1126 POSTER

Cyclic RGDfV-peptides inhibit colorectal tumor growth in a chemically induced rat model

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Background: Integrins are cell surface molecules that mediate cell adhesion, but are also important regulators of tumor cell interactions with their microenvironment, tumor cell survival and growth. In addition, they have been found to take part in the regulation of tumor-induced neoangiogenesis. The alpha v-beta3-integrins appear to mediate stimulatory signals during these processes. In the present study, we used a chemically induced colon carcinoma model in rats for the evaluation of integrin receptor-blockage as a novel therapeutic approach in colorectal cancer.

Methods: Tumor induction was performed in male Sprague-Dowley rats using 1,2 Dimethylhydralazin (21 mg/kg) twice a week. After 20 weeks of tumor induction 100% of the animals developed adenocarcinomas with a mean of 4.1 macroscopic tumor nodules, but no distant metastases. During further tumor induction for additional 10 weeks rats (n=6/group) were treated three times/week with (a) 15 mg/kg cyclic RGDfV -peptide that can block vitronectin and fibronectin receptors; (b) an equimolar amount of an ineffective control peptide; or (c) with NaCl 0.9%. After 30 weeks of tumor induction rats were sacrificed, and tumor load was quantified macroscopically and confirmed by histological examination. Microvessel density was determined in tumor nodules using immunohistochemical stating for CD31.

Results: After 30 weeks of tumor induction control animals (group c) developed an average of 11.1±3.8 tumor nodules with a mean diameter of 3.8±1.3 mm. If rats were treated with RGDfV-peptide (group a) the number of tumor nodules was reduced (6.6±2.5), whereas their mean diameter was comparable in treated (4.3±1.0 mm) and untreated animals. Treatment with the nonspecific peptide (group b) did not show effects on the number of tumor nodules (11.3±4.0) or their diameter (3.7±0.7 mm). Microvessel density was significantly reduced in the RDGfV-treated group.

Conclusions: Our results demonstrate that integrin-receptor blockage appears to be a novel therapeutic strategy for treatment of colorectal cancer. Late onset of treatment with integrin-blocking peptides at a time where all animals had already developed adenocarcinomas resulted in an inhibition of further tumor growth in our rat model and a reduced tumor load after 30 weeks of tumor induction. Therefore, inhibition of integrins may be used as a novel therapeutic strategy in colorectal cancer.

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Study to compare tolerability of standard versus modified mayo regimen 5-fluorouracil

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Purpose: This study compared toxicity and dose modifications necessary in patients treated with "standard" versus "modified" adjuvant Mayo 5-Fluorouracil (5-FU) for Duke's B or C colorectal cancer.

Methods: In this study, the notes and chemotherapy charts of 60 patients who received adjuvant Mayo 5-FU for Duke's B or C colorectal cancer at Addenbrooke's Hospital, Peterborough Hospital or West Suffolk Hospital between 1998 and 2000 were reviewed. Patients had initially been prescribed either the recommended "standard" intravenous 5-FU dose of 425mg/m2/day (plus 20mg/m2 folinic acid) once daily x5 every 4 weeks for 6 cycles or 5-FU at a modified dose of 370mg/m2/day. This is the modification recommended in the QUASAR trial for patients unable to tolerate a higher dose of 5-FU.

Results: Of 41 patients prescribed 5-FU at 425mg/m2, only 12 (30%) completed all 6 cycles of chemotherapy at full dose. The remaining 29 (70%) patients experienced toxicity that required either dose reduction (54%) or premature termination of treatment (16%). Most of these patients experienced grade II-IV mucositis (54%), but also neutropaenia and diarrhoea. Most dose reductions were performed during in the first 3 cycles of chemotherapy. The 41 patients initially prescribed 425mg/m2 5-FU received an average cumulative 5-FU dose of 10594mg/m2, the equivalent of 353mg/m2/day.

Of the 19 patients prescribed the modified dose of 370mg/m2 5-FU, 11 (61%) completed all 6 cycles of chemotherapy at full dose and 7 patients required dose reduction due to toxicity: mucositis (38%), diarrhoea or neutropaenia. The 19 patients prescribed 370mg/m2/day 5-FU received an average cumulative 5-FU dose of 10235mg/m2, the equivalent of 341mg/m2/day.

Conclusion: This study shows that patients prescribed modified Mayo 5-FU at a dose of 370mg/m2/day experienced less toxicity and needed less dose modification than those on the "standard" 5-FU dose of 425mg/m2/day. Patients treated with 425mg/m2/day 5-FU had unacceptably high levels of toxicity and, taking dose modification into account, received similar cumulative amounts of 5-FU as those in the "modified" treatment group. In view of these findings, we now recommend the modified Mayo 5-FU dose of 370mg/m2/day for all patients.

1128 POSTER

Local recurrence rate in rectal cancer patients with distal resection margin less than 9 mm

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Introduction: Distal resection margin (DRM) always represents the greater problem for the restorative surgery of low rectal cancer.

Methods: We report our experience at National Cancer Institute of Milan, Italy, with the technique of total rectal resection (TRR) and total mesorectal excision (TME) with coloendoanal anastomosis (CEAA). From March 1990 to December 1999 were performed 366 consecutive TRR with CEAA at our Institute; 154 patients with a mean follow-up of 51 months (range 21-100 months) were treated for a primary cancer without preoperative chemo-radio therapy. In this series we are evaluated the DRM in 77 patients without node metastases. In 35 of 77 N0 patients the DRM was less than 9 mm (mean: 4.6 mm; range: 0.0-8.8 mm). Patient's stratification based on definitive pathological report staging was 10 Astler-Coller stage B1 (T2 N0) and 25 Astler-Coller B2 (T3 N0). The mean number of examined lymph nodes was 41.5 per specimen. The DRM was microscopically negative in 30 pts and microscopically positive in 5 pts: all these patients refused a subsequent abdominoperineal resection. The specific pathologic evaluation was performed by the same pathologist (S.A.) in all cases.

Results: In the group of the 30 DRM- patients the recurrence rate was 3.3% (1/30). Overall recurrence rate for 35 patients was 11.4% (4/35). Pattern of local recurrence according to stage of disease and DRM was one patient Astler-Coller stage B1 with DRM+, 2 patients Astler-Coller stage B2 DRM+ and one patient at stage B2 with a distal resection margin of 5.1 mm. Of the five patients DRM+ of this series 3 (60%) presented a local recurrence whereas the last two (40%) were free of disease after respectively 92 and 53 months. In this series hand dissection of the surgical specimen showed a mean of 41.5 lymph nodes for patients. Astler-Coller B2 patients received post-operative chemo-radio therapy.

Conclusion: Our data in accordance with other authors seem to highlight that a distal resection margin less than 9 mm did not influence clinical outcome of No patients when a radical surgery was performed.

1129 POSTER

CPT-11 combined with 5 fluorouracil bolus (B)/folinic acid (5FU/FA) nordic schedule as front line therapy in patients (pts) with advanced colorectal cancer (CRC)

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The recommended dose of CPT-11 combined with 5 FU b/FA Nordic regimen has been established in phase I (ESMO 2000, #201). A phase II with CPT-11 administered at 210 mg/m2 day 1, followed by 5 FU b 500 mg/m2 and FA 60 mg/m2 day 1 and 2 every 2 weeks was conducted to assess efficacy and safety of the combination. The main eligibility criteria were measurable lesion, WHO performance status (PS) ≤ 2, adequate haematological, renal and hepatic function, no prior chemotherapy or only (neo) adjuvant CT ended more than 6 months before study entry. Seventy-four pts have been treated. The main characteristics are median age 59 (32-74), PS 0/1 64/34%, colon/rectum/colon rectosigmoid (pt) 31/28/15, median organ involved 1 (1-3). Liver, lung, lymph nodes were involved in 78/28/11% of pts respectively. 860 cycles (cy) have been administered, median (range) 12 (1-26). The median relative dose intensity is 85% for CPT-11, 84% for 5FU

and 88% for FA. Overall response on 68 evaluable pts: 7 CR (10%), 19 PR (28%), 15 MR (22%), 16 SD (24%) and 11 PD (16%) have been reported. Median time to progression: 6.6 months and median duration of response: 11.1 months. The combination is well tolerated with G 3/4 diarrhea (pt/cy) of 15%/1% and G 3/4 neutropenia (pt/cy) 68%/20%. Febrile neutropenia was reported in 2 pts and G3/4 infection with neutropenia in 7 pts. Only 5% of the cycles were administered with a reduced dose. This combination appears to be very promising with a good benefit risk/ratio. A phase III is ongoing to compare this regimen to the reference CPT-11 combined with 5FU/FA de Gramont schedule.

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CPT-11 and 5 fluorouracil/folinic acid (5-FU/FA) mayo clinic regimen in advanced colorectal cancer (CRC) as front line therapy: a phase I/II study

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CPT-11 combined with 5- FU either infusional or bolus is the new reference regimen in front line treatment of CRC. Mayo clinic bolus (b) regimen is also widely used in this setting. The combination of CPT-11 combined with Mayo clinic regimen has been assessed in a phase I/II. CPT-11 was administered as 30-90 min IV infusion, day 1 immediately followed by FA 20mg/m2 15 minutes followed by 5-FU at a fixed dose of 425mg/m2 IV, 15 min, from day 1 to day 5 every 4 weeks. Two dose of CPT-11 were tested in phase I: level 1: 250 mg/m2, level 2: 300 mg/m2. Major inclusion criteria: measurable lesion, no previous chemotherapy for advanced disease, WHO performance status less or equal to 2. Twenty-three patients have been treated in phase I, 14 males/9 females. Median age is 58 (30-69), median organ involved 2 (1-4). 43 cycles (cy) and 63 cy were administered at level 1 (10 patients, pts) and 2 (13 pts) respectively. RDI of CPT11/5-FU/FA was 94.0% for each compound and for both levels. At first cycle, dose limiting toxicities at level 2 were: diarrhea grade 4 (4 pts). Overall, main grade 3-4 toxicities were diarrhea (4pt/5cy) at level 1 and 6pt/9cy at level 2, neutropenia (5pt/6cy) at level 1 and (7pt/15cy) at level 2. Three partial responses were observed at each dose level. The recommended dose was defined as CPT-11 250 mg/m2. Efficacy is promising and safety is manageable. The combination was assessed in phase II: 50 patients have been treated at RD. Preliminary results will be presented at the meeting.

1131 POSTER

Radiotherapy of inoperable recurrent rectal carcinoma

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Purpose: Radiotherapy (RT) is the treatment of choice for inoperable locoregional recurrent rectal carcinoma (ILRCR). The aim of this work was to present that radical doses of RT as well as different RT techniques influence overall response rate (ORR) and overall survival (OS) in this group of patients (pts).

Methods: From 1995 till 2000, at the Institute of Oncology and Radiology of Serbia, Belgrade, 60 pts had been treated for ILRCR, median age 60 years (37-76), male:female ratio 1:1,4. There were 26 pts with Dukes B stage, 30 pts with Dukes C stage while 4 pts had unknown primary stage. Abdominoperineal resection was the most common initial therapy (in 65% of pts) with median disease free survival (DFS) of 24 months (12-60). The sites of recurrent disease were: presacral (21 pts), presacral and vaginal (18 pts), presacral and perineal (11 pts), vaginal (7 pts), at anastomosis (2 pts) and 1 perineal. Each pt was treated with radical RT doses. External beam RT (EBRT) was solely applied in 35 pts, 3 and 4 fields technique and doses of 50-62 Gy. Combined EBRT and brachitherapy (BHTH) was applied in 25 pts. EBRT doses were 30-65Gy and BHTH doses 12-40Gy. Acute skin RT complications were notified in 29 pts (48%) of GI and GII.

Results: The ORR was registred in 40/60 pts (66%) (CR-33%, PR-33%) and was estimated 2 months following RT. The median follow-up time was 19 months (8-60) and 27 pts (46%) had disease free, 7 pts (12%) residual disease, 4 pts stable disease, 15 pts local progression (25%), 6 pts distant progression and 1 pt was lost. There was 38 pts (63%) alive and 22 pts had died (37%). In the group of complete responders (20 pts), 3 yrs DFS was 63,92% and 3 yrs OS 84,85%. Among treated pts (60) there was 3 yrs DFS of 41,14% and 3 yrs OS of 55,11%.

Conclusion: The radical doses of RT improved the local control and OS. We find that there was not statistically significant difference between different RT techniques (EBRT and EBRT+BHTH) regarding DFS and OS.

1132 POSTER

Serum levels and tumor expression of HER-2 in colorectal cancer (CRC) - a prospective analysis

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Rationale: The oncogene HER-2 is overexpressed in 20-25% of breast and ovarian cancers and is the target for novel therapeutic strategies with monoclonal antibodies or small molecules. Reports on the expression levels of HER-2 in CRC have been inconsistent, potentially due to differening methods of detection. Recently, soluble HER-2 has been characterized in the serum of patients with various carcinomas, however the correaltion between tumor expression of HER-2 and respectibe HER-2 serum levels is still unknown. Therefore, we prospectively analyzed sera and tumor samples of patients with metastatic CRC for the expression of HER-2 using standard ELISA and immunohistochemistry (IHC) techniques and tried to correlate it with the clinical course of the disease.

Patients and Methods: Serum levels of HER-2 were determined in 88 pts (52 m, 36 f) with metastatic CRC and 20 healthy controls using a commercially available ELISA system (Dako). In 46 pts, tumor expression of HER-2 was analyzed by IHC (Hercept-Test®, Dako). Routine lab parameters and tumor markers CEA and CA19-9 were recorded in all patients.

Results: HER-2 serum levels were significantly higher in pts with CRC compared with the control group (mean 2511 vs. 2184 U/ml; p=0.038). 21 of 88 pts (23.9%) showed elevated serum levels (>3000 U/ml), but in only 6 of 46 pts (13%) weak expression of HER-2 could be detected in tumor samples (2x 1+, 4x 2+, 0x 3+ Dako-score!). However, a positive correlation could be found between serum levels and tissue expression of HER-.2 (p=0.035). HER-2 serum levels were further significantly correlated with CEA (p=0.031), bilirubin (0.04) and with ongoing anti-tumor therapy (p=0.0083), but not with CA19-9, CRP, LDH, creatinine, hematological parameters (Hb, leukocytes, platelets) and age. Patients with liver metastases were more likely to demonstrate elevated serum levels of HER-2 (p=0.0033), but did not show HER-2 overexpression in the respective primary tumors. In preliminary analysis, HER-2 serum levels did not correlate with overall survival.

Conclusions: Very few colorectal cancers overexpress HER-2 when assessed by standard IHC. Therefore,molecular approaches targeting this oncogene in CRC are not necessarily warranted. The pathophysiological role of elevated levels of soluble HER-2 in the serum of a substantial number of patients with CRC has yet to be determined. Supported by a research grant from Hoffmann-La Roche.

1133 POSTER

Preoperative 5FU and mitomycin-c with concomitant radiotherapy for locally advanced rectal cancer

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Purpose: Investigate the effectiveness and toxicity of pre-operative chemoradiation for adenocarcinoma of the rectum.

Methods: Eight-six patients were assessed. Pre-Operative pelvic radiotherapy was delivered in three or four fields. 50~50.4Gy in 25~28 fractions over 5 weeks. Concurrent chemotherapy with mitomycin C at 10 mg/m2 on day 1 and continuous infusion of 5-fluorouracil (5-FU) at 1000mg/m2/day on days 1~4 and days 29~33 was delivered to the patient during radiotherapy. Total mesorectal excision of the rectal tumor either by anterior or abdomino-perineal resection was planned at 6~8 weeks from completion of pre-operative radiotherapy. Response to therapy was assessed by microscopic measurement of the surgical specimen.

Results: All 86 patients undergoing chemotherapy and radiotherapy completed therapies as planned, with no treatment-related interruptions. Nine patients refused to have surgery. Grade 3 or more diarrheas was observed in 36(42%) patients, leukopenia 17(20%), and infection 4(5%) patients. Anal preservation rate in patients whose tumor located within 5 cm to anal verge was 86%. Complete pathologic remission was observed in