(p=0.033). A correlation was also found between the post-CT-RT positive MIBI and CR (p=0.030).

Conclusion: This preliminary report showed that pre-CT-RT MIBI, Ki-67, and p53 were not predictive for response to CT-RT, but the post-CT-RT MIBI and the decrease of uptake were correlated with the response. Pre-CT-RT MIBI was also correlated with low expression of mutated p53. These data suggest that changes of MIBI uptake after CT-RT can be related to the response to treatment.

Gynaecological cancer

157 POSTER

Overall survival advantage for pegylated liposomal doxorubicin compared to topotecan in recurrent epithelial ovarian cancer

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Background: A recent phase III study compared the efficacy and safety of pegylated liposomal doxorubicin (Doxil®/Caelyx®) with topotecan in patients with recurrent epithelial ovarian cancer that recurred after or did not respond to first-line, platinum-based chemotherapy (Gordon, et al. *J Clin Oncol.* 2001;19:3312-3322). Response rates were found to be similar for both treatment groups. Final survival data from this study are now reported.

Material and Methods: Patients (N = 474) were randomly assigned (1:1 ratio) to treatment with pegylated liposomal doxorubicin 50 mg/m^2 every 28 days or topotecan 1.5 mg/m^2/day for 5 consecutive days every 21 days. Patients were stratified prospectively based on whether they had platinum-sensitive/refractory disease and the presence/absence of bulky disease. Primary efficacy endpoints were progression-free and overall survival.

Results: Overall survival was longer in patients treated with pegylated liposomal doxorubicin compared to those treated with topotecan (median 63 and 60 weeks, respectively; P = 0.05, HR = 0.82 [0.68, 1.00]). In the subset of patients with platinum-sensitive disease (46%), this survival advantage was even more striking for patients treated with pegylated liposomal doxorubicin compared to topotecan (median 112 and 77 weeks, respectively; P = 0.002, HR = 0.63 [0.47, 0.85]). In the subset with platinum-refractory disease, survival was similar in the 2 treatment groups (median 36 and 41 weeks, respectively; HR = 1.01 [0.78, 1.31]). As of December 2002, 29 patients initially treated with pegylated liposomal doxorubicin and 10 topotecan-treated patients remain alive. A more favorable toxicity profile was reported with pegylated liposomal doxorubicin, as patients experienced fewer severe adverse events and required less hematologic support and significantly fewer dose modifications.

Conclusions: Patients treated with pegylated liposomal doxorubicin had longer overall survival compared to topotecan-treated patients. The overall survival advantage was more than 35 weeks in patients with platinum-sensitive disease treated with pegylated liposomal doxorubicin. To date, this is the only head-to-head study demonstrating a survival advantage in recurrent epithelial ovarian cancer.

158 POSTER

Phase I dose finding study of capecitabine, cisplatin and radiotherapy in the treatment of locally advanced squamous cervical cancer

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Background Materials and methods 13 patients with Stage II (7) or Stage III (6) received pelvic radiotherapy (45Gy in 25f) plus a selectron intra-uterine insertion (median A point dose 26.00Gy at 1.53Gy/hr). All but one patient (4 cycles only) received 6 weekly cycles of cisplatin (40mg/m^2). It was planned to give daily capecitabine for 42 days to cohorts of 6 patients using escalating doses. The MTD was defined as 2 patients experiencing Grade(G) 3 toxicity in any one cohort. The starting dose level was 600mg/m^2 BD and the second 900mg/m^2/BD

Results Capecitabine dosage 6/6 patients in cohort 1 and 5/7 in cohort 2 received capecitabine at or very close to the protocol dose. Capecitabine was discontinued after 27 days in 1 patient in cohort 2 because of Grade 3 diarrhoea, febrile neutropenia and thrombocytopenia. 1 patient in cohort 2 had difficulty swallowing the tablets, discontinued treatment after 4 days and was replaced. Two patients in cohort 2 experienced G3 toxicity (diarrhoea and febrile neutropenia).

Survival 4 patients have died. The actuarial progression free survival at 12 months is 64% (se = 15%)with a 15 month survival of 55% (se = 17%).

Acute toxicity 1 patient in cohort 1 developed G 3 diarrhoea. 2 patients in cohort 2 developed febrile neutropenia and 1 of these also had G 3 diarrhoea.

Late Toxicity 2 patients (1 from each cohort) developed RTOG/EORTC G 3 late toxicity (bladder and vaginal mucosa respectively) at 9 and 15 months after treatment.

Conclusion The MTD of capecitabine given with pelvic irradiation and weekly cisplatin was found to be 900mg/m^2/BD. The recommended dose level of capecitabine in this combination is 600mg/m^2/BD.

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Phase II study of OSI-774 given in combination with carboplatin in patients (pts) with recurrent epithelial ovarian cancer (EOC): NCIC ctg Ind.149.

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Background: Response rate to carboplatin in pts with recurrent EOC is proportional to the progression free period after completion of first-line platinum-chemotherapy. Pts relapsing within 6 months are considered platinum resistant (PR), and pts relapsing after 6 months, sensitive (PS). OSI-774 is an orally active, potent, selective inhibitor of EGFR tyrosine kinase inhibitor with single agent activity in ovarian cancer (Finkler et al P ASCO Abstract 831, 2001). EGFR inhibitors may potentiate the antitumour effects of cytotoxic agents, and may beneficially modulate drug resistance.

Methods: Pts with relapsed EOC, measurable disease, and $\leq$ 2 prior chemotherapy regimens (the first regimen must have contained platinum) were entered into one of 2 strata: PR or PS. Both strata have 2-stage designs, with sample sizes of 30 pts (15: 15) and 15 pts (8:7) respectively. Carboplatin was given at AUC 5 IV q 21days with OSI-774 150mg day.

Results: 34 pts have been accrued to date. Acneiform rash, fatigue, diarrhea, nausea and dry skin were the most common toxicities. 2 pts had carboplatin hypersensitivity allergic reactions. No grade 4 hematologic toxicity occurred. 18 PS pts were accrued in 2 stages; preliminary response data suggest 10 of 16 currently evaluable pts have achieved as yet unconfirmed objective responses. 16 PR pts have been accrued in stage 1. Response data are as yet immature.

Conclusion: OSI-774 can be administered in combination with carboplatin at a dose of AUC 5. The combination has activity in PS patients; mature response data on both PR and PS strata will be updated.

160 POSTER

Patterns of relapse influenced by hematogenous tumor cell dissemination in patients with cervical carcinoma of the uterus

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The presence of isolated tumor cells (ITC) in the bone marrow at the time of primary diagnosis has been found to indicate an increased risk for subsequent development of distant metastases in various solid tumors. This study evaluates the prevalence and prognostic significance of ITC in patients with primary carcinoma of the cervix uteri.

We immunocytochemically analyzed bone marrow aspirates of 130 patients with newly diagnosed carcinoma of the cervix uteri for the presence of cytokeratin(CK)-positive cells from May 1994 until January 2001. We used a quantitative immunoassay with the monoclonal anti-CK antibody A45-B/B3 and evaluated 2 x10^6 bone marrow cells per patient. Patients were followed prospectively for a median of 43 (range, 1-85) months.

ITC were found in the bone marrow of 38 patients (29%). The presence of ITC did not correlate with the FIGO tumor stage (P = 0.61), pelvic and paraaortal lymph node involvement (P= 0.41), nor with histopathological grading (P= 0.67), the histological type of the carcinoma (P= 0.93), invasion of lymph (P=. 93) and blood vessel (P= 0.92), or menopausal status (P= 0.17). The bone marrow status at the time of primary diagnosis did not correlate with the overall survival as estimated by Kaplan-Meier-Analysis (P= 0.30). However, distant metastases occurred in 5% of the patients (n=5) with negative and in 15% of the patients (n=6) with positive bone

marrow status (P= 0.054). The median distant disease free survival was 78 months (73 82, 95% CI) in patients with negative, and 72 months (61 82) in patients with positive bone marrow status (P= 0.051). Multivariate analysis revealed the presence of ITC as significant, independent risk factor for the subsequent development of distant metastases (relative risk 3.6, P= 0.046).

Despite the locoregional predominance of cervical cancer at the time of primary diagnosis, the presence of ITC in the bone marrow is frequent and indicates an increased risk for the development of distant metastases. This information may prove useful to stratify patients for systemic treatment.

161 POSTER

Radical pelvic radiation for uterine cervix cancer in the elderly

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Radical radiation treatment in the elderly remains a controversial issue. A sufficient number of recent references confirms comorbidity but not age itself as a limiting factor of both radio and chemotherapy. Upon the analysis of our historical group of patients with uterine cervix cancer we have tried to examine whether radical pelvic radiation in elderly patients could be advocated, whether it had the same effect and whether it did not compromise the patient status. 2 272 patients with uterine cervix cancer have been treated at the Institute of Radiation Oncology, Prague, Czech republic in the period 1972-1990. Median age was 56 years (18-89) (s=13,6). 1033 of them were eligible for a retrospective analysis i.e. there was a continuous evidence of their status within 5 years after their treatment. This group consisted of 111 pts. more (elderly) and 922 less (younger) than 70 years old at the time of treatment onset. There was a good correlation of disease stage between these subgroups (χ^2 = 5,47) (In the elderly: stage IA 1 pt., IB 18 pts., IIA 9 pts., IIB 38 pts., IIIA 5 pts., IIIB 30 pts., IV 11 pts.). All patients have been radically treated by a combined radiation therapy (40-48 Gy, Linac, Co and 30-35 Gy brachytherapy), predominantly by less sophisticated techniques than current patients (including 2 opposed fields technique). The retrospective data were not sufficient to provide reproducible information on late effects of therapy. However there are reliable data on mortality related to cancer.

The cause of mortality within 5 years after treatment - related vers. not related to cancer - was not significantly influenced by the age (p=0,141). Moreover the probability of death within 5 years related to cancer was very similar in both subgroups (0,32 younger vers. 0,39 elderly, p=0,58). There were no severe or lethal complications of radiotherapy. There was no significant difference between younger and elderly in survival time of those, who died for either reason within 5 years (20 vers. 18 months, p=0,805). The 5 year survival rate was 62% and 48% for younger and elderly patients respectively. These results confirm the age itself does not influence the natural history of the disease and the effects of pelvic radiation. Therefore radical radiation therapy should be administered in elderly patients except cases with a substantial comorbidity.

162 POSTER

Significant impact of integrin beta-3 expression in cervical cancer treated with radiotherapy +/- chemotherapy

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Objective: To investigate the prognostic role of integrin beta-3 (b3) expression in patients with cervical cancer (cCa) treated with radiotherapy ± chemotherapy.

Patients and Methods: Eighty-two biopsy specimen from locally advanced cCa patients (median age: 63yrs) could be evaluated in regard to integrin beta-3 expression by immunohistochemistry (- / + / ++). All patients were treated with radiotherapy (median total dose: 69Gy), in 27 patients combined with cisplatin ± 5-FU. Mean follow-up was 41 months.

Results: Thirty-two out of 82 (39%) primary tumors were 'negative', 50 (61%) were 'positive' ('+': n=31; '++': n=19) for beta-3-expression. The actuarial 5-yrs-local-progression-free-survival difference was statistically significant (p=0.002) with 85% for 'negative' patients and 51% for 'positive' patients ('+': 46%; '++': 56%). The corresponding values are 85% vs 57% ('+': 67%; '++': 50%) for distant-metastasis-free-survival (p=0.037) and 78% vs 41% ('+': 44%; '++': 39%) for cause-specific-survival (p=0.013).

Conclusion: For the first time we could demonstrate that integrin-beta-3-expression offers the possibility to stratify between different risk profiles in patients with cervical cancer.

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Capecitabine chemoradiation for stage II B- III B cervical cancer: preliminary phase I results, Mexican Oncology Study Group.

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Background: cisplatin (DDP) and radiotherapy for advanced locoregional cervical cancer has been adopted in many centers as standard first line treatment. However, toxicity and the need for weekly inpatient iv infusion makes DDP an inconvenient and intermittent radiosensitiser. Capecitabine (X) is an oral fluoropyrimidine which mimics continuous 5-FU infusion through twice-daily administration. Final conversion of X depends on thymidine phosphorylase (TP). Levels of TP are 5 times higher in cervical tumor cells compared with normal tissue and radiotherapy upregulates TP activity in tumor but not in healthy tissue. X dose with pelvic radiotherapy has been defined in phase I trials for rectal cancer, but fields, dose and local tissue toxicity differ in cervical cancer thus we performed a phase I trial.

Materials and methods: we escalated X to determine the maximum tolerated dose with simultaneous standard pelvic radiotherapy (1.8 Gy/day x 5/week total 4-field external dose 45 Gy followed by brachytherapy). X was administered twice daily, 5 days a week.

Results: to date, 21 patients with squamous cell cervical cancer, stage IIB 15, IIIB 6, median age 51 years (range 39-66) have been treated at: 2x250 mg/m^2 (n=4), 2x375 mg/m^2 (n=4), 2x500 mg/m^2 (n=4), 2x650 mg/m^2 (n=3), 2x825 mg/m^2 (n=6). Mild toxicity was: diarrhea 15 pts, stomatitis 2 pts, hand-foot syndrome 1 pt, vomiting 2 pts, external skin and vulvar dermatitis 3 pts, cystitis 3 pts, neutropenia 1 pt, thrombocytopenia 1 pt, liver ALT/AST rise 3 pts. The only dose-limiting toxicities (one patient with grade 3 ALT rise and one patient with bilirubin grade 2 rise for more than 1 week) were reached at a dose level of 2x825 mg/m^2. Three more patients are still under treatment for this dose level 2x825 mg/m^2. Twelve pts are currently evaluable for response: 10 CR with a median DFS of 5.5 months; one PR and one progression.

Conclusions: X can be safely administered concurrently with radiotherapy in cervical cancer with encouraging early efficacy results. X is a particularly convenient option for chemoradiaition and the final safe dose will be tested in a phase II study by MOSG.

164 POSTER

Primary therapy of ovarian cancer with Paclitaxel/Carboplatin/Gemcitabine (TCG): a Phase II Study (Ovar-8 protocol)

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Introduction: The addition of a third, non-cross-resistant substance to Paclitaxel (T) and Carboplatin (C) might be considered as a method to improve the primary therapy of ovarian cancer. In preparation of a phase III study (*Ovar-9*), the addition of Gemcitabine (G) was tested under a multicenter, non-randomized 2-cohort study.

Methods: In the period from October 2000 until July 2002, the study included 55 female patients with a median age of 54 years (range 25-73). After the first operation of a primary ovarian cancer (FIGO Ic- IVa), they were treated with a combination of T (175 mg/m^2 3 h IV on day 1), C (AUC 5 IV on day 1) and G (800 mg/m^2 IV on days 1+8), q 3 weeks. G wasn't applied in the first cohort with ANC <1000/µl and in the second cohort with WBC <1500/µl on day 8 (dosage level -1). A prophylactic dose of G-CSF wasn't required in the protocol. The toxicity was recorded according to NCI-CTC and response was assessed per the RECIST (response evaluation criteria in solid tumors) criteria.

Results: The toxicity data of 52 female patients (261 cycles) were assessable. 40 women were assigned to the cohort 1 and 15 to cohort 2. As haematological toxicities of grade 3/4 in % of cycles occurred: anaemia 3.8/0, thrombocytopenia 11.8/1.5, leucopoenia 31.4/ 3.4 and febrile neutropenia 0.4/0. As non-haematological toxicities grade 3/4 were