the first day with 3 weekly intervals. Patients without a definite clinical or radiological evidence of disease progression underwent surgical laparotomy for response assessment.

Results: Pathologic complete response was attained in 19 pts. (73.1%). One patient (3.8%) had progressive disease. After a median follow-up period of 29 months (10-64), 13 pts. (50%) are alive with no evidence of disease, 4 pts. (15.4%) are living with their underlying disease and 9 pts. (34.6%) have died due to tumor progression. Median response duration in those with primary and persistent disease are 17 months (0-48) and 12 months (0-40), respectively. Out of 205 cycles, WHO grade III and IV toxicities were documented as follows: anemia 3 pts (11.5%), neutropenia 2 pts. (7.7%), thrombocytopenia 2 pts. (7.7%), emesis 6 pts. (23.1%), renal toxicity 3 pts. (11.5), diaarhoae 1 pt. (3.8) and alopecia 17 pts (65.4%). A neutropenic febrile episode was observed in 1 patient. Intraperitoneal treatment caused grade III abdominal pain in 3 patients.Three pts. (11.5%) had catheter-related complications; which necessitated an alteration to intravenous (IV) cisplatin treatment in 2 pts. In 3 pts. intraperitoneal cisplatin had to be replaced by IV carboplatinum due to severe nephrotoxicity. There were 4 cycles of treatment delays due to hematologic toxicity in 2 pts., nephrotoxicity and severe emesis in 1pt. and an autitis episode in 1 pt.

Conclusion: Intraperitoneal cisplatinum combined with IV paclitaxel at 135 mg/m2 as a 3 hour infusion is an effective and safe combination for the treatment of advanced ovarian cancer.

1197 POSTER

Independent prognostic factors who predicted progressive disease in advanced ovarian cancer

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This study was undertaken to assess the prognostic value of thirteen variables in 222 patients with advanced ovarian cancer related to the interval to progression.

Besides the pretreatment CA125 values, marker kinetiks and CA125 half-life (T1/2), ten other common clinicopathological variables were investigated: age, type of surgery, disease stage, Karnofsky index, residual disease, histological type, histological grade, type of cisplatin chemotherapy (PAC, PC, PA), number of chemotherapy cycles (CT) and treatment response.

Serial determination of tumor marker CA125 were performed in all patients. T1/2 was calculated in 122/222 patients, according to the van der Burg's formula. CA125 kinetics could be estimated only for patients whose prechemotherapy levels were above 35 U/ml, i.e. 134/222 patients.

A univariate analysis (log-rank, Tarone-Ware, Breslow and univariate Cox analysis) estimates the effect of each prognostic factor individually, not taking into consideration coexisting prognostic factors. Statistical significance was observed for the following out of 13 investigated variables: age, type of surgery, FIGO stage, histological grade, residual disease, Karnofsky index, number of chemotherapy, CA125 kinetics and C A125 half-life (T1/2). A multiple regression analysis based on Cox's proportional hasard model was used to test the relative importance of variables as predictors of free interval to progression. The indipendent predictors in order of significance are: Karnofsky index ($p<0.0001$), T1/2 ($p=0.0011$), CA125 kinetics ($p=0.0014$), histological grade ($p=0.0087$) and residual disease ($p=0.0191$).

As consequence, the possibility to predict treatment response by the CA125 half-life during CT and the time need for normalization of CA125 levels can divide patients into good and poor prognostic group early during CT.

1198 POSTER

Are p27,p21 and p53 prognostic factors in ovarian carcinoma patients?

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p21, p27 and p53 have been shown to be of prognostic significance in different human tumors.

Material and methods: Using immunohistochemistry, we examined p27, p21 and p53 in a series of 76 consecutive SEN (Serous Epithelial Neoplasia) pts. Thirteen borderline tumors were excluded from this analysis, leaving 53 primary ovarian (31 serous papillary, 22 other histotypes) and 10 serous surface papillary carcinomas, with a median follow-up of 38 months (range: 2-84).The carcinomas were graded according to WHO (3 G1, 33 G2, 19 G3 and 8 G4) and staged according to the FIGO criteria (24 S I-II and 39 S III-IV).Immunostaining monoclonal antibodies were K2502 (p27), EA10 (p21) and DO7 (p53).Cases were considered positive if the percentage of stained tumor cells was above the median value of 20% for p27 and p53, and 2.5% for p21.

Results: Among the 63 evaluable tumors, 55.5% showed a clear p53 overexpression and 49.2% showed low p27 and p21 expression.

No relation was seen neither between p53 and p21 nor between p27 and p21.

No significant relation was also observed between these markers and tumor histotype, grade or stage, although a trend was seen for higher grade tumors to overexpress p53.DFS and OS appeared to be correlated with grade ($p=0.02$ and $p=0.01$), stage ($p<0.0001$ and $p=0.004$) and p53 expression ($p=0.03$ and $p=0.02$), but not with the combined p53/p21 phenotype.At 4 years, DFS and OS were statistically worse (30% and 56%) in p53 positive tumors than in p53 negative (61% and 75%).

Conclusions: these data appear to confirm the worse prognosis of p53 overexpressing ovarian cancers, while p21 and p27 don't seem to correlate with clinical outcome.

1199 POSTER

A phase II trial of a paclitaxel and oxaliplatin combination in advanced ovarian cancer patients pretreated with cisplatin or carboplatin ± taxanes: Preliminary results

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Purpose: The aim of this ongoing study is to evaluate the efficacy and safety of a paclitaxel and oxaliplatin combination in patients with advanced ovarian cancer (AOC) and clinically measurable disease, pretreated with one platinum based regimen ± taxanes, with a platinum-free interval of at least 6 months.

Patients and Methods: As of March 2001, the first 24 patients (pts) entered in 9 French centers had been externally reviewed. Median age was 61 years (40–76), and performance status was 0 = 12 pts, 1 = 9 pts, 2 = 3 pts. Platinum free interval (PFI) was >12 months in 16 pts, and 6–12 months in 8 pts. Paclitaxel 175 mg/m^2 was administered over 3 h followed by oxaliplatin 130 mg/m^2 over 2 h every 21 days for a maximum of 6 to 9 treatment cycles.

Results: Twenty-two pts (115 cycles) were eligible and evaluable for efficacy and toxicity, 14 of whom were taxane-pretreated. An ORR of 91% was achieved with CR observed in 5 pts, PR in 15, and SD in 2. Median follow up was 7 months (4–16); 6 pts progressed (at 7, 7, 8, 10, 11, and 12 months), and no deaths occurred. The median number of cycles received was five (2$^+$–9). Grade 3 and grade 4 neutropenia occurred in 33% and 13% of cycles, respectively, with a single episode of febrile neutropenia. Grade 3 thrombocytopenia was observed in 1% of cycles, grade 3/4 nausea and vomiting in 3%, grade 3 asthenia in 4%, and grade 3 allergic reaction in 2%. Reversible neurotoxicity ≥ grade 2 (NCI-CTC) was observed in 54% of pts after a median of 4 cycles (3–6) and led to treatment discontinuation after six cycles for one patient.

	Prior taxanes	N = 14	No prior taxanes N = 8		Total (N = 22)
PFI (months)	6–12	>12	6–12	>12	-
CR + PR (pts)	6	7	1	6	20 (91%)
SD (pts)	1	–	–	1	2 (9%)

Conclusion: These encouraging results indicate that the paclitaxel and oxaliplatin combination is safe and very active in platinum-pretreated AOC patients with a platinum-free interval of at least 6 months.

1200 POSTER

Relapsed ovarian cancer after failure of first-line chemotherapy with platin and paclitaxel -a phase II study

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Background: Topotecan (T), a topoisomerase I- inhibitor, is approved for

the treatment of recurrent ovarian cancer, and Gemcitabine (dFdC) has also shown demonstrable activity against ovarian cancer. Both drugs affect DNA synthesis, and in addition, Topotecan, inhibits DNA repair. We performed a monoinstitution dose-finding study with T administered on d1-d5 and dFdC on d1+8/q22d as 30 min infusion without growth factors (ASCO 1999, *1482).

Methods: For this multicenter phase II study patients with relapsed epithelial ovarian cancer and prior treatment with platinum- and paclitaxel-containing chemotherapy, ECOG status 0-2 were eligible. All patients gave their written informed consent. T was given at a initial dose of 0.5mg/m2/d and dFdC of 800mg/m2 on day 1 and 600mg/m2 on day 8.

Results: From 3/1999 to 1/2000 21 patients (median age 58 years, range 36-70) with 1-3 pre-treatments were recruited. Ninety-four courses (median: 6; range:1-8) have been applied. The topotecan dosage has been escalated to 0.75 mg/m2 after the first course in eight patients, in two patients to 1.0mg/m2 topotecan. Dose reduction was not necessary in any case. Only 1 patient developed leucopenia CTC-grade 4 after the first cycle, while 3 patients suffered from grade III/IV anaemia. There were no episodes of neutropenic fever, sepsis or chemotherapy-related fatalities. Four patients experienced thrombocytopenia grade IV but without clinical sequelae. The incidence of non-haematological toxicities was very low. Grade 2 alopecia occurred in ten cases. Ten patients were evaluated for clinical tumour response by standard radiographic methods: 3 CR, 4 PR, 1 SD, 2 PD. No evidence of disease (NED) was observed in four and 7 patients were not evaluable for response. With a mean follow up of 15 months the median disease free survival of patients was 8.8 months (95%CI 8-9.5) and the mean 10.4 months (95%CI 7.4-13.3). The median of overall survival has not yet been reached with a mean overall survival of 18.6 months (95%CI 15.3-21.9). 14 of patients are still alive.

Conclusion: Topotecan in combination with Gemcitabine had a favourable toxicity profile and showed encouraging response and survival. A phase III study to compare a mono- with a combination chemotherapy has been started. Supported by SmithKline Beecham Germany

1201 POSTER

Topotecan (T) and cyclophosphamide (CY) in second line treatment of advanced ovarian cancer (AOC): a gineco phase II trial

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Purpose: Based on in vivo studies showing synergy between T and Cy and on a previous phase I study (Murren et al, J Clin Oncol 148-157, 1997), the GINECO group initiated a phase II trial to investigate the efficacy and tolerance of combined T and Cy in patients (pts) with recurrent AOC treated with only one previous platinum and taxane based regimen.

Methods: From 08/98 to10/00, a total of 86 pts received a q3 weeks schedule of T (0,75 mg/m2/d) for 5 consecutive days and Cy (600 mg/m2/d) on day 1.

Results: Pts characteristics were the following: age (median 60 yrs, range 33-79), serous histology (60%), PS 0-1 (95%), chemosensitive disease (DFI >6 months)(58%), measurable tumor (50%), CA 125 level >40 UI/ml (88%). Pts received a median of 4.5 courses (1-9). Hematologic toxicity was NCI grade 3-4 neutropenia (59% of cycles), thrombocytopenia (9%) and anemia (18%). Febrile neutropenia occurred in 8%. G-CSF, red blood cell and platelet transfusions respectively were required in 17%, 15% and 1%. Dose reduction and course delay were observed in 9% and 20%, mainly due to hematological toxicity. Non-hematological toxicity was moderate except alopecia (49%) and grade 3 fatigue (19%). To-date 80 pts are evaluable yielding an overall response rate of 24% (19/80) including 3 pts (4%) achieving clinical complete remission. Response rate is 3% in pts with <6 months relapse (1/35) and 40% in chemosensitive disease (18/45). Median progression-free survival and overall survival is respectively 5 and 10 months.

Conclusion: the combination of T and Cy is feasible and tolerable in outpatient treatment of recurrent AOC. T+Cy combination achieves an encouraging 40% response rate in pts with relapse >6 months after platinum and taxane treatment.

1202 POSTER

Topotecan and paclitaxel in second line treatment of advanced ovarian cancer (AOC): a gineco phase II trial

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Purpose: Topotecan (T) and Paclitaxel (P) have been demonstrated to be effective in second line treatment of ovarian cancer and are among the two best candidates for a non-platinum doublet in the treatment of AOC.

Methods: A total of 34 patients (pts) with recurrent AOC after a previous platinum-based regimen without taxane received a q3w schedule of T (0,75 mg/m*/d, d1-5) and P (135 mg/m*, 3 hours, d1).

Results: Pts characteristics were age (median 59 yrs, range 40-74), serous histology (65%), PS 0 (59%), platinum-sensitivity (DFI >6 months) (70%), measurable tumor (71%), CA 125 level >40 UI/ml (83%). Pts received a median of 6 courses (1-9). Hematologic toxicity was NCI grade 3-4 neutropenia (54% of cycles), anemia (14%) thrombocytopenia (2%). Febrile neutropenia occurred in 6%. G-CSF, red blood cell and platelet transfusions respectively were required in 20%, 5% and 1%. Dose reduction and course delay were observed in 8% and 15%, mainly due to hematological toxicity. Non-hematological toxicity was moderate including alopecia (83%), grade 3 fatigue (20%), grade 2-4 nausea/vomiting (20%), grade 2 and 3 neuropathy (10 and 3%). The overall rate is 40% (14/34) including 6 pts (18%) achieving complete clinical remission. Stable disease was observed in 6 pts. Response rate is 22% in pts relapsing within 6 months (2/9) and 48% in platinum-sensitive disease (12/25). Median progression-free survival and overall are respectively 9 and 22 months for responders, 7 and 19 months for pts with stable disease, 3 and 6 months for pts with progressive disease.

Conclusion: the combination of T and P is feasible and tolerable in outpatient treatment of recurrent AOC and achieves an impressive activity in patients who had received a prior platinum-based regimen without a taxane.

1203 POSTER

Toxicity-adapted dosing of topotecan in non-taxane-pre-treated, recurrent ovarian cancinoma

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Purpose: A toxicity-adapted schedule of the topoisomerase I inhibitor Topotecan was evaluated in a non-randomised, multi-center, phase II study. Women with epithelial ovarian cancer which relapsed after a prior non-taxane containing chemotherapy were analysed with regard to safety, toxicity and efficacy.

Patients and Methods: Including criteria were a recurrent ovarian cancer, no previous taxane treatment, bidimensionally measurable disease, ECOG-performance status of 2 or less, sufficient bone marrow, liver and renal function. Topotecan was administered in the first cycle as a 30-minute infusion with 1.25mg/m2 for 5 consecutive days and was repeated every 21 days. Topotecan dose was adapted dependent on the maximal haematological toxicity after the first cycle to 1.5mg/m2, to 1.0mg/m2, or continued at 1.25mg/m2. No prophylactic use of granulocyte colony stimulating factor (G-CSF) was allowed.

Results: 26 patients were recruited into the study. 25 patients were evaluated for toxicity and 23 for efficacy. 18 patients (78%) had one previous chemotherapy, four patients (17%) underwent two and one patient five prior regimens. A planned dose reduction to 1.0mg/m2 was done in 6 patients, whereas an increase to 1.5mg/m2 was possible in 8 patients. After dose-adaptation grade 3/4 leucopenia occurred after the 1st cycle in the 1.0mg/m2 group in 44%. In the 1.5mg/m* group a leucopenia occurred after the 1st cyclein 18%. Thrombopenia occurred only in the first cycle with 24%. Non-haematological side-effects were generally mild, one a grade 4 stomatitis along with a grade 3 pain and infection. The overall response rate was 30,4%. For the dose-reduced group, the dose-increased group, and the initial-dose group the response rate was 50%, 28.6%, and 25%, respectively. Patients who required a dose reduction were treated with a median of 6 (range 3-9) cycles of Topotecan, while both others were treated with a median of 4 (range 2-8 for 1,25mg/m2 and 3-6 for 1,5mg/m2) cycles.

Conclusion: Toxicity-adapted dosing of Topotecan maintains efficacy but can reduce toxicity in systemically pre-treated patients with recurrent ovarian carcinoma.