cancer drugs (e.g. paclitaxel). Our aim is to develop different experimental glioma models in mice with intact and locally disrupted BBB to study the efficacy of better treatment modalities for gliomas.

Methods: Tumor cell lines of different origin were implanted intracranially in nude mice. To allow non-invasive monitoring of tumor growth in vivo, cell lines were tagged with the firefly luciferine-gene. Tumor growth was monitored using the IVIS camera (Xenogen Inc.). Vascular leakage in the tumor (a measure for BBB properties) was detected using 7T contrast enhanced MRI with gadolinium-DTPA. Mice implanted with Mel57 cells were treated with i.v. paclitaxel at 9, 11 and 13 days after tumor cell implantation.

Results: The implantation of the different cell lines resulted in xenograft mouse models for glioma, displaying the infiltrative, invasive and expansive growth characteristics of a glioma with or without intact BBB properties (Table). Tumor growth could already be visualized 6 days after implantation of the tumor cells. The relationship between tumor mass and bioluminescence was validated using standard histological techniques. So far, we have tested the efficacy of paclitaxel against intracranial Mel57 cells and did not observe a significant decrease of tumor growth.

Cell-line	Species	Origen	Growth pattern	BBB
U-87	Human	Glioblastoma	Expansive, angiogenic	Not intact
U-118	Human	Glioblastoma	No growth	–
K1735	Murine	Melanoma	Infiltrative, co-optive	Intact
Mel57	Human	Melanoma	Invasive, co-optive	Intact
Mel57VEGF165	Human	Melanoma	Expansive, angiogenic	Not intact
SMT	Human	Melanoma	Expansive, some invasion	To be determined
MDA MB 435	Human	Breast	Expansive, angiogenic	To be determined

Conclusions: We have successfully developed several glioma models in mice. In vivo imaging by luciferase allows convenient follow-up of tumor growth for intervention studies. Paclitaxel is not effective against implanted Mel57 cells, a tumor that is protected by the BBB, and we expect that the BBB plays an important role in this inefficacy of paclitaxel. To further study the role of the BBB in the protection of brain tumors, we are currently extending our experiments in the other tumor models. Moreover, since paclitaxel is a substrate of the drug transporter P-glycoprotein (Pgp), we are also studying the effect of Pgp in the BBB using Pgp deficient mice.

Ovarian cancer

36 ORAL

Paclitaxel/Carboplatin (TC) vs Paclitaxel/Carboplatin sequentially followed by Topotecan (TC-Top) in first-line treatment of ovarian cancer Figo stages IIB - IV interim results of a gynaecologic cancer intergroup phase III trial of the Ago ovarian cancer study group and Gineco

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Between 12/1999 and 03/2002 1308 patients were randomized to receive 6 cycles of Paclitaxel (175 mg/m2 3h iv) and Carboplatin (AUC 5, Calvert formula) followed by surveillance (TC) or by 4 cycles of Topotecan (1.25 mg/m2 iv d1-5) (TC-Top) on a 3 weekly schedule. The primary objective was to test for superiority of TC-Top in terms of overall survival. Currently 929 end of therapy reports have been issued, 87% completed 6 or more therapy courses. Treatment and toxicity data are complete in 98%. TC-Top produced a markedly higher myelotoxicity resulting in treatment delays in 21% of the Topotecan courses. Grade 3/4 anemia occurred in 17% of all Topotecan courses, thrombocytopenia in 30%, neutropenia in 77%. There was no clinical relevance in terms of febrile neutropenia (2%) or infections (3%). The mean Topotecan dose/course for all 4 courses was 1.22 mg/m2. In non-hematologic toxicity no significant differences between TC and TC-Top could be observed. TC-Top is a safe first line regimen in advanced ovarian cancer. In both study arms TC and TC-Top the mean and median doses were given as scheduled, as were the median and mean intervals between therapy courses. Follow up will be updated in summer 2003. First efficacy data (response, progression free survival and survival) will also be available in summer 2003.

37 ORAL

Paclitaxel plus carboplatin versus paclitaxel plus alternating carboplatin and cisplatin for initial treatment of advanced ovarian cancer (AOC): long-term efficacy results

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Introduction: Carboplatin combined with paclitaxel are considered treatment of choice as initial chemotherapy for advanced ovarian cancer. We compared this combination with a regimen combining alternating carboplatin and cisplatin plus paclitaxel. The two platinum derivatives have been previously combined as they are considered not totally cross-resistant and as they share no overlapping toxicities, in order to increase the total platinum dose intensity and consequentially the disease outcome.

Material and methods: Patients with AOC after the initial cytoreductive surgery were stratified according to the FIGO stage and the presence of residual disease and were randomized to either combination of 6 courses of chemotherapy with paclitaxel at 175mg/m^2 as 3h infusion plus Carboplatin 7AUC (Arm A) or paclitaxel at the same dose plus Carboplatin 7AUC for cycles 1,3,5 and Cisplatin at 75mg/m^2 for cycles 2,4,6 (Arm B). Primary endpoints were disease free survival (DFS) and overall survival (OS).

Results: 247 patients are analyzed 121 in arm A, 126 in Arm B. 73% of the patients had stage III and 18% stage IV disease. Chemotherapy was generally well tolerated and treatment delays or dose reductions were not necessary. Toxicity and short-term efficacy results have been reported previously [Seminars in Oncology, 1997, 24 (5), (suppl 15), 15-21. Proc Am Soc Clin Oncol 1999;18:367a (1416)]. With a median follow up of 61 months statistically significant differences were not found, both in terms of time to progression (38 vs 39 months, p=0.95) and overall survival (40.6 vs 38.6 months, p=0.79). There is not also difference in 5-year survival rate (35% vs 39%) or 5-year disease free survival rate (23% vs 28%).

Conclusion: Both regimens are well tolerated and effective as first line chemotherapy of advanced ovarian cancer with very good long term outcome. Alternating cisplatin with carboplatin does not improve the results as compared with the standard carboplatin/paclitaxel combination.

38 ORAL

Influence of amifostine on neuroprotection in 1st-line treatment of advanced ovarian cancer with carboplatin/taxane-based chemotherapy - a double-blind, placebo-controlled, randomized phase II-study from the AGO Ovarian Cancer Study Group

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Neurotoxicity (NT) is one of the most important problem of platinum/taxane-based therapy of ovarian cancer (OC) with high impact on quality of life (QoL). We therefore performed a double-blind randomized and placebo-controlled multi-center trial to evaluate the influence of the cytoprotectant amifostine (AM) on NT in 1st-line therapy of OC with paclitaxel (T)/ carboplatin (C) +/- epirubicin (E). 71 patients were stratified for 1st-line chemotherapy with T 175 mg/m^2 and C AUC5 with or without E 60 mg/m^2 (q21x6) and randomized for premedication with AM 740 mg/m^2 i.v. (n = 37) or a placebo i.v. (n = 34) (30 min. prior to chemotherapy). NT was evaluated by an objective assessment with measurement of Patella (TRA) and Achilles tendon reflex activity, vibration perception threshold (VPT) and 2-point discrimination (2-PD) and additionally by a questionnaire concerning specific neurotoxic symptoms and motoric abilities. Supplementary, toxicities were assessed according to the NCI-CTC and QoL. The majority of NT criterions showed a significant impairment during therapy in both treatment arms. A significant protective effect of AM was observed for the objective assessment with TRA, 2-PD, and VPT with regard to intensity and time dependence of pathological findings. AM significantly improved a number of QoL-subscores, but failed to better the global health status score significantly (p= 0,3469). Toxicities according to NCI-CTC showed improved sensory neuropathy (0,0046) in the AM group but on the other hand a significant higher