M; mean age 50, range 30–72) and 16 non-acromegalic control subjects (7 M; mean age 52, range 28–75) without colorectal neoplasia.

Results:

Serum DCA (μmol/l) (+/−SEM)

Subjects	Unconjugated	Conjugated	Total
Controls	0 13 (0 06)*#	0 31 (0.02)**	0 44 (0 07)**
Acromegalics – no neoplasia	0.34 (0.05)*	0.13 (0.02)**	0 47 (0.06)
Acromegalics – with neoplasia	0.76 (0.17)**#	0.31 (0.06)**	1.07 (0.21)**

*p < 0 05, **p < 0 01, #p < 0.0001

Conclusions: Significantly increased levels of serum unconjugated DCA, originating from the colon, are associated with colorectal neoplasia in acromegaly and might be involved in the pathogenesis of these lesions.

768 PUBLICATION

Phase II study of a multi-targeted antifolate (LY231514) (MTA) as first line therapy in patients with locally advanced or metastatic colorectal cancer (MCC)

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MTA, a pyrrolopyrimidine analog of folic acid, is a multi-targeted antifolate inhibiting thymidylate synthase and other enzymes. A multi-center phase II trial was conducted in previously untreated patients (pts) with MCC to determine the response rate (RR) and toxicity of MTA iv q21 days. The starting dose of 600 mg/m2 was decreased to 500 mg/m2 when several early pts experienced toxicities requiring dose reduction. 33 pts were entered on the study, 9 treated at 600 mg/m2 and 24 at 500 mg/m2. 17 were female and 15 male. The median age was 68. ECOG performance status for pts was 0:12;1:18;2:2. 9 pts had prior adjuvant therapy 12 months or more prior to study entry. 32/33 pts had measurable disease with liver being the most common site. 1 pt was found to have no measurable disease at baseline and was ineligible. The median number of cycles received was 3 for 600 mg/m2 (range 1–8) and 4 for 500 mg/m2 (range 1–9). 32 pts were evaluable for toxicity and 29 for response: 3 pts went off study early because of toxicity. There was considerable interpatient variability in toxicity at both dose levels. Overall, Grade (GR) 3/4 hematologic toxicities were as follows: 6 GR 4: 9 GR 3 granulocytes;3 GR 4:1 GR 3 platelets; 4 GR 3 hemoglobin. Related non-hematologic GR 3–4 toxicities were diarrhea 3, pain 3, infection 3, febrile neutropenia 5, rash 13. There was 1 death related to febrile neutropenia. Objective tumor responses were observed in 6/29 pts with 1 CR and 5 PR. The response rate was 20.7% with a 95% confidence interval: 8–39.7%. The median duration of the responses was 5 months. All responses were seen in patients treated with 500 mg/m2. Data suggest that MTA is active in MCC.

769 PUBLICATION

Increased serum α-L-fucosidase activity in colorectal cancer patients

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Purpose: In colorectal carcinoma patients, accurate staging and early detection are of great importance for the therapeutic procedure. In a prospective study, the value of serum α-L-fucosidase activity of patients with colorectal cancer has been evaluated.

Methods: α-L-fucosidase enzymatic activity was determined in 44 patients with colorectal cancer and in 50 healthy subjects using a fluorimetric method with 4-methylumbelliferyl-α-L-fucoside as substrate. All malignancies were staged according to the Dukes' classification for colorectal cancer.

Results: We found that the serum α-L-fucosidase activity level in patients with colorectal cancer (0.08 ± 0.007 nmol/mg/min) was significantly higher than that found in controls (0.05 ± 0.003 nmol/mg/min; $P < 0.001$). After dividing colorectal cancer patients according to de Dukes' classification, an increment of α-L-fucosidase activity was detected in each Dukes' stage subgroup when compared with the levels in normal subjects. Furthermore, higher levels of this enzyme were observed with the progression of the disease (from stage A to stage D).

Conclusion: Our results clearly show that there is a relationship between the increment of α-L-fucosidase activity in serum and the presence of malignancy. These preliminary findings suggest that the measurement of serum α-L-fucosidase activity, could be a promising approach in the search for markers to detect colorectal cancer at an early stage.

770 PUBLICATION

Phase I dose finding study of irinotecan hydrochloride trihydrate (CPT11) with tomudex (TX.) in patients with 5-FU refractory colorectal cancer

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CPT11 and Tx. are 2 effective cytotoxic agents in the treatment of solid tumours with a different mechanism of action. In order to define an effective combination schedule, a phase I study of CPT11 with Tx is on going in patients with advanced adult solid tumours. CPT 11 is administered on day 1 as a 30 minute i.v. infusion. The dose escalation schedule was 175, 200, 250, 300, and 350 mg/m^{2}q.3wk. Tx was administered at doses ranging from 2.6 to 3 mg/m^2/day as a 15 minute infusion one hour after the CPT11. Dose limiting toxicity (DLT) was assessed at first cycle. Pharmacokinetic (PK) parameters of CPT11, SN-38 and Tx will be analysed in all patients. Since September 1996: 13 pts. have been treated and were evaluable for toxicity. Patient characteristics: median age 56 (44–71), median PS 1 (0–2), sex: M/F 9/4, primary site: colon/rectum 2/11. Median number of administered cycles was 2 (1–6). The first four dose-levels (CPT11 175–300 mg/m^2 with Tx. 2.6 mg/m^2) have been completed (the 5th [350/2.6 mg/m^2] is on-going) and no DLT (CTC grade 3/4 toxicity) observed. No grade 3/4 diarrhoea has been observed. Grade 3/4 neutropenia has been observed in 8% and 17% of cycles at 250/2.6 and 300/2.6 mg/m^2 respectively. PK results are not yet available. Three partial responses and one minor response have been observed with this combination. The remaining 6 patients currently evaluable for response all have stable disease. Although few patients have been enrolled so far, preliminary analysis shows this combination is well tolerated. Accrual continues as maximum tolerated dose has not yet been established.

771 PUBLICATION

Preoperative 5-fluorouracil and radiotherapy in rectal cancer

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Purpose: The optimal treatment of large rectal cancer remains controversial. Combined modality therapies with surgery, radiotherapy and chemotherapy have been used to improve local control and survival. In this study we evaluated the tolerance of preoperative chemoradiotherapy and the impact on the staging and resectability.

Methods: From 1990 to 1995 sixty-three patients with biopsy-proven rectal adenocarcinoma >3 cms, involving the entire rectal wall and without metastases, were entered into the study. Radiotherapy was delivered by a linnear accelerator; a total doses of 45 Gy, at 1.8 Gy/day, 5 days/week, was administered on whole pelvic volume. Concomitant chemotherapy with 5-fluorouracil (300 mg/m2/day by IV bolus injection) was given for days 1–5 and 21–25 of radiotherapy. Surgery was performed 4–6 weeks after completion of chemoradiation.

Results: Hematological toxicity grade I–II was observed in 6 patients (9.5%); diarrhea-tenesmus grade I–II in 15 (24%) and grade III in 4 (6%); dysuria grade I–II in 10 (16%). Three patients refused surgery; in five pts (8%) the complete tumor resection was not possible; 42 pts (70%) underwent low anterior resection and 13 (22%) abdominoperineal resection. Pathological examination of the surgical specimens (n = 55) revealed: 8 sterile specimens (14.5%), 9 stage A (16.5%), 12 stage B1 (22%), 16 stage B2 (29%) and 10 stage C (18%). The 4-year actuarial survival was 62% (median follow-up 46 months) and the incidence of local failure was 4%.

Conclusion: Preoperative chemoradiotherapy showed an acceptable toxicity and enhanced the rates of downstaging, resectability and sphyncter-sparing surgery.