(<1/2) G1 = 29%, G2 = 20%, G3 = 8%, I stage = 54%, II stage = 4%; for volume (>1/2)) G1 = 11%, G2 = 19%, G3 = 27%, I stage = 30%, II stage = 12%. In the (<1/2) group 63% of the patients did not received RT, in the other 32%.

Results: In the whole group, relapses were 16.4% (local 8.7%, distant 6.8%, both 0.9%). The incidence of the local relapses (<1/2) vs (>1/2) is 5% vs 11%, distant relapses 3% vs 11%, NED survival after 60 months is 92% vs 73% (p = 0.0001).

The most important prognostic factors using multivariate analysis are: for Local relapse Vol. >1/2; for Distant relapse G3, Vol. >1/2, stage II; for Mortality G3, Vol. >1/2. Radiation therapy decreases significativaly the risk for local relapse

Discussion: in our series tumoral volume seems to be a very important prognostic factor influencing relapse and mortality rates, as showed in the table. Further studies are required to confirm these data, especially using more precise and rigorous criteria in anatomo-pathological analysis.

932 POSTER

8-hydroxydeoxyguanosine in cervical cells DNA: Correlation with HPV infection and grade of dysplasia

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In this study, the 8-OhdG level was assessed in human cervical cells by an immunoperoxidase method and was related to the presence of HPV infection and dysplasia. After optimising the immunohistochemical method in detecting oxidative DNA damage by testing it on AFB1 treated MCF-7, we have used this technique to estimate the oxidative damage in cervical cells collected during a routine PAP tests. 38 women (age range: 20–55, mean age 36.8, s.d. 9.6) were enrolled into the study. After informed consent was obtained, cervical cells were spread on slides precoated with 0.2% poly-D-lysine. Quantitation of specific nuclear staining in AFB1 treated MCF-7 confirmed the ability of the method to detect and differentiate between different damage in a linear dose-related fashion. The analysis of variance (ANOVA) of the data from human samples showed significant differences in standard deviation of the 8-OHdG level between normal, low grade and high grade of dysplasia (p < 0.0001). Comparing the three groups, statistically significant differences were detected between normal and high grade dysplasia (p < 0.001, Bonferroni corrected) and between low grade and high-grade dysplasia (0.003, Bonferrroni corrected), whereas non statistically significant resulted the difference between normal and low grade dysplasia (p = 0.174, Bonferroni corrected). Grouping observations by HPV status, no significant difference was detected in 8-OHdG levels between HPV+ and HPV− subjects (p = 0.8767). The ordered logistic regression analysis showed that while at low 8-OhdG levels the probability of dysplasia was higher for HPV+ subjects, at high 8-OhdG levels the probability of presenting a dysplasia was similar in both HPV− and HPV+ subjects. In conclusion, the immunoperoxidase method, applied to single human cervical cells, provides clear evidences that significant differences exist in 8-OHdG content between normal and dysplastic cells and that oxidative DNA damage might be able to promote cervical carcinogenesis independently by HPV status.

933 POSTER

Phase I study of topotecan (T) with carboplatin (C) alternating with paclitaxel (P) via 3 hour infusion with carboplatin (C) in treatment of newly diagnosed ovarian cancer (OC)

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Objective: Myelosuppression has made it difficult to incorporate T into a triplet with P and a platinum. This study was designed to find the maximum tolerated dose (MTD) of T in combination with C. Alternate cycles of P and C were given to gain exposure to all three active agents.

Methods: C (AUC 5 or 4) was administered first on Day 1 followed by T (0.75 mg/m^2 × 5 days for the first cohort of patients. Due to grade 4 thrombocytopenia, T was reduced to 0.6 mg/m^2 × 3 days and then re-escalated in subsequent cohorts) in cycles 1, 3, 5, and 7. P (175 mg/m^2) was given over 3 hours, then C on Day 1 of cycles 2, 4, 6, and 8. All cycles were to be at 21-day intervals. Dose limiting toxicity (DLT) included: ANC < 500 for >5 days, or grade 4 neutropenia with fever (>38.5 C), platelet count <10,000 or <25,000 with associated bleeding, delay of >7 days in recovery, or non-hematologic toxicity ≥Grade 3. If 1 of 3 patients had a DLT, another 3 were added. If DLT was due to neutropenia or delay in recovery of ANC, granulocyte colony stimulating factor (G-CSF) would be incorporated into the regimen. Due to platelet toxicity at the first dose level, T was changed to a 3-day regimen.

Results: 29 patients enrolled, 27 Stage III, and 2 Stage IV. Ages were 41 to 74 (median 56). A total of 85 cycles were given with the 3-day T. Delays occurred in 33 (39%), but were >7 days in only 11 (13%). 6 cycles were dose reduced. Grade 4 granulocytopenia occurred in 33 cycles (39%), but only 2 cycles (2.3%) were associated with febrile neutropenia. Platelets were <25,000 in 20 cycles (24%), but ≤10,000 in only 7 (8.2%), platelet transfusions were required in 3 cycles.

Conclusions: Myelosuppression is frequent but manageable with T and C. The MTD has not been reached at 1.0 mg/m^2/day. Cummulative toxicity in later cycles will probably prohibit further significant escalation of T.

934 POSTER

Positive progesterone receptor [PR+] and negative estrogen receptor [ER−] expression is associated with improved long term survival in ovarian cancer

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Purpose: Estrogen, progesterone as well as their receptors seem to be involved in the tumorigenesis in ovarian cancer. Their prognostic role is controversial.

Methods: Clinical, histological prognostic factors and steroid receptor status using semiquantitative immunohistochemistry (APAAP-method) were obtained retrospectively from 190 patients' records and stored formalin-fixed, paraffinembedded tumor tissue. Antibodies used: ER (clone 1D5) and PR (polyclonal) both DAKO Hamburg, Germany).

Results: Kaplan-Meier analysis revealed a significant influence of progesterone receptor expression ($P_{Log\ Rank}$ = 0.009) on survival and no influence of estrogen receptor expression. Both steroid receptors were coexpressed (ER+PR+) in 32.6%. ER+PR− tumors were found in 30.0%, ER−PR− tumors in 27.4%, and ER−PR+ in 10.0%. ER−PR+ tumors show a distinct better long-term survival if compared to the other steroid receptor combinations (mean survival 12.9 years; $P_{Log\ Rank}$ = 0.009). Correlation analysis reveals favorable associations between ER−PR+ receptor status and FIGO stage (P_{chi^2} = 0.039) as well as the volume of ascites at the time of primary surgery (P_{chi^2} = 0.069).

Conclusion: The reasons why ER−PR+ ovarian carcinomas are associated with favorable outcome, remain unclear, however, endocrine autoregulative processes, lack of susceptibility to unfavorable influences of estrogen and influences of progesterone, inducing cell differentiation and apoptosis may explain this effect.

935 POSTER

DICEP high dose (HD-DICEP) chemotherapy (CT) with or without peripheral blood stem cell support as consolidation treatment of patients (pts) with advanced epithelial ovarian cancer (AOC)

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Purpose: To analyse the impact and feasibility of consolidation treatment with HD-DICEP on disease-free survival (DFS) and overall survival (OS) in high risk AOC pts.

Patients and Methods: AOC pts (35) entered the study between 1992–1998. All patients were chemosensitive (platinum-CT, +/−taxol) and had low tumor burden at consolidation (determined by surgery in 29/35 pts). High-dose DICEP Seattle-protocol (Proc. ASCO 1993; 12: 50A) was applied. Median PS, 90 (80–100). Median age, 53 years (21–64). FIGO stages: IIIB, 2 pts; IIIC, 18 pts; IV, 6 pts. recurrent disease: 9 pts. Histologic subtype: Serous (S): 13 pts; endometrial (E): 10 pts; undifferentiated (U): 7 pts; mucinous (M) 2 pts; clear cell (C): 1 pts; unclassified (UN): 2 pts. Histologic grade (G): G-III, 22 pts; G-II, 4 pts; G-I, 1 pts; unknown, 8 pts.

Results: With a median follow-up of 51 months (4–75 m), median DFS is 12.5 months (3–68 m+), (median OS not reached). Most pts completed the treatment protocol (62 cycles-cy-/35 pts). 10 pts are long-time disease-free survivors: 2 pts had stage IV-liver parenchymal metastasis (UN: 38 m, and U-GIII: 42 m), 2 pts had recurrences (S-GII: 48 m, S-GIII: 24 m), 5 pts were

stage IIIC (S: 36 m, S-GIII: 39 m, S: 43 m, U-GIII: 48 m, E-GIII: 68 m), and 1 pts was stage IIIB (S-GIII: 31 m).

Relevant toxicities: Emesis (grade III, 19/62 cy; IV, 1/62 cy); mucositis (III, 1/62 cy); diarrhea (III, 4/62 cy; IV, 7/58 cy); neuro-constipation (III–IV, 6/62 cy). Median duration of grade IV neutropenia and thrombocytopenia, 11 d (6–20 d) and 13 d (3–23 d). Fever (58/62 cy). There were 3 toxic deaths (8.5%).

Conclusions: These results suggest that a subset of patients with poor prognosis AOC might benefit from the HD-DICEP treatment. The toxicity profile does not differ from previously reported series.

936 POSTER

Treatment of advanced ovarian cancer by cytoreductive surgery associated with intra peritoneal hyperthermic perfusion

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Introduction: The role of appropriate and extensive surgery to treat ovarian cancer was stressed by different Authors. Cytoreductive Surgery (CS) that consists in a complete removal of all tumor dissemination, is associated with longer survival either in the management of primary or recurrent ovarian cancer. The conventional approach to primary ovarian cancer with surgery and systemic chemotherapy permits to achieve complete responses in 20–40% of treated patients. Second line chemotherapy responses ranges from 22–37% but the prognosis remain poor (median survival 43–61 weeks).

Procedures: In a phase II clinical study, 26 patients with advanced ovarian cancer were treated by CS and Intra Peritoneal Hyperthermic Perfusion (IPHP). All patients were treated before by surgery (mean 2 procedures) and systemic CT (mean 3 scheduled treatments). In 16 patients a diffuse peritoneal carcinomatosis (PC) was observed; remaining 10 patients presented a limited PC. Cytoreductive surgery was conducted in 15 patients that received partial peritonectomy, and intestinal resection was done in 9 patients. The IPHP was carried out with the closed abdomen technique, using a preheated polysaline perfusate containing CDDP (mean 250 mg) and MMC (mean 30 mg) using a heart-lung pump at a mean flow of 700 ml/min for 60 minutes from the true hyperthermia phase (42.5°C). Fifteen patients had macroscopic complete resection of the tumor by CS while in 11 patients a residual disease ranging from 0.25 to 5 cm remained.

Results: Two-year overall survival is 55%; one-year overall disease-free survival is 60%, while one-year local control was obtained in 73% of treated patients. The overall survival is correlated to the completeness of cytoreduction ($P < 0.001$), the Karnofsky status ($P = 0.0018$) and the extension of peritoneal carcinomatosis ($P = 0.028$).

Conclusions: Patients with peritoneal carcinomatosis of ovarian cancer are responsive to combined treatments (CS + IPHP) even if heavily pretreated. The aggressive and complete surgery enables us to obtain a minimal or microscopic residual disease curable with the contemporaneous administration of high temperature and high drug concentration. Further clinical trials could define the role of this approach in the early phase of treatment of ovarian cancer. This study was partially supported by the Associazione Italiana per la Ricerca sul Cancro.

937 POSTER

Docetaxel-vinorelbine combination for platinum resistant paclitaxel pretreated ovarian cancer. A hellenic co-operative oncology group phase II study

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Purpose: Prognosis of relapsed ovarian cancer (OC) patients resistant to platinum is very poor and the treatment of choice has not been defined yet. Vinorelbine was proven effective in OC, while docetaxel is highly effective and appears not totally cross resistant with paclitaxel.

Methods: Eligible are patients with relapsed OC resistant to platinum and previously treated with paclitaxel. Chemotherapy is consisted of Docetaxel at 70 mg/m^2 (day 8) and Vinorelbine at 25 mg/m^2 (days 1.8), repeated every 3 weeks. Up to 2 previous platinum-based regimens are allowed.

Results: So far 22 patients entered the study, with a median age of 59 (43–72) years. The mean number of previous regimens is 1.5 and the median chemotherapy-free interval was 4.7 (0–6) months. Toxicity was considerable, mainly leucopenia-neutropenia (70% of patients), anaemia (58%), neurotoxocity (35%) and alopecia, while severe toxicities included leucopenia-neutropenia (24% of patients). Dose reduction was performed in 17% of patients. There are not treatment-related deaths. So far 13 patients are evaluable for response. Three patients achieved partial response lasting from 3+ to 7+ months, while another 3 patients demonstrated stabilization of their disease.

Conclusions: Our preliminary results appear quite encouraging.

938 POSTER

Paclitaxel, cisplatin and epirubicin (PCE) combination chemotherapy for newly diagnosed patients with advanced epithelial ovarian cancer (AEOC)

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Purpose: To evaluate the activity and toxicity of the PCE combination after cytoreductive surgery in patients with AEOC.

Methods: Forty consecutive patients with AEOC (7 optimally and 33 suboptimally debulked) were treated with paclitaxel 135 mg/m^2 as a 3 hour intravenous infusion, cisplatin 75 mg/m^2 IV, and epirubicin 50 mg/m^2 IV every 3 weeks on an outpatient basis.

Results: Among 29 patients with measurable disease, 24 (83%) achieved an objective response including 19 complete and 5 partial responses. Among 18 patients who underwent second-look laparotomy, pathological complete remission was confirmed in 9 (50%). With a median follow-up period of 34 months the overall median survival has not been reached yet. The median remission duration was 14 months, and the median time to progression for patients with measurable disease was 17 months. The treatment was well tolerated; the most common toxicity was neutropenia (WHO grade 3 + 4) which occurred in 30% of patients. Neuropathy (grade $\geq$ 2) developed in only 8% of patients.

Conclusion: PCE at the dose levels given is an active and welltolerated outpatient regimen in the treatment of AEOC.

939 POSTER

Phase I study of repetitive high-dose topotecan (T) carboplatin (C) and paclitaxel (P) in previously untreated ovarian cancer

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Purpose: In view of the significant activity of T in ovarian cancer with dose limiting toxicity of myelosuppression, we evaluated the addition of T to C and P with peripheral blood progenitor cell support.

Methods: Patients received 2 cycles of C AUC 5 and P 175 mg/m^2 with collection of progenitor cells after the second cycle. They then received 3 cycles of intensive therapy with T on a daily × 5 schedule, P 250 mg/m^2 (24 hr) on day 3 and C AUC 12 on day 4. Eligibility included previously untreated stage 3 or 4 ovarian cancer with either macroscopic residual disease following primary debulking surgery or clear cell histology.

Results: 14 patients, median age – 49 (range 21–63). T was escalated in 4 patient cohorts up to a dose of 3.5 mg/m^2/d. This dose level met the criteria for defining the dose limiting dose level with 2/4 patients experiencing grade 4 mucositis. The preceding dose level with T 2.5 mg/m^2/d is the recommended dose. Toxicities in the 3 patients treated at this dose level were grade 3 mucositis in 1/9 high dose cycles and febrile neutropenia in 2/9. Responses in 14 patients who have had second look laparoscopy or laparotomy: pathologic CR – 7, microscopic residual – 1, PR – 5, PD – 1.

Conclusion: When combined with C (AUC 12) and P (250 mg/m^2) the recommended topotecan dose is 2.5 mg/m^2/day. This outpatient high dose regimen combines 3 of the most active drugs in ovarian cancer with acceptable toxicity and promising activity.

940 POSTER

Adherence to a regional guideline for treatment of malignant epithelial ovarian carcinoma

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Purpose: to study quality of chemotherapy for malignant epithelial ovarian carcinoma (OC) according to a guideline in a university hospitall.