

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.

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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.

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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/m² (day 8) and Vinorelbine at 25 mg/m² (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%), neurotoxicity (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.

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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/m² as a 3 hour intravenous infusion, cisplatin 75 mg/m² IV, and epirubicin 50 mg/m² 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 ≥ 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.

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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/m² with collection of progenitor cells after the second cycle. They then received 3 cycles of intensive therapy with T on a daily $\times 5$ schedule, P 250 mg/m² (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/m²/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/m²/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/m²) the recommended topotecan dose is 2.5 mg/m²/day. This outpatient high dose regimen combines 3 of the most active drugs in ovarian cancer with acceptable toxicity and promising activity.

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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 hospital.

Methods: This guideline advised chemotherapy with cyclophosphamide 750 mg/m² (C) and cisplatin (P) 75 mg/m² i.v. q21 days for OC FIGO stage IIB with macroscopic tumor rests to IV and with melphalan (M) 0.2 mg/kg p.o. d1-5 q28 days for stage I to IIB (except Ia well differentiated and IIB with macroscopic tumor rests). From the regional cancer registry 37 patients were found treated for OC from 1992 to 1995.

Results: 13 patients were eligible for M, 4 of them did not receive chemotherapy at all, 1 received M and 8 received CP, 22 patients were eligible for CP. They all had chemotherapy but alternative schedules as C adriamycin (A) P or C carboplatin (Ca) q 21 days were given. In total 182 cycles were given: 5 M, 143 CP, 26 CAP and 8 CCA. Excluding M treatment, 155 cycles were longer than 22 days. Median duration per cycle was 25 (range 20-34) days. Important reasons for delay were bone marrow toxicity (WBC < 3 or Platelets < 100), 26 cycles with lab control on day 20-22, 46 cycles with lab control <20 days after last chemotherapy, and hospital logistics, 53 cycles. Median total DI (tDI) defined as given dose/intended dose for all CP, CAP and CCA cycles given was 0.96 (range 0.73-1.03), reasons for dose alterations were calculation faults, and no dose reduction as advised in the guideline when $3 \leq \text{WBC} < 4$. The relative DI (rDI) defined as tDI \times number of cycles \times 21/actual duration of therapy median was 0.79 (range 0.48-0.89). 7 of 30 patients had a rDI > 0.85.

Conclusion: rDI is considerably affected by delay, due to guideline violations as hospital logistics, time of lab control and no dose reductions as indicated. These are important factors interfering with optimal treatment outside a study protocol, even when a guideline is used.

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POSTER

A combination of a fixed dose of carboplatin plus paclitaxel and adriamycin in first line therapy for advanced ovarian cancer and suboptimal surgical cytoreduction. A phase I trial of the Spanish group for ovarian cancer research and treatment (GEICO)

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To develop a tolerable treatment of carboplatin at a fixed dose (AUC = 5) plus paclitaxel, given in 1 hour, and adriamycin every 21 days, the GEICO group carried out a phase I trial. Inclusion criteria were: histologically confirmed ovarian cancer, PS < 3 and normal liver, kidney, heart and marrow function. Patients after initial surgical debulking were included in 5 consecutive levels of dose:

Level 0 consisted in Paclitaxel 135 mg/2 and Adriamycin 40 mg/2. Level 1 rised adriamycin up to 50 mg/2 and maintained paclitaxel at the same dose than level 0. Level 2 went up to 150 mg/2 of paclitaxel and kept adriamycin at 50 mg/2. Level 3 rised again paclitaxel to 175 mg/2 and kept adriamycin at 50 mg/2. Level 4 was planned at the same previous dose of paclitaxel and adriamycin was given at 60 mg/2. From November-97 to September-98, 23 patients were accrued in 5 different institutions. Mean age was 61 (41-73). Three patients were respectively included at dose levels 0, 1 and 2. At dose level 3 8 cases were registered and 7 were accrued at dose level 4. Carboplatin was given at a dose calculated by the Calvert's formula at AUC = 5. Dose limiting toxicity was assessed after the first course of therapy and was febrile neutropenia at dose level 4. No other non hematological toxicity was detected as limiting. One patient at dose level 2 and 3 at dose level 4 had neutropenic fever. Level 4 was considered Dose limiting toxicity and the dose level 3 was the recommended dose for further phase II trials.

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POSTER

Cytokines IL-1b, IL-2, IL-6, IL-8, MCP-1, GM-CSF and TNFa in patients with epithelial ovarian cancer and their relationship to treatment with paclitaxel

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In-vitro work suggests that cytokines may be important modulators, both of the cytotoxic effects of paclitaxel and subsequent drug resistance. This has been investigated in-vivo in women with ovarian cancer. ELISA was utilized to evaluate the expression of 7 cytokines in serum and peritoneal fluid. This included 12 paired samples of serum and peritoneal fluids from post operative patients and serum from an additional 18 women with ovarian cancer. Samples were taken prior to, 24 hours after and approximately 7 days after treatment with paclitaxel. Serum concentrations of the cytokine

IL-6 and the chemokine IL-8 were elevated in women with ovarian cancer in comparison to healthy controls ($p < 0.05$). There was no increase in the expression of IL-1b, IL-2, GM-CSF or TNFa in either serum or peritoneal fluid. Peritoneal fluid concentrations of IL-6, IL-8 and MCP-1 were two to three logs greater than those in serum. Serum concentrations of IL-6 and IL-8 were associated with the response to chemotherapy. Raised concentrations of IL-6 correlated with a poor final outcome ($p = 0.039$) and raised IL-6 and IL-8 correlated with a poor immediate response to chemotherapy ($p = 0.041$ and $p = 0.041$ respectively). MCP-1 did not correlate with treatment outcome. There was a relatively clear pattern of change in all three cytokines. In serum, IL-6, IL-8 and MCP-1 decreased with the administration of steroids prior to paclitaxel, and increased in the 24 hours after paclitaxel. Levels in peritoneal fluid tended to decrease in the 24 hours after paclitaxel. Post operative drainage fluid was relatively acellular preventing flow-cytometric analysis of epithelial cells for apoptosis, but suggested activation of T cells by paclitaxel, particularly an increase in CD25+4+ cells. IL-6 and IL-8 appear to be of prognostic importance in epithelial ovarian cancer. Treatment with paclitaxel is associated with upregulated expression of a limited number of cytokines in women with ovarian cancer, notably IL-6, IL-8 and MCP-1.

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POSTER

Tumor angiogenesis, hepatocyte growth factor, and c-Met expression in endometrial carcinoma

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Purpose: This study was designed to evaluate the significance of tumor angiogenesis and angiogenic factors such as hepatocyte growth factor (HGF) and c-Met in endometrial carcinoma.

Methods: To evaluate tumor angiogenesis, the microvessels within the primary endometrial carcinoma were highlighted by immunostaining their endothelial cells for von Willebrand factor. HGF and c-Met expression were identified with specific antibodies. The correlation between these factors and prognosis were analyzed in 93 patients with endometrial carcinoma.

Results: A high microvessel count (>110 in a 0.90 mm² area) was significantly correlated with stage III and IV, G3, positive lymph node involvement, and shorter survival. c-Met was significantly correlated with stage III and IV, G3, and shorter survival. HGF was significantly correlated with stage III and IV. Multivariate analysis showed that stage III and IV, G3, myometrial invasion >1/2, and a high microvessel count were independent indicators.

Conclusions: Microvessel count and c-Met expression were significant prognostic indicators for patients with endometrial carcinoma.

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POSTER

Neoadjuvant chemotherapy (NC) in patients with locally advanced cervical cancer (LACC)

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Purpose: To investigate the impact of NC in the operability rate, local control, progression free survival (DFS) and overall survival (OS) in patients with LACC.

Methods: Inclusion criteria was unresectable stage IB2-III cervical carcinoma diagnosis. Treatment consisted of two cycles of Cisplatin 50 mg/m², bleomycin 30 mg and ifosfamide 5 gr/m². Patients considered to be resectable after chemotherapy underwent a type II radical abdominal hysterectomy and postoperative radiation therapy. Those considered not to be resectable were treated with radical radiotherapy.

Results: Fifty four evaluable patients were included in the study. Median follow-up time was 41 months (range, 26-165). Clinical responses were observed in 34 (64%) out of 54 patients: CR was in 2 (4%) patients and PR in 32 (59%). Seventeen (31.5%) had disease stabilization and 3 (5.5%) progressed. Fifty percent of patients underwent radical surgery (6 out of 7 (85%) stage Ib2, 3 (100%) out of 3 stage IIa, 17 (63%) out of 27 stage IIb and 1 (5%) out of 17 stage IIlb). Median DFS was 96 months for the group treated with radical surgery versus 60 months for the rest of patients ($p = 0.009$). Median OS was not reached in patients undergoing surgery versus 42 months in those not resected ($p = 0.005$).

Conclusions: NC is active in LACC allowing radical surgery in a high percentage of patients. The potential benefit of this strategy respect to radiotherapy alone should be investigated in prospective randomized trials.