and dose distribution was evaluated and compared to that of a standard cervical applicator and CT based planning.

Results: The specially designed adjustable cervical applicator prevented overdosage of the organs at risk and undertreatment of the distant tumor spread in all cases. With no hazard of a possible radiation, or mechanical injury the radiation doses could be increased without increasing the possibility of acute or late complications rate. Local tumor control was excellent in 12 patients (75%), moderate in 3 cases (18%) and poor in 1 patient (6%). The treatment was well tolerated by the patients. Unlike other adjustable intraluminal applicators due to the thin diameter of the catheter, the insertion of the applicator was possible without the need of previous dilatation and was fixed by a surgical suture for the whole period of the treatment.

Conclusion: The used MR compatible, flexible applicator allows safe and reproducible cervical radiotherapy with no added discomfort or hazard for the patient. The technique is suitable for other intraluminal applications, too, such as the treatment of malignant airway obstructions, bile ducts, pancreatic duct, ureter and the vascular system.

185 POSTER

Early results of a phase II study of oral topotecan and intravenous cisplatin in epithelial ovarian cancer recurring more than 6 months following initial platinum therapy

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Background: Combination chemotherapy is being evaluated for recurrent platinum sensitive epithelial ovarian cancer. In-vitro studies suggest synergy between topotecan (TOP) and cisplatin (CDDP). This combination administered intravenously has been shown to have activity in epithelial ovarian cancer and is being evaluated as part of first line therapy. The oral formulation of TOP has been trialed as single agent therapy in recurrent ovarian cancer. It appears to possess similar efficacy to intravenous TOP and has the advantage of convenience of administration. We report the preliminary results of a Phase II clinical trial of oral TOP in combination with IV CDDP in patients with late recurrence of epithelial ovarian cancer.

Materials and Methods: Patients with ovarian cancer relapsed >6 mo following initial platinum therapy and with measurable disease were treated with oral TOP (1.25 mg/m^2) administered daily for 5 consecutive days every 21 days plus IV CDDP (50 mg/m^2) being administered on day 1 of each 21-day course. Colony Stimulating Factor support was allowed during therapy.

Results: To date 30 eligible pts have been enrolled. Preliminary data is available on 20 pts. The median age was 54 (range = 42 to 70) with a PS of 0 (8pts) or 1 (12pts). Median follow-up is 63.5 weeks (range = 15.9 to 109.3). Out of 16 pts whose response results were available there were 8 responders (50%) including 2 CR (12.5%) and 6 PR (37.5%). An additional 4 pts (25%) completed treatment with stable disease. The median time to disease progression was 36.7 weeks (95%CI=19.3 to 40.3). Median survival has not yet been reached. Toxicity data has not currently been fully analysed but generally has been predictable. Available haematological toxicity reports 6/20 (30%) grade 3 and 12/20 (60%) grade 4 neutropenia, 4/20 (20%) grade 3 and 4/20 (20%) grade 4 thrombocytopenia, and 6/20 (30%) and 1/20 (5%) grade 3 and 4 anaemia respectively. Updated results on toxicity and efficacy will be presented at the meeting.

Conclusion: Oral TOP with IV CDDP in platinum sensitive relapsed ovarian cancer has activity that compares favourably with the same combination given intravenously.

186 POSTER

Clinical significance of beta catenin immunoexpression in epithelial ovarian cancer

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Backround: Beta catenin plays a dual role in the cell: it is a component of the E-cadherin-catenin complex, linking the cytoplasmic domain of cadherin to the actin cytoskeleton of the cell and plays a role in the Wnt signaling transduction pathway.

Aim: To determine the biological and clinicalpathological relevance of beta catenin immunoexpression pattern in ovarian cancer and determine its relationship with patient survival.

Materials and Methods: Beta catenin was immunohistochemically evaluated in formalin-fixed, paraffin embedded samples of 104 patients with primary ovarian carcinomas.

Results: In 104 carcinomas, beta catenin immunoreactivity was negative in 15 (14%) cases, and present in 89 (86%) cases. Absence of beta catenin immunoexpression correlated with the serous and clear cell histological subtypes (p=0.026). Negative immunoreactivity for beta catenin significantly predicted poorer overall survival as compared with the membranous expression of beta catenin in both univariate (P=0.022) and multivariate analyses (P=0.0039). The presence of residual tumour also predicted poorer overall survival in both univariate (P<0.001) and multivariate analyses (P=0.0340).

Conclusion: The presence of residual tumour as well as the negative immunoexpression of beta catenin seems to be a useful marker in selecting patients with ovarian carcinomas likely to run a less favourable course. In the future, a large prospective study will need to be performed to determine whether the expression of beta catenin can provide important evidence on which to base therapeutic strategies.

187 POSTER

The role of 3rd therapy in recurrent ovarian carcinoma or primary peritoneal carcinoma

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Objectives: 3rd line chemotherapy is routinely applied for recurrent ovarian carcinoma. However, its role is unclear. We retrospectively evaluate our experience with this approach.

Methods: From January 1990 to December 1999, we registered 615 pt's with ovarian or primary peritoneal carcinomas. Of them, 49 (7.9%) received at least 3 different chemotherapeutic treatments. CA 125 response is presented according to Rustin criteria. Survival and time to progression times were calculated with Kaplan-Meier curve using Epistat 5.0.

Results: Median age was 59 (36-78) years, median P.S 1 (0-2). Forty one (83.7%) Pt's had ovarian carcinoma and 8 (16.3%) pt's had primary peritoneal carcinoma. Optimal debulking was possible in 31 (68.8%) pt's. Median CA 125 level was 108 (4-4244) IU/ml. First therapy defined 29 (59.1%) pt's as cisplatin sensitive. Second therapy included taxanes/platinum-based regimen in 14 (28.5%), platinum-based in 33 (67.3%) pt's paclitaxel/5-FU in a single pt. Third therapy was initiated a median of 27.1 (7.2-85) months from diagnosis. It included topotecan in 14 (28.5%) pt's, taxanes-based in 16 (32.6%) pt's, platinum-based in 5 (10.2%) pt's, 5-FU/leokoverine or gemcitabine each in 3 (6.1%) and various single agents in 8 (16.3%). CA 125 50% response occurred in 13 (26.5%) pt's (95% CI, 14.9%-41%). CA 125 75% response was noted in 6 (12.2%) pt's, while CA 125 stabilization occurred in 20 (40.8%) pt's. Median time to progression was 4.2 (0.7-48.5) months, longer in the CA 125 responders (7.2 vs 3.4 months, P=0.034). The median survival of all the Pt's was 16.7 (2.1-116.5+) months, longer in CA 125 responders (29.5 vs 12 months, P=0.02). It was not statistically affected by initial optimal debulking, or primary cisplatin sensitivity. Subsequent treatments were delivered as the following: 4th- 39 (79.5%) pt's, 5th- 22 (44.8%) pt's, 6th- 12 (24.4%), 7th- 2 (4%) pt's 8th and 9th in single pt's.

Conclusions: 3rd line therapy is active in selected pt's with recurrent ovarian carcinoma. These Pt's may enjoy prolonged survival which is not affected by initial optimal debulked state or cisplatin-sensitive disease.

188 POSTER

Determining predominating histologic component in malignant mixed mullerian tumors: does it really work?

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Background: Malignant mixed mullerian tumors (MMMT) are aggressive tumors, usually diagnosed in advanced stage. Cases of MMMT derive from either ovary or uterus. In our study, we investigated the role of carcinomatous and sarcomatous component on response to chemotherapy and on disease outcome.

Methods: We retrospectively analyzed 17 patients with MMMT who were treated in our outpatient clinic from 1998 to 2003. All the parraffin specimens were revealuated according to the histopathologic features (primary site and percentages of carcinomatous and sarcomatous component) and the effect of dominant histologic type on response to treatment.

Results: Median age of the patients included in the study was 59.9 years (range, 40-80). Mean carcinomatous and sarcomatous component were 55.2% (range, 10-95%) and 44.7% (range, 5-90%), respectively.

Primary tumor sites were ovary and endometrium in 59.9% and 47.7% of patients, respectively. There were 5.8% of patients in stage IIB, 11.7% in stage IIIB, 47.1% in stage IIIC and 23.5% in stage IV. 94.1% of patients had metastatic disease. The most common metastatic sites were omentum, ovaries, colon, appendix and tuba. There were also two patients with liver metastasis. 10 out of 17 patients (58.8%) were treated with a combination chemotherapy regimen of cisplatin-ifosfamide (PI) and seven patients (40.2%) were treated with paclitaxel-carboplatin (PC) protocol. One patient whose tumor contains 80% carcinomas and 20% sarcomas had a consolidation radiotherapy to the pelvic region after chemotherapy. Median number of chemotherapy cycles was 6(range: 3-9). 18.8% of patients had progressive disease despite chemotherapy. The remaining 13 patients (81.2%) responded to chemotherapy; there were 7 patients with CR and 6 patients with PR and stable disease. Response rates of patients treated with PC (100%) were remarkably higher than the response rates of patients treated with PI (80%). Patients with predominating carcinomatous component had a higher response rate(88.8%) than patients with predominating sarcomatous component(60%).

Conclusion: MMMT are highly chemoresponsive tumors, irrespective of primary site. One of the best predictors to response is the histologic pattern. Predominating histopathologic feature (carcinoma or sarcoma) should be taken into consideration in predicting the response and planning the chemotherapy regimen.

189 POSTER

Evaluation of human papilloma virus infection in cervical cancer and P53 gene mutations.

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Cancer of uterine cervix is one of the most prevalent cancers in women, after breast cancer. Infection with high risk Human Papilloma Virus (HPV) and disfunctioning of P53 tumor suppressor gene due to molecular lesions are thought to be the main carcinogenesis factors in cervical cancer. To study the prevalence of HPV infection and status of P53 tumor suppressor gene, 50 paraffin embedded tissue samples with stage specific pathological diagnosis of cervical cancer collected from the university hospitals. DNA was extracted from tissue sections and PCR amplified using general, HPV16, and 18 type specific primers. To detect mutations in P53 gene, after PCR amplification of the desired exons the PCR products were subjected to single strand conformation polymorphism (SSCP) analysis. Thirty-seven samples were positive for HPV infection. Out of these 37 samples, 23 were positive for HPV16 and 4 samples for HPV18. Results of SSCP analysis of P53 gene demonstrated polymorphism in 4 samples, among which 3 were from HPV positive and 1 from HPV negative samples. Our results clearly demonstrate the importance of HPV infection in cervical cancer. HPV16 showed higher prevalence than HPV18 which indicates the important rol of HPV16 in cervical neoplastic transformation. Also there might be a relationship between P53 mutations and HPV infection in this cancer among the patients under study.

190 POSTER

E-cadherin and beta catenin immunoexpression in primary ovarian carcinomas: an association with clinicopathological features.

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Backround Epithelial cadherin is an cell-cell adhesion molecule that forms a complex with alpha, beta and gamma catenin proteins. Reduced expression of E-cadherin and catenins has been associated with low histological differentiation, invasiveness and metastatic disease in human carcinomas.

Aim: Evaluate E-cadherin and beta catenin immunoexpression pattern (reduced *versus* preserved phenotype) in ovarian carcinomas and its relation with clinicopathological features

Materials and Methods Immunohistochemical analysis of E-cadherin and beta catenin in 104 carcinomas.

Results The immunoexpression pattern of E-cadherin correlated with histological subtype ($p<0.01$), peritoneal implants ($p=0.006$), and residual tumour ($p=0.04$). The preserved phenotype of E-cadherin in 37/104 carcinomas associated with mucinous carcinomas, absence of peritoneal implants and residual tumour. Whereas, the reduced phenotype of E-cadherin in 67/104 carcinomas associated with advanced stage tumours, serous carcinomas, presence of peritoneal implants and residual tumour >2cm after cytoreductive surgery.

The immunoexpression pattern of beta catenin correlated with histological subtype ($p<0.01$), tumour differentiation ($p=0.02$), and peritoneal implants ($p=0.04$). The preserved phenotype of beta catenin in 27/104 carcinomas associated with well/moderately differentiated tumours, serous, mucinous and endometrioid histological subtypes, absence of peritoneal implants and residual tumour. Whereas, the reduced phenotype of beta catenin in 77/104 carcinomas associated with advanced stage tumours, poorly differentiated serous and clear cell carcinomas, presence of peritoneal implants and residual tumour.

The immunoexpression pattern of E-cadherin correlated with that of beta catenin ($p<0.001$). The simultaneous immunoexpression patterns of E-cadherin and beta catenin significantly associated with peritoneal implants ($p<0.001$), and histological subtypes ($p=0.001$).

Conclusion The immunohistochemical profile of E-cadherin and beta catenin was shown to be of biological relevance and may provide new insight into the biology of ovarian carcinogenesis. Since, the reduced phenotype of these molecules was shown to associate with aggressive biological behaviour, increased invasiveness and peritoneal implants.

Other gastro-intestinal tumours

191 POSTER

Phase II trial of gemcitabine and capecitabine (GemCap) in patients with advanced biliary cancer.

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Background: Advanced biliary cancer is an aggressive cancer with a median survival time of under 6 months. Chemotherapy has shown minimal activity with little impact on overall survival. Recent phase II trials suggest that newer agents such as gemcitabine or capecitabine have activity (19-35% RR) in this disease. Preclinical data suggests synergy between gemcitabine and capecitabine. We conducted a phase II trial to study the efficacy and toxicity of both drugs in combination in patients with advanced or metastatic biliary cancer.

Methods: Patients with unresectable cholangiocarcinoma or gallbladder cancer were enrolled from July 2001 onward. Eligible patients had histologically or cytologically confirmed adenocarcinoma, no prior systemic therapy, ECOG PS $\leq$ 2, serum total bilirubin up to 3 x normal and measurable disease. Treatment consisted of gemcitabine 1000 mg/m ^{2} IV day 1, 8 concurrent with capecitabine 650 mg/m ^{2} PO BID day 1 to 14, on a 3 week cycle (Hermann et al, Proc. ASCO, 2000). Tumor response was assessed by RECIST criteria.

Results: Of the 25 patients enrolled to date 12 (48%) had cholangiocarcinoma and 13 (52%) had gallbladder cancer. Median age was 62 (range 45-81). A total of 128 cycles of chemotherapy was administered, for an average of 5.4 cycles per patient (range 1-15). At median follow-up of 4.2 months, 25 patients are evaluable for toxicity and 21 for response. There are 6 partial responses (29%), plus an additional 9 patients with stable disease > 3 cycles (43%). Median time to disease progression is 6.3 months. Overall survival is 9.6 months. No grade 4 toxicity was seen (see table below). Grade 3 neutropenia (no febrile neutropenia) and manageable hand-foot syndrome were most common.

Common Toxicity	Percentage of patients (worse toxicity, n = 25)	
	NCI grade 2	NCI grade 3
Neutropenia	4	20
Thrombocytopenia	0	12
Hand-Foot syndrome	12	16
Fatigue	16	4
GI	12	0

Conclusions: GemCap is an active and extremely well tolerated chemotherapy regimen in patients with advanced biliary cancer. GemCap has an objective response rate comparable to or better than most other phase II data, but also demonstrates durable disease stabilization, encouraging median survival and mild toxicity. Anticipating that this regimen will have