00001$). The smaller the residual disease, the better the survival ($P = 0.0001$) both for stage III alone and for all stages, and the most marked improvement in survival was seen between <2 cm and microscopic residual disease, rather than between 2 and 5 cm as in previous series. Omentectomy and BSO/TAH were clearly associated with a survival benefit. The most common treatment regimen for advanced disease was the cisplatin/cyclophosphamide CP combination (n = 122). In both stage III and stages III/IV combined there was a clear benefit of the order of 6 months in favour of platinum containing regimens ($P < 0.0002$). This difference was not apparent for single agent treatments. There was little difference between cisplatin (n = 227) and carboplatin (n = 91) regimes, but these were clearly better than other drugs ($P = 0.0007$). Re dose intensity there was consistently a trend in favour of those patients receiving cisplatin at a dose of 20 mg/m^2/week ($P = 0.03$ in pts. receiving CP × 4 or more cycles). ECOG performance status 0 or 1, and age <70 yr. were also found to be associated with favourable survival. The data suggest that further improvement in survival may be achieved by aggressive debulking of stage III patients, and confirm the survival benefit of platinum based chemotherapy.

503 POSTER

HIGH DOSE CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA WITH BULKY RESIDUAL DISEASE

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From February 1989 to December 1991, 80 patients: stages IIIc (*58*)—stages IV (*22*). Suffering from bulky ovarian adenocarcinoma with important residual diseases after first surgery were included in a study testing the feasability and the potentiality of a three drug association chemotherapy. All patients had to accept a second look laparotomy and to give an informed consent. Cisplatin (100 mg/sqm), Carboplatin (300 mg/sqm), Cyclophosphamide (300 mg/sqm), were infused every 4 weeks according to the protocols of each participating Center. Antiemetic drugs transfusions, rehydratation and hospitalizations were left to each clinician's decision. Precise guidelines were given for the delay of the chemotherapy, according to the toxicity.

However only 4 G 3 infections and 7 G 2 hemorragic toxicities were observed, one patient died the day of the first course, and one stopped due to intolerable hematological toxicity. Late toxicity was observed included parasthesias tinnitus, and severe ototoxicity.

Immediate results are encouraging with pathological complete responses in 27% (stage IIIc) and 23% (stage IV) patients.

Survival seems also better than with current treatments: median survival 31 months stage III and 19 months for stage IV.

Since June 1992, a phase III study comparing a classical regimen (Cisplatin-Cyclophosphamide) with this three-drugs association is now underway.

504 POSTER

PHASE I STUDY WITH PACLITAXEL IN COMBINATION WITH IFOSFAMIDE IN PRETREATED PATIENTS WITH ADVANCED OVARIAN CARCINOMA

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Introduction: Patients (pts) with advanced ovarian carcinoma and an inadequate response to first line platinum based combination chemotherapy have a very poor prognosis. Salvage regimens were clearly needed. In order to determine the maximal tolerable dose (MTD) of the combination paclitaxel (P) and ifosfamide (IFO), we performed this ongoing phase I study.

Treatment: Pts were treated with P 3 h i.v. infusion after standard premedication on day (d) 1, IFO was given as 1 h i.v. infusion with the standard use of Mesna i.v. on d.2-5. The next cycle was given on d.22. Number of cycles depending on response and toxicity. We chose the following dose levels (dl): [mg/m^2] dl1: P 135/IFO 1500; dl2: P135/IFO 2000; dl3: P 175/IFO 2000; dl4: P175/IFO 1500. MTD was defined: neutropenia 4° longer than 5 days or febrile neutropenia, thrombopenia $\geqslant$3°, other organ toxicity >2° according to WHO criteria.

Patient Characteristics: 14 pts entered this ongoing trial. 13 pts entered dl1-3 and so far 1 pt dl4; age 52 yrs (37–66), WHO PS 1 (0–2).

Pretreatment: All pts had had a platinum based combination chemotherapy for advanced stage ovarian carcinoma prior to study entry. 10/14 pts had cisplatinum refractory disease with disease progression while receiving prestudy treatment. Number of prior treatment regimens 1.5 (1–3).

Toxicity and Results: With regard to P treatment, after standard premedication neither mild nor severe HSR's occurred. The following toxicities could be observed in 10 pts and 51 treatment cycles at dl's 1 + 2 [grade WHO (number of cycles)]: neutropenia 2° (6), 3° (21), 4° (24); anemia 2° (24), 3° (6); thrombocytopenia 1° (7), 2° (6); nausea/vomiting 1° (33), 2° (18); myalgia 1° (33); peripheral neuropathy 1° (36), 2° (12); mucositis 1° (39), 2° (8); diarrhea 1° (13), 2° (3). After we performed dose escalation of IFO up to 2000 mg/m^2 during dl 2 and 3 in 2 out of 8 pts treatment interruptions have to be performed because of CNS toxicity 3° WHO and in one additional patient suffering from nephrotoxicity grade 3 WHO. The MTD of IFO used in the combination with P and given over 4 days is 1500 mg/m^2. In order to enhance the efficacy of P we escalated the dose up to 175 mg/m^2 and intend to treat the following pts according to dl4. At all dl's responses could be observed. dl1 (5 pts): PR 2, SD 3; dl2 (5 pts): CR1, SD3, PD 1; dl3 (3 pts): CR1, PR2; dl4 (1 pt): not evaluable for response and toxicity so far.

Conclusions: The combination of P and IFO is leasable and active in the treatment of pretreated advanced ovarain carcinoma pts. Dl4 will be further evaluated during this ongoing study.

505 POSTER

A PHASE II STUDY OF CARBOPLATIN AND HEXAMETHYLMELAMINE AS INDUCTION CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA (AOC)

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The effect and feasibility of combination chemotherapy with carboplatin (C) and hexamethylmelamine (HMM) was evaluated on 27 patients with AOC. Two in FIGO stage IIC, 1 in IIIB, 8 in IIIC and 16 in stage IV. Carboplatin was given as 7 (GFR + 25) mg iv on day 1 and HMM 150 mg/m^2 orally on day 2–15, every 28 days. Three patients were not evaluable for response. Clinical response was seen in 17 patients (71%), with 6 (25%) complete and 11 (46%) partial responses. The median progression free survival was 15.6 months and the median cancer related survival 21.3 months. Four patients (15%) experienced grade 3 mental depression, none had peripheral neuropathy above grade 1. The hematologic toxicity was moderate, none had grade 4 leucopenia, but 4 (14%) had grade 4 thrombocytopenia. Carboplatin plus HMM had a high response rate with few side effects and a survival comparable to other platin based combinations.

506 POSTER

EFFECTIVENESS OF TWO CISPLATIN-BASED DRUG COMBINATIONS IN THE TREATMENT OF ADVANCED OVARIAN CANCER

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The therapeutical effectiveness of two cisplatin-based drug combinations have been compared in a prospective trial with 83 advanced ovarian cancer patients. 39 patients received epirubicin-cisplatin (EP) combinations, whereas 44 patients were treated with a combination of cyclophoshamide-cisplatin (CP). Metoclopramide or 5-HT-3 receptor antagonists were used to control nausea and vomiting during therapy. The response rate to the cytostatic therapy was 71.8% (28 patients) in the EP group, and 84.1% (37 patients) in the CP group. There were no significant differences in the length of the progression free interval and in the survival rate either. The average survival times were 23 months and 21 months respectively. In the control of vomiting 5-HT$_3$ receptor antagonist (Navoban) is more effective.

507 POSTER

A PHASE II STUDY OF TAXOL® (T) (PACLITAXEL) OVER 3 HOURS (H) IN 192 PLATINUM PRETREATED PATIENTS (PTS) FOR OVARIAN CARCINOMA (OC)

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Eligibility criteria: histologically proven OC, measurable/evaluable disease, relapse/progression after at least one platinum based CT, $\leqslant$ 3 prior CT. *Treatment:* 1 or 2 prior CT, T = 175 mg/m^2 [Group A (A) = 151 pts]; 3 prior CT, T = 135 mg/m^2 [Group B (B) = 41 pts] both by 3 hour IV infusion q 3 w. *Pts(192):* median (med) age: 57 yrs (25–72); PS 0 = 74 pts, PS 1 = 88 pts, PS 2 = 34 pts. nb prior CT : 1 = 81 pts, 2 = 73 pts, 3 = 36 pts. Toxicity (% cycles): 1184 evaluable cycles (cy) (983 in A, 201 in B) with a med nb per pt of 6 in A (1–21), 5 in B (1–11). *Cardiac tox.:* bradycardia: ($\leqslant$60 bpm) always asymptomatic = 13% (63 pts), hypotension ($\leqslant$90 mm/Hg) = 3% (24 pts), drop in systolic blood pressure $\geqslant$30 mm/Hg = 3% (23 pts). Out of 841 cy EKG 3% were abnormal (13 pts). *Minor hypersensitivity reactions (HSR):* 18% (A = 19%, B = 9%) in 73 pts, flushing (12%) and skin rash (4%). In 80 cy (7%) symptomatic treatment was required but never T discontinuation. No severe HSR occurred. *Hematologic tox.* induced treatment delay in 4% (A = 3%, B = 6%) and dose reduction in 1%. Gr 3–4 neutropenia: A = 32%; B =22%. Eleven pts experienced in 18 cy. any degree of fever of infection associated with a Gr 4 neutropenia, all in A. Thrombocytopenia Gr 3–4 = 1% (10 cy). Anemia Gr 3–4 = 3%, **Creatininemia** Gr 3 = 1 pt. **Liver Tox.** = 11 pts (6 with liver metastasis): ALP Gr 3–4 = 1%; ASAT Gr 3 = 0.3%. **Nausea/vomiting** Gr 1–2 = 13%.; Gr 3 = 2 cy. **Mucositis** Gr 1–2 = 4% all in A. **Paresthesias** (present in 45 pts at inclusion) Gr 1–2 : A = 43%, B = 28%, Gr 3: A = 5 cy. **Myalgias/arthralgias** Gr 1–2 = 18% (A = 20%, B = 7%) and Gr 3 in 3 cy. **Fatique** Gr 1–2 = 26%. **Edema** Gr. 1–2 = 6% and Gr 3 in 1 cy. No toxic death occurred. *Efficacy:* 185 evaluable pts, RR = 20% (CR = 5%, PR = 15%), SD = 32% (3 pts pCR). *Conclusion:* Taxol® given by 3 H infusion, is well tolerated. The RR seems not different from those observed with 24 H infusion.

508 POSTER

COST EVALUATION OF TWO CHEMOTHERAPIES IN OVARIAN TUMOURS BASED ON A CONTROLLED CLINICAL TRIAL (CCT)

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Nowadays, the choice between two therapeutic schemes should not depend only upon treatment efficacy but also upon overall treatment cost including economic cost as well as time spent for treatment and nursing. A first evaluation of economic cost was performed on the first 24 patients (12 in each group) enrolled in a CCT comparing cisplatin (CDDP 100 mg/m^2, dl) and cyclophosphamide (CY 600 mg/m^2, d1) (CP arm) to carboplatin (CBDCA 300 mg/m^2, d1), CDDP (100 mg/m^2, d2) and CY (300 mg/m^2, d21) (CCP arm) to a total of 6 courses. Cost evaluation was limited to hospitalization, drugs, haematological and biological supplies that were induced by therapy. Financial evaluation was based on the actual cost for the institution during the 1992–1993 period. Results are expressed as the ratio of the cost induced by the CCP arm relative to that of the CP arm. The Wilcoxon rank sum test was used for comparisons.

Results: For hospitalization, the overall ratio was 1.5 (P = 0.01), mainly based on an increase in days due to toxicity (ratio = 7.2, P = 0.002); for drugs, the ratio was 10.0 ($P < 0.001$); it was 13.4 ($P < 0.01$) for haematological products (due to platelets transfusion, ratio = 53.4); for biological exams, the ratio was 1.5 (P = 0.01). Overall, the overcost induced by CCP relative to CP was 11.2 ($P < 0.001$) when drug, haematological and biological expenses were considered. *Conclusion:* A second evaluation will consider additional costs (transportation or general practitioner help) and, above all, time spent by physicians as well as nurses. This approach should allow the calculation of the "cost by year of life won".