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.

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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