was lost to follow-up. There have been 4 deaths from disseminated disease, and 4 patients admitted in the first 6 weeks after treatment for various reasons. No patient experienced liver failure or veno-oclusive disease. Responses measured by CEA and CT or MRI scans showed that 25% of patients had at least a >50% reduction in tumor burden; 55% of patients had stable disease or <50% response, and 20% of the patients failed distantly.

Conclusion: Radioactive 90-yttrium microspheres induce a 25% partial response rate in patients with chemo refractory metastases from colorectal cancer. It is a safe and low toxicity outpatient treatment in the dose range reported.

1070 POSTER

Sphyncter preserving procedures for low rectal cancer

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Introduction: Total rectal resection (TRR) with coloendoanal anastomosis (CEAA), mesorectum 'en bloc' excision (TME), radical abdomino-pelvic lymphadenectomy (RAPL) and J colic reservoir represents a valid alternative to the traditional surgery for the restorative management of low rectal cancer.

Methods: We report our experience at National Cancer Institute of Milan, Italy with this procedure. From March 1990 to December 2000, 346 consecutive TRR with CEAA were performed at our Institute; 262 patients, with a minimum follow-up of 18 months, were treated for a primary cancer of distal rectum at a distance ranging from 3 to 8 cm within the anal verge. Patient's stratification based on definitive pathological report staging was 64 (20%) Dukes' stage A, 101 (32%) stage B and 155 (48%) stage C.

Results: Overall recurrence rate was 8.7%; (23 patients) pattern of local recurrence according to stage of disease was 3 Dukes' A, 6 Dukes' B and 14 Dukes' C after an interval ranging from 8 and 47 months. A specific pathologic evaluation was performed by a dedicated pathologist (S.A.) in the last consecutive 147 cases.

Blood vessel invasion (BVI) was present in 10 out of 51 No patients. Tumour recurrence occurred in 5 out of 41 BVI+ patients versus 3 out of 41 BVI- patients (2 positive distal resection margin and one positive circumferential margin of mesorectum). Perineural invasion (PNI) was present in 8.8% of 45 Dukes B patients and 41.1% of 73 Dukes C patients (47% N1 and 53% N2). In the 17 PNI+ patients local recurrence occurred in 74% (35% N1 and 65% N2) versus 45% of 15 PNI- patients (40% N1 and 60% N2). Four Dukes A patients and 17 Dukes B patients have distal resection margin (DRM) less than 9 mm (median follow-up 40 months). No recurrence occurred in Stage A patients; 3 Stage B patients had lung metastases (2 BVI+ and one DRM+), one experienced local recurrence (DRM+). Dukes B patients received postoperative radiotherapy.

Conclusion: Our data, in accordance with other authors, seem to highlight that important pathologic prognostic factors turned out to be BVI in No patients, PNI in C patients. DRM less 9 mm plus RT did not influence clinical outcome of No patients.

1071 POSTER

Thymidylate synthase and p53 expression do not predict chemotherapy outcome in metastatic colorectal carcinoma

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Introduction: Thymidylate synthase (TS) and p53 have been reported to predict the results from chemotherapy in advanced colorectal carcinoma (ARCR).

Methods: One hundred and twenty-two patients with ARCR have been treated with 5-fluorouracil (5-FU)-based therapy at the University Hospital in Uppsala in four different randomised clinical phase III studies between 1989 - 1997. The paraffin-embedded tumours at primary diagnosis were retrospectively analysed with immunohistochemical technique. TS enzyme levels were evaluated using the monoclonal antibody TS 106 and the p53 expression with the monoclonal antibody DO-7.

Results: Fifty-three (43%) of the patients had advanced disease at diagnosis. There were 26% radiological responders. Seventy-eight % had high TS expression and 60% of the tumours were p53 positive. None of the markers predicted the outcome of the later palliative treatment. However, the TS values had prognostic information and significantly predicted time to recurrence (median for low TS 30 months and for high TS values 11 months, p = 0.001).

Conclusion: Immunohistochemical investigation of TS and p53 of the primary cancer is not useful to predict outcome after palliative chemotherapy in ARCR. TS can instead be regarded as a marker of proliferation.

1072 POSTER

Expression of CEACAM6 in colorectal cancer: significant association with overall and disease-free survival

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Members of the carcinoembryonic antigen family,CEACAM1,CEA, and CEACAM6 are co-expressed in normal colorectal epithelia but are deregulated in many colorectal tumors.Very recent studies have shown that human CEACAM1 which is often downregulated in colorectal cancers has tumor suppressive activity in prostate cancer. CEA or CEACAM6 which can block differentiation, disrupt cell polarization and tissue architecture, and inhibit apoptosis (anoikis) are overexpressed in many human tumors. The aim of our study was to investigate a possible relationship between tissue expression of these functionally active molecules and prognosis in patients with colorectal cancer.Patients have been enrolled in a randomized, controlled clinical SAKK study. Immunohistochemical analysis was carried out on tissue microarrays from 240 paraffin embedded biopsies with specific monoclonal antibodies (mabs) against CEACAM1, CEA, or CEACAM6.Staining of tumor microarrays was scored from negative (-) to strongly positive (+++).Long-term overall (OAS) or disease-free survival (DFS) in patients with enhanced (++/+++) or reduced (-/+)individual CEA family antigen expression was calculated by use of Kaplan-Meier estimates and the Cox proportional hazards model.The median follow up time was 13 years. Tissue expression of CEACAM1 was reduced (-/+) in 102 patients whereas CEA and CEACAM6 were enhanced (++/+++) in 226 and 132 patients, respectively.CEACAM1 or CEA showed no significant relationship to overall or disease-free survival of colorectal cancer patients.In the case of CEA, however, only 14 patients showed reduced expression.In contrast, unvariate analysis demonstrated that enhanced expression of CEACAM6 (55.4%) was associated with far worse OAS (hazard ratio = HR, 2.19; p = 0.00014) and DFS (HR, 2.44; p = 0.000029). Multivariate Cox analysis including sex, age, tumor localization, tumor staging, lymph node status, and treatment showed that CEACAM6 overexpression independently predicted survival (OAS, HR, 1.89; p = 0.0027; DFS, HR, 2.00; p = 0.0085).To our knowledge this study is the first to demonstrate the prognostic significance of immunohistologically detectable overexpression of CEACAM6 in patients with resectable colorectal cancer. This may help to identify patients who need to be selected for adjuvant treatments or an intensive postoperative follow-up protocol.The data are in good agreement with recent functional findings.

1073 POSTER

Extended phase I study of capecitabine and weekly irinotecan as first-line chemotherapy in metastatic colorectal cancer

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Purpose: Capecitabine (CAP) demonstrated efficacy in metastatic colorectal cancer (CRC). Preclinical data on nude mice bearing human colon tumor xenografts demonstrated significant synergistic antitumor activity for the

combination of CAP and irinotecan (CPT). Based on these data a phase I study of CAP combined with weekly CPT was conducted in patients (pts) with measurable metastatic CRC as first-line chemotherapy.

Methods: CAP (bid) d 1-14 and d 22-35, CPT 30 min. inf. weekly x 6 followed by a one week rest (one cycle). Dose level [DL]1: CAP 1000 mg/m2 bid and CPT 70 mg/m2; DL2: CAP 1250 mg/m2 bid and CPT 70 mg/m2; DL3: CAP 1250 mg/m2 bid and CPT 80 mg/m2.

Results: 37 patients (pts) were entered on 3 DL and 89 cycles have been administered. Pts characteristics: Male/female 26/11 pts; PS 0 (0-2); median age 60 years (32-71); prior adjuvant CTx or/and RTx 14 pts. In the first 17 pts treated at DL1-3 the MTD has been reached at DL3 with diarrhea and neutropenia being dose-limiting. In order to confirm the recommended dose (RD), this DL2 was extended to 15 pts, demonstrating an incidence of DLTs in 5 (33%) out of 15 pts (diarrhea, neutropenia, one toxic death). Because the incidence of DLTs was considered to be too high, DL1 was extended to a total of 16 pts. DLTs were observed in 3 (19%) out of 16 pts. The main toxicity observed was diarrhea. So far, 13 out of 29 response evaluable pts (DL 1-3) (45%; 95%CI: 26-63%) and 6 out of 13 pts (46%; 95% CI 19-75%) at the RD (DL1) achieved an objective response.

Discussion: DL1 is the recommended dose for further studies. The combination of CAP and CPT is feasible and showed promising efficacy as first-line chemotherapy in advanced colorectal cancer.

1074 POSTER

Preoperative chemoradiation with raltitrexed ('Tomudex') alone or in combination with oxaliplatin in T3 rectal carcinoma: review of four phase I-II studies

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Aims: Preoperative radiation plus 5-fluorouracil (5-FU) increases the likelihood of sphincter preservation during surgery for rectal cancer. Tumour downstaging following chemoradiation also correlates with improved prognosis. Hence, there is a demand for more potent downstaging drugs to replace 5-FU in chemoradiation. The efficacy of raltitrexed ('Tomudex'), alone or combined with oxaliplatin, in preoperative chemoradiation was studied in patients with T3 rectal carcinoma.

Methods: Since 1998, 62 patients (pts) with stage II-III extraperitoneal rectal carcinoma have been studied in 4 trials. Radiation plus raltitrexed (2 trials): (1) Phase I study to determine the recommended dose (RD) of raltitrexed (2.0, 2.5, 3.0 mg/m2) concurrent to radiation; (2) Phase II study of raltitrexed (3.0 mg/m2)/radiation. Radiation plus raltitrexed and oxaliplatin (2 trials): (1) Phase I study to determine the RD of oxaliplatin (65, 85, 110, 130 mg/m2)concurrent to radiation plus raltitrexed (3.0 mg/m2); (2) Phase II study of oxaliplatin (130 mg/m2)/raltitrexed (3.0 mg/m2)/radiation. Pts received 45 Gy pelvic radiation (1.8 Gy/day, 5 days/week) with 5.4 Gy boost on the tumour bed. Raltitrexed, with or without oxaliplatin, was administered on Days 1, 19 and 38.

Results: Radiation plus raltitrexed: in Phase I (n=15) the RD was determined as 3.0 mg/m2, and 40% and 66% of pts had downstaging (pT0-1) and sphincter-saving surgery, respectively; only 1 pt had >G2 toxicity (G3 leucopenia, recovery in 3 days). Similar results were observed in Phase II (n=20): 50%, 80% and 15% of pts had downstaging, sphincter-saving surgery and G3 toxicity, respectively. Radiation plus raltitrexed and oxaliplatin: in Phase I (n=18) the RD was determined as oxaliplatin 130 mg/m2 combined with raltitrexed 3.0 mg/m2 and radiation. Overall, 66% and 72% of pts had downstaging and sphincter-saving surgery, respectively. Two pts had >G2 toxicity (G3 leucopenia and G3 proctitis). The Phase II study (n=9) confirmed these results: 55%, 89% and 11% of pts had downstaging, sphincter-saving surgery and G3 toxicity, respectively.

Conclusion: The high rates of tumour response and sphincter-sparing surgery plus low levels of toxicity suggest that raltitrexed is effective with an acceptable toxicity profile, both alone and combined with oxaliplatin, when given concurrently to pelvic radiation preoperatively.

'Tomudex' is a trade mark of the AstraZeneca group of companies

1075 POSTER

Weekly combination of oxaliplatin (OX) and irinotecan (IRI) in 5-FU resistant colorectal cancer (CRC)

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Purpose: OX and IRI are active agents in CRC. The combination of both drugs could enhance the efficacy of a salvage regimen in patients (pts) in whom progression (PD) occurs while they receive a 5-FU based chemotherapy (CT): 5-FU resistant 2nd-line population (FRP). In a recently published trial with OX-IRI only 14/36 pts were FRP and 31/36 received G-CSF to ameliorate risk of neutropenic fever (J Clin ONCOL 17:902).

Methods: We performed a prospective multicenter phase II trial with OX 60 mg/sqm/1h and IRI 80 mg/sqm/1h both on days 1, 8, 15 q 28d, without any use of G-CSF. Instead individual dose optimisation (IDO)was performed in case of toxicity (TOX) by dose modification and omitting scheduled days according to predifined guidelines.

Results: 68 pts received 1 to 9 cycles and are evaluable for TOX: In 27 pts CT was stoped due to objective or subjective TOX before PD occurred and 9 pts had to be admitted to the hospital mainly due to diarrhea. CTC ° III/IV TOX by pts: Diarrhea 26/3, Neutropenia 6/1, no case of neutropenic fever and no toxic death occurred. CTC ° II/III TOX by pts: Nausea 19/1, Emesis 15/1, Asthenia 16/3, Alopecia 8/0, Neurotox 9/5. In 25/225 and 65/225 cycles of CT scheduled day 8 resp. day 15 was omitted due to persisting diarrhea. IRI was increased to 100 mg/sqm in 5 pts (no TOX cycle 1) and reduced to 60 mg/sqm in 20 pts and to 50mg/sqm in 5 pts in forthcoming cycles due to diarrhea or neutropenia. EFFICACY: FRP = 49 pts with median TTP 5 months, median survival from start of 2nd-line 16 month. Response was evaluable in 44 FRP cases. Best response: 5 CR, 10 PR, 15 confirmed NC, 5 not confirmed NC, 9 PD: ORR 34%. In 3rd-line and pts pretreated with OX or IRI actvity was poor.

Conclusion: Weekly OX-IRI showes a remarkable activity in 5-FU resistant CRC compared to IRI alone or OX combined with 5-FU but despite IDO the objective and subjective TOX of the reported schedule is substantial and a starting dose of 60 mg/sqm of both drugs should be tested to define a safer protocol. Neutropenia, Nausea and alopecia seem to be less pronaunced than in other pubished OX-IRI combinations.

1076 POSTER

Integrated analysis of overall survival from two multicenter randomized trials of 5-fluorouracil (5-FU) and leucovorin (LV) with or without trimetrexate (TMTX) in patients with advanced colorectal cancer (ACC)

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Purpose: TMTX is a biomodulator of 5-FU cytotoxicity, especially in combination with LV. Favorable results are seen in Phase II studies of TMTX/5-FU/LV in ACC. Two Phase III, multicenter, randomized trials, one in the United States (TMTX-0034) and one in Europe (TMTX-0509), are designed to compare the efficacy and safety of TMTX/5-FU/LV with 5-FU/LV in first-line treatment of ACC. Survival data from these two studies will be integrated to increase statistical power to detect clinically relevant survival differences between the two treatment arms.

Methods: TMTX-0034 is a double-blind, placebo-controlled trial in 384 patients with ACC, and TMTX-0509 is an open-label trial in 365 patients with ACC. Both studies are similar in design, have identical objectives, include patient populations with similar baseline demographics, and are conducted in parallel. In TMTX-0034, patients receive TMTX 110 mg/m2 (Arm I) or placebo (Arm II) as 60-minute infusions followed 24 hours later by LV 200 mg/m2 as a 60-minute infusion, 5-FU 500 mg/m2 as a bolus infusion, and LV 15 mg orally q6 hours for 7 doses starting 6 hours after 5-FU. The same schedule was used in TMTX-0509, but without the placebo control and with 5-FU at 600 mg/m2 in the control arm. In both studies, each cycle of treatment consists of 6 weeks chemotherapy followed by 2 weeks