ments. The optimal sequence at the starting dose formed the basis for subsequent dose escalations.

Results: 15 patients have been enrolled over 10 months; median age 56, range 46–68; PS median 1, range 0–2; 2 FIGO stage Ic, 8 stage III, & 5 stage IV; 8 with grade 3 histology, 5 grade 2 & 2 grade 1. 2 patients had clear cell morphology. All had undergone 1 previous platinum-based regimen, with a median treatment-free interval of 5 mths, range 6 wks to 29 mths. Dose-limiting neutropenia (CTC IV) & ALT rise (CTC III) was encountered at gemcitabine 1000 mg/m^2 and paclitaxel 175 mg/m^2. 2 patients who received gemcitabine prior to paclitaxel on day 8 at dose level 1 (1000/135) developed grade 3 transaminase rise. No other sequence-specific toxicities have been identified, and no significant PK differences defined. Four out of 10 evaluable patients have so far achieved a partial response (UICC).

Conclusion: Gemcitabine MTD is being explored at paclitaxel 150 mg/m^2. Further work will be presented utilising paclitaxel day 1, gemcitabine day 1 and 8.

544 POSTER

Ifosfamide and Hexamethilmelamine as rescue treatment for cisplatin refractory ovarian cancer

L. Torrecillas, G. Cervantes, A. Erazo. *Medical Oncology Department 20 de Noviembre ISSSTE hospital, Mexico*

Purpose: Before the taxane clinical introduction, the drugs with >30% response rate used as second line treatment were Ifosfamide (*I*) and Hexamethilmelamine (*H*). No experience has been published yet with the *IH* combination. We describe the results of 21 patients (pts) with cisplatin refractory ovarian cancer.

Methods: pts received *I* 2.5 g/m^2 days 1–2, mesna 500 mg/m^2 iv hours 0 + 4 and 1000 mg/m^2 po hours 8 + 12 on days 1–2 and *H* 150 mg/m^2/day on days 3–16 every 28 days, on an ambulatory setting. Pts median age was 52 years (range 35–70); previous cisplatin/carboplatin based cycle number 4–10 (median 7).

Results: the overall response was 38% (8 pts) with 2 complete responses (9.5%), 5 pts with stable disease (23.8%) and 8 pts with progression (38%). Toxicity for 77 delivered cycles (3.6 median cycles/pt): neutropenia G0 = 39.5%, G1 = 27.6%, G2 = 17%, G3 = 12%, G4 = 3.9%; two episodes of trombocythopenia and anemia G1; other mild side effects: abdominal cramps, muscular pain, nausea, astenia. The DFS for CR was 14–19 months, the free-progression interval for PR was 4, 6, 7, 8, 8 and 9 months respectively. The median overall survival for the entire group was 13.3 months (range 3–31 months). The observed median dose intensity: *I* 1.14 g/m^2/week (91.2%) and *H* 481.55 mg/m^2/week (91.72%).

Conclusions: 1. the low toxicity profile allowed a 91% dose intensity in a heavily pretreated group of pts with poor known prognosis; 2. *IH* can be safely delivered in an ambulatory setting; 3. *IH* can be considered a good option for rescue treatment in cisplatin refactory OC due to a high response rate, a good palliative effect and survival impact. This combination deserves more experience in larger population.

545 POSTER

Paclitaxel (PX) – Carboplatin (CBP) versus cyclophosphamide (CTX)-carboplatin supported by G-CSF as first line chemotherapy in figo III–IV ovarian carcinoma (O.C.)

A. Polyzos, N. Tsavaris, L. Giannikos, N. Kalahanis, K. Christodoulou, K. Giannakopoulos, G. Nikou, A. Toskas, J. Papargyriou, N. Katsilambros. *1st Dept of Propedeutic Medicine LAIKON Hospital, Goudi, Athens, Greece*

Purpose: To evaluate and compare the efficacy and toxicity of the combination of PX-plus-CBP versus CTX-plus-CBP as first line treatment in advanced O.C.

Method: Sixty patients (pts) – so far – with measurable or evaluable disease, aged 55 (40–70), stage III 48 pts, stage IV 12 pts, were randomized to receive: PX 175 mg/m2 over 3 h and CBP 7 (AUC) or CTX 600 mg/m2 plus CBP 7 (AUC). Both arms were supported by G-CSF 5 μg/kg/day × 5 days.

Results: Thirty pts for each arm were eligible and evaluable for response and toxicity. In PX-CBP arm 27/30 pts (90%) (95% CL 74–98) responded with 3PCR, 15 CCR and 9 PR. In CTX-CBP 22/30 pts (73%) (95% C.L. 54–88) responded with 3 PCR, 10 CCR and 9 PR ($p < 0.18$). Peripheral neuropathy (100%) and alopecia were the main toxicities of the PX-CBP arm. Apart from 20% grade 2 thrombocytopenia in both arms there was no other hematologic toxicity. Disease progression during treatment was recorded in 3/30 and 8/30 of the two arms respectively.

Conclusion: PX-CBL combinations is highly active. Both regimen supported by G-CSF are very well tolerated. Survival is pending. Patient's accrual continues.

546 POSTER

Chemotherapy in advanced ovarian cancer (AOC)

S. Ionescu Goga[1], N. Gutulescu[1], M. Ionescu-Goga[2]. [1]*Oncological Institute Bucharest;* [2]*University Paris VII, Romania*

The study designs an optimising therapy strategy with platinum derivatives in the aim to obtain surgical reconversion and consolidation of the results in AOC. The data presented, were from 86 cases of epithelial AOC, stage III and IV followed up between jan. 1993–dec. 1996. Features of the cases: age 29–69, diagnosis by citology of ascites (36% of cases), or histopathology after laparotomy or anexectomy. All had locally-advanced disease. We performed: a) neoadjuvant chemotherapy with 3–4 CAP schedules (CDDP 75 mg/m^2 or carboplatinum 450 mg + cyclophosphamide 500 mg/m^2 + farmorubicine 75 mg/m^2); b) debulking or radical surgery and c) 6 CAP schedules q 3 weeks. In 65% of cases radical histerectomy, bilateral anexectomy and omentectomy was possible; 35% of cases underwent citoreduction. Correct hydratation and antiemetic treatment realized good tolerance. Disease free survival (DFS) obtained was 6–11 months with good quality of life (QOL). After 12–24 months 35% of patients were submitted to second look: 55% had CR, 30% had restant tumors <2 cm and 15% progressive disease. For the last two categories we repeated chemotherapy with 3–4 CP courses (cyclophosphamide 500 mg/m^2 + CDDP 100 mg/m^2 or carboplatinum AUC 6). Overall response was 76% with good QOL. The 4 years follow-up underlines the value of platinum based regimens in the treatment strategy of AOC, realizing better DFS and good QOL.

547 POSTER

Serum concentrations of soluble interleucin-2 receptors (sIL-2R) in patients with benign and malignant ovarian tumors

G. Gebauer, M. Rieger, W. Jaeger, N. Lang. *Department of Obstetrics and Gynaecology, University of Erlangen-Nuremberg, Germany*

Purpose: In sera of patients with several benign and malignant diseases soluble interleucin-2 receptors (sIL-2R) are found in sometimes very high concentrations. We wanted to investigate if measurement of sIL-2R in serum could be useful for differentiation between benign and malignant ovarian tumors.

Methods: In sera of 130 patients with benign ovarian tumors and 112 ovarian cancer patients at different FIGO-stages concentration of sIL-2R was measured preoperatively with a chemolumineszenz assay.

Results: sIL-2R serum concentrations in patients with benign diseases were between 197 and 3236 U/ml (median 573 U/ml), in those with ovarian cancer between 237 and 6230 U/ml (median 807 U/ml). An upper normal level of sIL-2R serum concentration in patients with benign ovarian tumors was defined at the 95th percentile (1200 U/ml) of the distribution of sIL-2R concentrations in these patients (cut-off). 33% of the ovarian cancer patients had sIL-2R concentrations above these cut-off. sIL-2R concentrations increased with FIGO-stage

Conclusion: We conclude that sIL-2R could become a new interesting tumor marker in ovarian cancer. Further studies should clarify the possibility of therapy monitoring by serial sIL-2R measurement.

548 PUBLICATION

Evidence of p*53*-independent activation of bcl-2 in advanced ovarian and endometrium carcinomas

T.J. Gilster, C.M. Kurbacher, A. Goor, M. Janat, M. Becker, H. Engel, P. Mallmann. *Department of Gynecology and Obstetrics, University of Cologne Medical Center,*

Purpose: p*53* and bcl-2 are important determinants of apoptosis. Inactivation of p*53* by mutation often results in high expression of bcl-2 that is known to block apoptotic pathways and may thus lead to chemo- or radioresistance. However, bcl-2 may also be activated by p*53*-independent mechanisms which are not fully understood. This study was initiated to evaluate the coexpression of p*53* and bcl-2 in advanced human epithelial ovarian (EOC) and endometrium carcinomas (ENC).

Methods: A total of 24 samples derived from patients advanced EOC (n = 18) or ENC (n = 6) were studied by immunohistochemistry. Antigen recovery

in paraffin-embedded sections was performed using standard techniques. P53 and bcl-2 were detected by primary monoclonal mouse anti-human antibodies in conjunction with red APAAP stain. Antigen-expression of 3 × 100 tumor cells per sample was evaluated by light-microscopy.

Results: In only 3 of 18 EOC (17%) and 1 of 6 ENC (17%) 10–90% of tumor cells were positively stained for p53. In contrast, 10–90% bcl-2-expressing tumor cells were found in 17 of 18 EOC (94%) and 5 of 6 ENC (83%). Samples with high expression of p53 (i. e. >50%) were also highly positive for bcl-2, whereas all bcl-2 negative specimens were found to carry wild-type p53.

Conclusion: In a substantial proportion of advanced EOC and ENC, bcl-2 appears to be activated by p53- independent pathways.

549 PUBLICATION

CA125 mimicry by SCFV-fragments of the monoclonal anti-idiotypic antibody ACA125 for immunotherapy of ovarian cancer

S. Reinartz, H. Schlebusch, P. Giffels, S. Köhler, D. Krebs, U. Wagner.
Dept. of Gynecology and Obstetrics, University Hospital of Bonn, Germany

Purpose: The $F(ab')_2$ fragment of the murine monoclonal anti-idiotypic antibody ACA125 mimicking the tumor associated antigen CA125 is used as a vaccine for the induction of an anti-tumoral immunity in patients with ovarian carcinoma. We tried to generate a single-chain fragment (ScFv) composed of ACA125 heavy and light chain variable domains.

Methods: Heavy and light chain genes of antibody producing mouse hybridoma cell line were separately amplified and assembled into a ScFv gene with linker DNA by PCR. The ScFv gene was ligated into the phagemid vector pCANTAB5E, which allows the production of both, phage displayed and soluble ScFv. Transformed *E. coli* TG1 cells were infected with M13K07 helper phage to yield recombinant phage, which display ScFv fragments as a g3p fusion protein on the surface of the filamentous phage M13. The *E. coli* non-supressor strain HB2151 was infected with an antigen-positive phage clone, previously screened by ELISA, to express soluble ScFv fragments.

Results: Functional soluble ScFv binding to the idiotypic antibody OC125 $F(ab')_2$ could be detected in the bacterial periplasm by Western blot and ELISA. The variable heavy and light chain genes of the ACA125 ScFv fragment were further sequenced and compared with known antibody sequences.

Conclusion: ScFv-Fragments of an anti-idiotypic antibody mimicking CA125 serves as the basis for a site-directed mutagenesis of the CDR-Regions in order to improve the immunological reactivity of the anti-idiotype vaccine.

550 PUBLICATION

The value of neoadjuvant chemotherapy (NACT) after surgical-pathologic staging (SPS) vs. failed debulking (FD) for inoperable ovarian cancer (IOC) and subsequent interventional laparotomy (ILAP)

D. Wallwiener, G.P. Breitbach, G. Bastert. *For the GTOC-Study Group; University of Heidelberg, Dept. of Obstetrics and Gynecology, Voss-Str. 9, 69115 Heidelberg, Germany*

Purpose: The role of a NACT for IOC (extensive peritoneal carcinomatosis and/or residuals (R) > 2 cm) after SPS and FD, respectively, was evaluated concerning remission, operability at ILAP und overall survival (OAS):

Methods: In a phase II multicenter study 64 patients with IOC after SPS or FD received a dose intensified NACT (Cisplatin 100 mg/m2/Treosulfan 5.000 mg/m2 i.v. + GCSF every 3 weeks, 3 cycles) with subsequent ILAP.

Results: To date, an ILAP was performed in 5 women with a FIGO-stage III (n = 24; 69%) und IV (n = 11; 31%) disease. A NACT was administered after SPS in 22 cases and after FD in 15. An R0 resection was possible in 53% of patients after SPS and in 27% after FD (p = 0.008). Remission (PR+CR) rates were 77% in the SPS and 76% in the FD group. The rate of PD und NC was comparable in the two groups.

Conclusion: Low toxicity of NACT (no WHO toxicity grade IV), good remission rates (76%) and operable findings at ILAP with the feasibility of optimal cytoreduction (R_0 43% and R_1 14%%) were achieved. The data also show a possible benefit in OAS in the SPS group. Final results are presently being evaluated.

551 PUBLICATION

High dose cyclophosphamide (C) and epirubicin (E) followed by cisplatin (P) and 5-fluoro-uracile (F) in patients with advanced epithelial ovarian adenocarcinoma (AEOC)

A.C. Braud, P. Cottu, J.M. Extra, M. Espié, C. Cuvier, M. Marty. *Dpt of Medical Oncology, Saint Louis Hospital, Paris 75010, France*

There are data supporting a dose-response relationship for alkylating agents in OC. High-dose P is neurotoxic but high-dose C has not been explored in combination chemotherapy with Anthracyclins in AEOC. We have studied since 1992 a densified regimen with 4 courses at 2 wks interval of C (1200 mg/m²) and E (75 mg/m²), followed by 4 courses at 3 wks interval of P (75 mg/m²) and F (1 g/m²/d × 3 by protracted infusion). 29 stage IIIC–IV pts, with a median age of 53 y (range 35–73) were included. Other eligibility criteria were PS: 0–2, no cardiac nor renal contra indication to E or P. 55% of pts had >2 cm residual implants after primary surgery. CE courses were administered whatever the WBC count, without hematopoietic growth factor, but were delayed if febrile neutropenia. Toxicities differed in the 2 parts of treatment. Grade 4 neutropenia was more prominent after CE (70%), but neutropenic fever was unfrequent (14%). Grade 2–3 anemia and Grade 3 emesis were more frequent after FP (39 and 46% respectively). Clinical CR was achieved in 72% of pts. Among 19 pts with objective response assessed by second look laparotomy, 9 obtained pathological CR (47%). After a median follow up of 25 months, 17 pts have progressed and 12 died. Median progression free and overall survival were 13 and 28 months, respectively. These results are in the same range than those of C-P regimens, despite a lesser cumulative dose of P.

552 PUBLICATION

Stimulation of cytotoxicity and cytokine production in tumor – Associated macrophages from ovarian, breast and lung cancer patients

E. Zavadova, E. Pedram, E. Hauptmann, L. Desser, M. Micksche. *Institute for Tumor Biology/Cancer Research, University of Vienna, Austria*

Purpose: The role of tumor-associated macrophages (TAM) as potential effector cells for eradicating malignant cells is not vet entirely clarified. In the present study TAM were phenotypically and functionally characterized. The second part of our investigation was the activation of TAM by cytokines rhGM-CSF, rhIFN-γ or with the polyenzyme preparation Wobe-Mugos used in the treatment of cancer patients with malignant effusions.

Methods: TAM were isolated from malignant effusions of breast, ovarian and lung cancer patients by gradient separation and characterized, by the following parameters: surface epitopes (moAb 27E10, 25F9), respiratory burst activity, cytotoxicity and TGF-β production measured in culture supernatants by ELISA/RIA. Additionally mRNA of TGF-β was detected in TAM by in situ hybridization.

Results: Incubation of TAM with GM-CSF, IFN-γ and polyenzyme preparation Wobe-Mugos resulted in an augmentation of cytotoxicity. In contrast, GM-CSF, IFN-γ and Wobe-Mugos reduced the production of TGF-β by TAM, as verified by ELISA assay as well as by in situ hybridization. TGF-β is known as an immunosuppressive molecule.

Conclusion: Our studies show that the cytotoxic capacity of TAM obtained from malignant effusions of cancer patients can be increased by GM-CSF, IFN-γ and Wobe-Mugos. TGF-β release was reduced. Whether this observation is of therapeutical relevance has to be determined by further studies.

553 PUBLICATION

The integration of consolidation whole abdominal irradiation in the multi-modality management of advanced ovarian carcinoma: Long-term results

A. Kuten[1], H. Goldberg[1], M. Steiner[2], E. Bar-Shefi[1], D. Beck[1], R. Rubinov[2]. *Departments of Oncology, [1]Rambam Medical Center; [2]Lin Medical Center; Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*

57 patients (pts) with advanced ovarian carcinoma were treated by primary cytoreductive surgery followed by 6–11 courses of cisplatin (50 mg/m²) and adriamycin (50 mg/m²), second look laparotomy (SLL) (46 pts) and consolidation whole abdominal irradiation ± pelvic boost. Only 42/57 pts (74%) tolerated radiotherapy (RT) and were able to receive the full planned whole abdominal RT dose of 30 Gy. The median follow-up time is 39 months (range, 12–197 months). The following 5 and 10 year actuarial