patient refractory to either platinum or taxane. Grade 4 neutropenia occurred in 48% and febrile neutropenia in 17%. Two septic deaths occurred during treatment (1 patient receiving 1.25mg/m2 over 5 days, 1 patient receiving 1.5mg/m2 over 5 days). Twenty seven percent (11) patients experienced dose delays (7of whom received 1.5mg/m2 dose) and 17% (7 patients) had a dose reduction (4 of whom received 1.5mg/m2).

Conclusions: The response rate is lower than was anticipated and is likely to be a function of dose delays and reductions, and the high frequency of platinum and/or taxane-refractory disease. Our data suggest that the optimal use of topotecan in the off study salvage setting is in minimally pre-treated, fit patients at a dose level of 1.5mg/m2 over 4 or 5 days. Randomised studies comparing topotecan with less toxic alternative therapies (such as oral VP16) in this setting are warranted.

1185 POSTER

Efficacy and toxicity of chemotherapy (Carboplatin/Ifosfamide) combined with whole body hyperthermia (WBH) in patients with recurrent ovarian cancer - a phase II study (dolphin-1-study)

B. Strobl[1], W. Janni[1], D. Rjosk[1], F. Bergauer[1], L. Kornya[2], H. Sommer[1]. [1] *I. Frauenklinik, Ludwig-Maximilians-University, Gynecological Oncology, Munich, Germany;* [2] *Péterfy Kórház Szülö-Nöbeteg Osztály, Klinikai Onkológus, Budapest, Hungary*

Purpose: Despite several improvements in the cytostatic treatment over the last years, the prognosis of patients with recurrent ovarian cancer still remains unfavorable. There is some evidence that the combination of whole body hyperthermia (WBH) with special cytostatic agents (e.g. carboplatin, ifosfamide) leads to a higher efficacy through increased cellular metabolism and immunostimulation.

Methods: In an ongoing prospective multicenter phase II Study we are evaluating the toxicity and efficacy of 11 patients (38 treatment courses) with recurrence of ovarian cancer receiving WBH (target temperature 41.8°Celcius over 1 hour) combined with carboplatin AUC5 and ifosfamide 3g/m2 every 28 days, for 6 cycles or until progression. Patients (=65 years) are required to have sufficient cardiac, pulmonal and renal function.

Results: Toxicity lead to dose reduction in 14 courses (36,8%). The following toxicities (NCI) were seen: myelotoxic side effects as grade 3 leucocytopenia in 11 cases (28,9%) and grade 4 leucocytopenia in 6 cases (15,8%). Thrombocytopenia grade 3 occurred in 9 courses (23,7%), grade 4 in 7 courses (18,4%). In 2 courses renal toxicity grade 2 appeared. In 10 courses (26,3%) skin burnings grade 2 and in 4 courses (10,5%) skin burnings grade 3 were reported. No other severe treatment related adverse events were noted. Preliminary data on efficacy include 5 patients with partial remission, 4 patients with stable disease and 1 patient with progression.

Conclusion: The combination of carboplatin and ifosfamide with WBH is well tolerated and appears to be feasible and safe. After the successful completion of the phase II sequence (15 patients) the study will continue as a randomised multicenter phase III study, comparing above treatment with normothermic cytostatic application. This will be the first phase III trial to evaluate the efficacy of WBH combined with chemotherapy.

1186 POSTER

Chemotherapy with carboplatin/docetaxel for primary and recurrent epithelial ovarian cancer

F. Beldermann[1], I. Lauschner[1], M. Geberth[1], A. Schneeweiss[1], J. Huober[2], A. Meyer[2], G. Bastert[1]. [1] *University of Heidelberg, Dep. of Obstetric and Gynaecology, Heidelberg, Germany;* [2] *University of Tuebingen, Department of Gynecology, Tuebingen, Germany;* [3] *University of Tuebingen, Department of Gynecology, Tuebingen, Germany*

The high incidence of peripheral neurotoxicity associated with platinum/paclitaxelcontaining chemotherapy for ovarian carcinoma is frequently a limiting factor with respect to long term treatment. A pilot study was conducted with docetaxel instead of paclitaxel to investigate if incidence of neurologic toxicities could be decreased withoutcompromising tumor response.

Sixty-one pts with epithelial ovarian cancer (FIGO II-IV), were treated with the combination of carboplatin (AUC 5) and docetaxel (75mg/m2), i.v., q3w. Twenty-nine pts received 6 courses of carboplatin/docetaxel as first-line treatment for ovarian carcinoma. A further 32 pts were treated with carboplatin/docetaxel for relapse >12 months as second line therapy.

A total of 300 courses was administered: Predominant WHO grade 3/4 toxicity was leucopenia (21/61). Grade 3 thrombocytopenia occurred in 5% of pts. No Grade 3 neuropathy was observed,. Grades 2 and 1 neuropathy was seen, respectively, in only 2/61 pts and 16/61 pts. In the second-line cohort, neurotoxicity was not increased. 12/61 pts complained of mild to moderate fluid retention, mild to moderate nausea and vomiting (WHO 2/3) occurred in 24/61 pts. No ototoxicity was observed.

Of 26 first-line patients evaluable for response, ORR (CR + PR) was 79%. Thirty second-line pts were evaluable for responsewith ORR of 75%. Calculated median TTP for first-(23/29) and second-line cohorts (23/32) was 10 and9,4 mos, respectively.

In summary, the observed efficacy of carboplatin/docetaxel combination therapy for ovarian carcinoma is comparable to that reported for platinum/taxane combinations. Nevertheless toxicities, particularly neurologic side effects are less severe and less predominant with carboplatin/docetaxel.

1187 POSTER

Complement activation in ovarian cancer

M. Swahn[1], M. Hahlin[2], M. Haeger[2], A. Bengtsson[3], M. Tylman[3], G. Horvath[1]. [1] *Sahlgrenska University Hospital, Department of Gynecological Oncology, Gothenburg, Sweden;* [2] *Sahlgrenska University Hospital, Department of Obstetrics and Gynecology, Gothenburg, Sweden;* [3] *Sahlgrenska University Hospital, Department of Anesthesiology and Intensive Care, Gothenburg, Sweden*

Background: Activation of the complement system plays a key role in the inflammation process and in protecting the host from pathogenic agents, e.g. viruses and bacteria. Complement activation has also been observed in connection with neoplastic disease. The aim of the present study was to determine whether complement is activated in patients with cystic ovarian tumors and if the degree of activation differs in malignant and benign tumors.

Methods: C4d, Factor Bb, C3a/C3a-desArginine and SC5b-9 were measured in 65 patients with lower abdominal cystic ovarian tumors, including 31 ovarian cancers and 35 benign ovarian tumors. Patient age and tumor size did not differ significantly between the two groups. The levels of C4d, Factor Bb and SC5b-9 were determined in plasma, in ascites and in cyst fluid with Enzyme Immune Assay (EIA) methods. Levels of C3a/C3a-desArginine were determined in the same compartments with an ELISA procedure.

Results: C4d and C3a/C3a-desArginine were significantly elevated in plasma, ascites and in cyst fluid in patients with malignant ovarian tumors compared to patients with benign tumors. Factor Bb and SC5b-9 showed significantly higher levels in plasma and in cyst fluid in patients with malignant cystic ovarian tumors compared to those with benign tumors.

Conclusions: This study shows that complement is activated in patients with ovarian cystic tumors. There is a significantly higher grade of activation in patients with malign ovarian tumors than in patients with benign cystic tumors in the ovaries.

1188 POSTER

Long-term survival with consolidation intraperitoneal chemotherapy (IP) in advanced ovarian cancer (AOC) with complete pathological remission

C. Tourrigand[1], C. Louvet[1], J. Molitor[1], N. Dehni[2], V. Lejeune[2], A. Sezeur[3], A. Pigné[5], L. Marpeau[4], J. Cady[5], A. de Gramont[1]. [1] *Hopital Saint Antoine, Oncoloy, Paris, France;* [2] *Hopital Saint Antoine, Surgery, Paris, France;* [3] *Hopital des Diaconnesses, Surgery, Paris, France;* [4] *Hopital Charles Nicolle, Gynecology, Caen, France;* [5] *Clinique Geoffroy Saint Hilaire, Surgery, Paris, France*

Intraperitoneal (IP) chemotherapy (CT) in AOC demonstrated significant activity in patients with small-volume residual disease (RD), as part of the initial chemotherapy or after failure of IV CT. However, long term evaluation is seldom reported. We report our results with consolidation IP CT in patients who achieved a complete pathological response after IV CT. This study included patients (pts) with AOC (stage III-IV, under 70 yrs) who entered in four prospective trials (1984-1997) including IV CT based on cisplatin (6 cycles) and anthracyclines, early debulking surgery after three cycles of CT in case of initial RD over 2 cm, second-look laparotomy (SLL) and intraperitoneal consolidation CT (Proc ASCO; 10:639, 1991; Proc ASCO; 12:888, 1993; Eur J Cancer; 28:53, 1992). Among 219 pts, 68 with biopsy negative second-look laparotomy received every 4 weeks 3 consolidation cycles of IP CT via a totally implantable port. Fifty six patients received mitoxantrone 25 mg/m2 D 1, VP16 120 mg/m2 D 1. In 16 pts, IP cisplatin 100 mg/m* was added (no previous neuropathy). Nine patients received high dose cisplatin (200 mg/m*) and 3 patients had cisplatin 200 mg/m*+cytarabine 2g. Only 13 pts (19%) did not receive the full 3 cycles.

Mean age was 56 years. Stage IIIA 3pts, IIIB 15pts, IIIC 45 pts, IV 5 pts. There was one toxic death (2%). With a median follow-up of the study of 8.25 years, median overall survival is 75 months and median progression-free survival is 41 months. At 5 years, 60% are alive and 32% didn't relapse. Intensive consolidation IP CT after negative SLL can improve survival in AOC. However, due to late relapses the cure rate remains disappointedly low, even in this most favorable patients category. Long-term follow-up (more than 5 years) is therefore needed to further evaluate strategic treatment options.

1189 POSTER

Cisplatin nephrotoxicity

C. Rodrigues Pereira[1], J. Baldaia[2], J. Maximino[3], A. Vasconcelos[4], F. Basto[5], A. Loureiro[6], E. Pinto Ferreira[7]. [1] *São João Hospital, Medicine III, Oporto, Portugal;* [2] *Portuguese Oncologic Institut Francisco Gentil, Nephrology, Oporto, Portugal;* [3] *Portuguese Oncologic Institut Francisco Gentil, Nephrology, Oporto, Portugal;* [4] *Portuguese Oncologic Institut Francisco Gentil, Oncology, Oporto, Portugal;* [5] *São João Hospital, Medicine III, Oporto, Portugal*

Introduction: Cisplatin (CP) is an antineoplastic agent active against ovarian tumours but nephrotoxicity is often dose- limiting.

Objective: To determine the incidence of acute and chronic nephrotoxicity of CP, the risk factors associated with its development and the influence of two different types of prophylactic hydration.

Materials and methods: We have retrospectively studied 132 patients who received CP in the treatment of ovarian cancer in the Portuguese Institute of Oncology Francisco Gentil between 1995 and 2000. They all had a normal plasma creatinine concentration before treatment. They received a dose per course of 75 mg/m2, with a minimum of 6 courses and a maximum of 12 courses of chemotherapy (CT). There were 2 different courses of prophylactic hydration: 'prolonged hydration'; (4000cc of saline in 20 hours) and 'short hydration'(3000cc of saline in 6 hours). Acute Renal Failure (ARF) was defined as a doubling in the plasma creatinine concentration and Isolated Tubulopathy (IT) as the appearance of hypomagnesemia without a concomitant rise in plasma creatinine concentration. Chronic Toxicity(CT) was defined as a doubling in the plasma creatinine concentration, 6 months after chemotherapy.

Results: There was evidence of nephrotoxicity in 78 patients (59%); 53 (40%) had ARF and 25 (19%) IT. Most toxicity developed after the 6th course of CT with an average cumulative dose of 720 mg. Age was significantly associated with nephrotoxicity (58,1 ± 11,8 vs 49,3 ± 14,1; $p<0,0001$), dose of CP per cycle (118± 17 vs 104 ±30; $p<0.005$), and highest cumulative dose (797 ± 254 vs 680 ± 221; $p<0,01$). In 12 patients CT was suspended due to side effects. 20 patients died during treatment. There was no significant statistical difference between the two types of prophylactic hydration. CT was seen in 29 patients (22%) and was significantly associated with age (59,5 ± 13,6 vs 53 ± 13,1; $p<0,05$).

Conclusion: Acute nephrotoxicity of CP has a high incidence. Age, dose of CP per course of CT and cumulative dose of CP, are risk factors for toxicity. There were no differences in the incidence of nephrotoxicity between the two prophylactic courses of hydration. Development of chronic nephrotoxicity is frequently related with the age.

1190 POSTER

The predictive value of computerized tomography (CT) for surgical findings in ovarian cancer patients

C. Arcuri[1], S. Brugnara[1], M. Centonze[2], F. Valduga[1], O. Caffo[1], A. Lucenti[1], A. Ferro[1], S. Santarossa[1], E. Arisi[3], E. Galligioni[1]. [1] *St. Chiara Hospital, Medical Oncology, TRENTO, Italy;* [2] *St. Chiara Hospital, Radiology, TRENTO, Italy;* [3] *St. Chiara Hospital, Gynecology, TRENTO, Italy*

Objective: Pelvic and abdominal computed tomography (CT) is usually performed in patients (pts) with ovarian cancer (OC) to evaluate the diseases extent as well as the response to therapy. The purpose of this retrospective study was to evaluate the role of CT scan in predicting pathologic response to systemic chemotherapy, in pts with OC.

Methods: We retrospectively reviewed the abdominopelvic CT scans performed after the completion of three or more cycles of Platinum based chemotherapy in 29 pts with proven epithelial ovarian cancer and residual lesions after primary surgery. These CT findings were compared with subsequent laparatomic findings.

Results: The correlation between radiologic and laparatomic findings was concordant in 72% (21/29) of pts and discordant in 27% (8/29).

After chemotherapy, 14 CT were negative (Clinical Complete Remission) and 15 were positive (14 Remission Partial and 1 Stable Disease), but between the 14 pts with negative CT there were only six pathological Complete Remissions whereas all 15 pts with positive CT were positive at surgery. Cumulatively laparatomy revealed either microscopic or macroscopic residual lesions in 23 pts, while 6 pts were completely tumour-free.

Conclusions: In our experience a positive CT always corresponded to positive surgical findings whereas a negative CT correlated with pathological Complete Remission only in 42% of the cases.

The positive predictive value was 100% and the negative predictive value of CT was only 38,4%.

1191 POSTER

Recurrent granulosa cell tumor of the ovary: Retrospective analysis

K. Uygun[1], Z. Kocak[1], P. Saip[2], M. Basaran[2], A. Aydiner[2], M. Dincer[2], F. Tas[2], E. Topuz[2]. [1] *Trakya University faculty of Medicine, Oncology, Edirne, Turkey;* [2] *Istanbul University Institute of Oncology, Oncology, Istanbul, Turkey*

Purpose: In this study, patients with Granulosa cell tumours (GCT) were evaluated retrospectively and recurrent cases characteristics and treatment outcomes were documented.

Methods: Forty-five patients (4.7%) with GCT were treated among 952 patients with ovarian cancer between 1979-1998. Nine of 45 patients (20%) developed recurrent disease on follow-up. All patients but one (stage Ia) had stage III disease. The specific recurrence sites were intraabdominal (liver, peritonea, spleen), 4; pelvic, 2; pelvic+intraabdominal, 2; lung, 1. Patients with only pelvic recurrence received only pelvic radiotherapy (2 patients) and patients with distant (intraabdominal, lung) ± pelvic recurrence received only chemotherapy of cisplatin, doxorubucine, cyclophosphamide (PAC) or cisplatin, cycphosphamide (PC) (5 patients). The other two patients with intraabdominal recurrence refused to receive treatment.

Results: The median age was 46 (16-54) years. The median recurrence time was 19 (5-29) months. Patients with only pelvic recurrence receiving only radiotherapy were dead of their disease progression 5 and 6 months from the diagnosis of recurrence. The other two patients who had no treatment were also dead of their disease progression 11 and 13 months after the recurrence. Among patients received chemotherapy, three complete and 1 partial responses were observed, for an overall response rate of 80%. One patient had progressive disease under the chemotherapy. Three of 5 patients receieved chemotherapy were dead of their disease progression 26, 41, 52 months while two patients who had complete response were alive without evidence of disease 25 and 33 months from the diagnosis of recurrence. The median survival after recurrence for all patients was 21 (5-52) months.

Conclusion: Despite the small number of patients in our study it can be concluded that chemotherapy may be the treatment of choice for recurrent granulosa cell tumour of the ovary.

1192 POSTER

Suppression of invasion and peritoneal carcinomatosis of ovarian cancer cell line by overexpression of bikunin

M. Suzuki[1], H. Kobayashi[1], Y. Hirashima[1], Y. Takei[2], Y. Saga[2], M. Suzuki[2], H. Itho[3], T. Terao[1]. [1] *Hamamatsu University School of Medicine, Obstetrics and Gynecology, Hamamatsu, Japan;* [2] *Jichi University School of Medicine, Obstetrics and Gynecology, Tochigi, Japan;* [3] *Miyazaki University School of Medicine, the Second Department of Pathology, Miyazaki, Japan*

Purpose: Bikunin, a Kunitz-type proteases inhibitor, was isolated from human amniotic fluid and urine. We previously reported that bikunin efficiently inhibits soluble and tumor cell-surface receptor-bound plasmin. Bikunin inhibits not only tumor cell invasion in an in vitro assay but also production of experimental and spontaneous lung metastasis in an in vivo mouse model. Recently, we reported that bikunin markedly supresses the cell motility possibly through negative regulation of PKC- and MEK/ERK/c-Jun dependent uPA expression.

In this study we first transfected an expression vector harboring a cDNA encording for human bikunin to human ovarian carcinoma cell line HRA, highly invasive cells, and investigated the effect of bikunin overexpression on the changes in tumor cell phenotype and invasiveness in the stably transfected clones.

Methods: We made bikunin transfectants and luciferase transfectants as a control vector. The parental cells were used as control. 1) Proliferation,