testinal toxicity. Single injection of irinotecan at 120 mg/kg (MTD) did not induce diarrhea. In contrast, i.v. injection of irinotecan at 100 mg/kg/day, administered three times every other day, caused gastrointestinal toxicity. We then compared three different schedules of the capecitabine/irinotecan combination. Irinotecan was given i.v. at 100 mg/kg/day on days 1, 3 and 5 with capecitabine being given p.o. 539 mg/kg/day daily for 14 days either simultaneously or sequentially. Both capecitabine and irinotecan caused diarrhea when administered as single agents. With the simultaneous schedule, the diarrhea was more severe compared with the irinotecan-alone or capecitabine-alone groups. In contrast, with the sequential schedule, in which capecitabine was given after 3-day or 1-day treatment intervals following irinotecan injections, diarrhea was no more severe compared with the single-agent groups. In COLO205 xenograft model, the antitumor activity of irinotecan in combination with capecitabine showed additive activity at all of the examined schedules. The efficacy of the sequential schedule was the same as the simultaneous schedule.

Conclusions: A sequential administration schedule of capecitabine and irinotecan appears to be equally effective and better tolerated than the simultaneous administration schedule. Clinical studies of sequential capecitabine and irinotecan in patients with CRC could be warranted.

265 POSTER

Capecitabine combined with radiotherapy in Chinese patients with advanced or relapsed rectal carcinoma

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Background: Capecitabine (Xeloda®) is a tumor-activated oral fluoropyrimidine, which is preferentially converted to 5-FU by exploiting the higher concentrations of thymidine phosphorylase in tumor tissue compared to normal tissue. In addition, radiotherapy upregulates thymidine phosphorylase in tumor cells but not in normal tissues. Combining capecitabine with radiotherapy further upregulates TP. This trial was designed to evaluate the synergistic effect and safety of capecitabine combined with radiotherapy in Chinese advanced or relapsed rectal carcinoma patients.

Methods: 59 patients (pts) were enrolled from June 2002 to March 2003. All had measurable advanced or relapsed rectal carcinoma, Karnofsky performance status ≥60, adequate bone marrow, renal and hepatic functions. Prior radiotherapy to other sites or adjuvant fluoropyrimidines (≥1 month previously) were permitted. We used a total irradiation dose of 60 Gy (1.8 Gy/d) over approximately 6 weeks and capecitabine 825 mg/m^2 twice-daily including weekends for the duration of radiotherapy.

Results: 38 pts are currently evaluable for safety and efficacy: 22 men and 16 women; median age 50 years (range 36-74); measurable lesions: rectum (18), pelvis (18), skin (5), others (4). Thirty-six pts were recurrent, 2 pts were previously untreated. Previous treatment: 3 pts radiotherapy, 13 pts adjuvant fluoropyrimidines. There were few grade 3 adverse events: Hand-Foot Syndrome (HFS) 2 pts (5%), diarrhea 1 pt (3%). There was no grade 4 toxicity. Most common adverse events (>20% grade 1-2) were leukopenia 15 pts (40%), HFS 13 pts (34%), diarrhea 9 pts (24%) and thrombocytopenia 8 pts (21%). At the end of treatment, there are currently 2 complete responses (6%), 15 partial responses (58%) and 11 patients with stable disease (29%). Median progression-free and overall survivals have not yet been reached.

Conclusion: Oral, tumor-activated capecitabine combined with radiotherapy has proven to be a highly active regimen in Chinese advanced or relapsed rectal carcinoma patients and is well tolerated.

266 POSTER

E-cadherin expression is commonly downregulated by promoter methylation in colorectal cancer cell lines.

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Background: E-cadherin, a cell adhesion molecule, is regarded as a tumor/invasion suppressor molecule. In our preliminary study for 94 colorectal cancer patients, reduced or lost expression of E-cadherin were observed in cancer tissues in comparison with matched normal mucosa. By using six colorectal cell lines, we aim to explore whether the methylation of the E-cadherin gene is responsible for the silence of E-cadherin protein expression.

Methods: Methylation status of the E-cadherin gene was investigated by a highly quantitative real time PCR (Taqman) method. The extent of methylation was expressed as methylation index. Protein levels of the E-cadherin were measured by western blotting. For E-cadherin low/negative cell lines, 5-Aza-2'-deoxycytidine, a demethylation agent, was applied with concentrations from 2um to 4 um for 4-6 days.

Results: Four out of six colorectal cell lines (Dukes B, C, C and D respectively) had low or absent E-cadherin. The other two cell lines (one Dukes C and another Grade I) expressed high levels of E-cadherin. Apparent methylation in the promoter region of the E-cadherin gene was observed in three E-cadherin low/negative cell lines. Treatment of 5-Aza-2'-deoxycytidine induced the re-expression of E-cadherin protein in these three cell lines.

Conclusion: Our results suggest that aberrant promoter methylation of the E-cadherin gene may play a role in the down-regulation of E-cadherin in colorectal cancers.

267 POSTER

Serum concentrations of MMP-2 and TIMP-1 are of independent prognostic value for cancer specific survival in patients with metastatic colorectal carcinomas under chemotherapy

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Background/Aim: Matrix-metalloproteinases (MMP) and their inhibitors (TIMP) are playing a major role in the invasion, angiogenesis and metastasis of colorectal carcinomas. Recently we could show the predictive meaning of MMP-2 and TIMP-1 during chemotherapy. In this study we analysed the prognostic value of different serum markers for survival of patients with metastatic colorectal cancer.

Material and methods: 49 patients presenting with metastatic colorectal cancer received first-line chemotherapy consisting of 5-FU / FA as a 24-h infusion (AIO regimen) in combination with (n=24) or without (n=25) oxaliplatin, respectively. Prior to treatment, serum was obtained of all 49 patients and analysed for circulating concentrations of collagen IV, VI, tenascin, MMP-2 and TIMP-1 (Bayer Immuno Analyser). Probes of 100 healthy persons were taken as control.

Results: The median cancer specicfic survival (CSS) of the 49 patients was 22 months. Serum concentrations of >541 ng/ml for MMP-2 and <1002 ng/ml for TIMP-1 were significantly associated with an improved survival, respectively. Cox regression analysis revealed these two markers as of independent significant value (p=0.043 for TIMP-1 and p=0.009 for MMP-2, respectively). All the other clinicopathological criteria (e.g. age, gender, chemo-regimen) as well as the concentrations of the other serum markers did not contribute to survival.

Conclusions: Serum concentrations of MMP-2 and TIMP-1 prior to treatment were shown to be independent prognostic factors for CSS survival in patients with metastatic colorectal carcinomas undergoing a palliative first-line chemtoherapy. Bearing in mind their predicitive value these both serum markers are promising new tumour markers in colorectal carcinoma treatment.

268 POSTER

A phase II trial of aroplatin (L-NDDP), a liposomal DACH platinum, in patients with metastatic colorectal cancer (CRC) – a preliminary report

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Aroplatin (L-NDDP) is a liposomal formulation of *cis-bis*-neodecanoato-*trans*-R, R1,2-diaminocycloxhexane (DACH) platinum. L-NDDP is a structural analog of oxaliplatin, which was recently approved for the second-line therapy in patients with metastatic CRC.

We have initiated a phase II trial of L-NDDP in patients with metastatic CRC refractory to 5-fluorouracil/leucovorin or capecitabine and irinotecan therapy. Patients with history of prior oxaliplatin therapy were excluded. The starting dose level for L-NDDP was 300 mg/m^2 with possible intra-patient dose escalation up to 375 and 470 mg/m^2. The L-NDDP is administered

intravenously, at the rate of 4 mg/min, repeated q 21 days. Pts are treated until disease progression or unacceptable toxicity. Fourteen eligible patients have been enrolled. All patients are evaluable for response and 11 are evaluable for response. Patient characteristics: male/female = 10/4; median age (yrs.) = 59 (range 46-69); ECOG PS 0-1. Toxicity: hematological toxicity has been minimal with gr 1 neutropenia in 4 pts, anemia (gr 2, 3, 4) in 3 pts and thrombocytopenia (gr 3) in 1 pt. Non-hematologic toxicity included infusion-related chest and back pain in 5 pts, transient transaminase elevation (gr 2/3) in 5 pts, transient hyperbilirubinemia (gr 2/3) in 3 pts and sensory neuropathy (gr 2) in 1 patient. Efficacy: one out of 11 evaluable pts had a confirmed PR (9%), 2 pts (18%) have had stable disease and 8 patients have progressed. Enrollment continues toward a planned accrual of up to 20 patients in the first stage of this trial.

Conclusion: L-NDDP is well tolerated in this group of heavily pretreated patients, causing minimal myelosupression and showing preliminary evidence of antitumor activity. (Supported by a grant from Antigenics).

269 POSTER

Predicting response of invasive rectal cancer to brachytherapy by mathematical modeling of p21, bcl-2 and p53 immunohistochemistry

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Background: The aim of this study is to predict response of invasive rectal cancer to pre-operative high dose rate brachytherapy by mathematical modeling of p21, bcl-2 and p53 immunohistochemistry.

Materials and Methods: Immunohistochemistry for p21, bcl-2 and p53 was performed on 34 pre-treatment rectal tumor biopsies known to have responded completely (T0), partially (microfoci of residual cancer) or not at all (residual cancer) to pre-operative high dose rate brachytherapy. Positive staining in tumor cells was scored quantitatively (as a percentage). Each tumor biopsy was represented as a point in the three-dimensional vector space with coordinates X, Y and Z corresponding to p21, bcl-2 and p53 immunoreactivity. Linear and non-linear regression was performed for each response group and the regression surfaces were used to predict response prospectively on nine new patients whose outcome to therapy was unknown.

Results: The linear and non-linear regression surfaces for the three response groups were represented graphically. The surfaces were significantly different suggesting that the p21/ bcl-2/p53 relationship in each group was distinct and could be employed to predict patient response. Immunohistochemistry for the new tumors revealed 2 tumors with coordinates X (p21), Y (bcl-2), Z (p53) near the origin. For these two, a prediction could not be made since tumors expressing these coordinates were found in all three response-groups. Of the 7 tumors remaining, 6 were correctly predicted (86%) to be completely, partially and non-responsive to brachytherapy using the non-linear regression model.

Discussion: In this study, linear and non-linear regression models were developed using p21, bcl-2 and p53 immunohistochemistry from pre-treatment rectal tumor biopsies whose response to high dose rate brachytherapy was known. The predictive power of this model was tested prospectively with a prediction rate of 86%. Mathematical modeling of tumor markers in pre-treatment biopsies may be useful in predicting tumor response to different treatment modalities.

270 POSTER

A phase II study of oral uracil/ftorafur (UFT) plus leucovorin in combination with mitomycin-C in patients with metastatic colorectal cancer

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Background: Both UFT+leucovorin and mitomycin-C are active drugs in advanced colorectal cancer. Prior reports have shown high response rates (RR), 30% and a long (>6 mo) time to progression (TTP) in patients treated with the combination of continuous infusion 5-fluorouracil and mitomycin-C. The main objectives of this phase II study were to determine the efficacy and safety of the combination of UFT + leucovorin and mitomycin-C in patients with metastatic colorectal cancer.

Material and methods: Patients were treated with UFT 250 mg/m^2 + leucovorin 90 mg days 1-28 q 5 weeks. During the first 4 cycles the patients also received mitomycin-C 7 mg/m^2 on day 1. Patients with benefit from the treatment at the end of 4 courses could receive further courses with UFT + leucovorin alone. The study included 97 patients and analyses were based on intention to treat (ITT). Median age was 65 years. Forty had a WHO performance status 0, 48 had WHO 1 and 9 had WHO 2. Fourteen patients did not complete the treatment due to adverse events or toxicity. Three died while on study medication. Fifty-seven stopped treatment due to progression and the remaining 23 patients either withdraw by their own request, physician decision or completed the treatment.

Results: Two patients (2%) had a complete response, 20 (21%) had a partial response, 40 (41%) had no change, 19 (20%) had progression and 16 (17%) were not evaluable for response. The overall RR in evaluable patients was 22/97 (23%). Median TTP was 5 months and median survival 13 month.

Severe (Grade 3/4) toxicity included: Anorexia in 3% of patients, nausea 6%, vomiting 7%, diarrhoea 7% and fatigue 9%. Febrile neutropenia, renal failure and thrombocytopenia were seen in 1% of the patients, respectively.

Conclusions: The combination of UFT+leucovorin and mitomycin-C shows similar clinical activity with respect to overall response rate (RR 23%) and survival (13 months) as other frontline line 5-fluorouracil-based therapies in metastatic colorectal cancer patients. The results indicate that mitomycin-C did not increase efficacy. Therefore, phase III trials with this regimen cannot be recommended.

271 POSTER

Savings in staff time as a result of switching from De Gramont to oral capecitabine for patients with advanced colorectal cancer.

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Background: To assess the potential reduction of workload on a UK Cancer Network of switching colorectal cancer patients currently treated with the Modified de Gramont (MdG) chemotherapy regimen (Folinic Acid and bolus 5FU given on day 1, followed by a higher dose 5FU infusion over 46 hours) to the alternative oral capecitabine (5FU analogue) treatment.

Materials and methods: The audit was designed as a time and motion' study aiming to identify the time spent by staff to prepare, administer and monitor intraveneous (IV) chemotherapy treatments. For the purpose of the study we observed patients who were undergoing disposable 5-Fluouracil pump treatment, using either the MdG regimen or the Lokich continuous 5-FU regimen. An independent nurse observed each activity related to the iv administration and recorded the time spent by each member of staff. We are here reporting only the results of the de MdG patients.

IV 5FU administrations were labour intensive and required the following activities: pre- chemotherapy assessment, insertion of catheter, check- up and maintenance of catheter, preparation of 5-FU infusions, administration and disconnection of 5FU infusions and removal of catheter. Several members of staff were involved in all the activities from nurses, to pharmacists, radiographers, registrar and consultant radiologists.

Results: It took 669 minutes of combined staff time to manage the administration of the MdG regimen for each patient treatment. This time did not include the pharmacist time to prepare the infusion under aseptic conditions. The time required for the administration of the oral capecitabine treatment, on the other hand, was estimated to be a total of 60 minutes for each patient treatment.

Switching an advanced colorectal cancer patient from the MdG regimen to oral capecitabine will save a minimum of 10 hours and 9 minutes (609 minutes) per patient per treatment. Therefore for each patient switched to capecitabine, the cancer network would release an additional 1.5 working days (one day = 7 hours) of staff time to treat more patients. In the case of capecitabine requiring 60 minutes per treatment, 7 more patients could be treated per patient switched onto oral capecitabine. In a cancer network with an average number of 50 patients, an additional 350 patients could be treated on oral medications.

Conclusion: Considerable staff time savings are possible by switching from a single-agent regimen like MDG to oral capecitabine, thus increasing the capacity to treat more patients. These are important in a climate of exponential growth of chemotherapy and staff shortages as in the UK.