time to progression and duration of response was 8 months (6-10) and 6 months (IC 95%: 5-7) respectively. To date, median survival time has not been achieved yet.

Conclusion: Biweekly combination of CPT-11 and 5-FU is an active and well tolerated regimen as first line chemotherapy in advanced or metastatic CRC.

1092 POSTER

CD97 expression in colorectal carcinomas and tumour cell lines

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CD97, a member of the EGF-like domain/seven-span transmembrane (EGF/TM7) family, is present in thyroid carcinoma cell lines but only at low level in normal thyroid epithelial cells. In thyroid carcinoma, CD97 expression correlates with the stage of differentiation and metastasis (Cancer Res. 1997). So far, there have been no studies on the detection of CD97 in other tumour cell lines or entities.

16 out of 16 (16/16) colorectal tumour cell lines investigated were CD97+, although the density of the molecule varied considerably. 15/16 also carried the ligand of CD97, CD55, but most cell lines showed weak or no expression of EMR-2, another closely related member of the EGF/TM7 family. The density of CD97 correlates with the in vitro invading potential and the immunohistological determined proliferation index. TGF-b down-regulates CD97 expression by 25 to 50% in the TGF-b sensitive-cell lines, LS1034 and LS513, but only slightly or not at all in insensitive cell lines such as Colo205 and WiDr.

We also examined 72 colorectal adenocarcinomas and corresponding normal tissues by immunohistology. The monoclonal antibody (mab) CD97EGF detects an epitope at the first EGF-like domain of the molecule, whereas the CD97stalk mab binds to the stalk region right before the transmembrane region. An immunoreactive score was set up based on the method devised by Remmele (RS 0-12).

CD97EGF was detected in 53/72 (mean ± SEM; RS 3.2 ± 0.4) and CD97stalk in 64/72 (RS 5.3 ± 0.3) of the carcinomas. The significant difference in the staining intensity between the CD97EGF and CD97stalk epitope is not caused by different affinities of the used mab, as CD97EGF showed the same or even a stronger staining as CD97stalk in 18/72 cases. The corresponding normal tissues were CD97- for both epitopes, or expressed CD97 more weakly than the tumours (RS 0.8 ± 0.1). Poorly differentiated or scattered cells within one tumour (28/72) were more strongly positive for CD97stalk (RS 10.0 ± 0.4) compared to the cells growing in tubular structures (RS 5.5 ± 0.5). The tumour cells of the invasion margin showed the strongest immune reaction. Dukes stage and preoperatively determined sCD97, CEA, CA15-3, and CA19-9 in the sera of the patients showed no correlation with the expression of CD97 in the tumours.

Taken together, colorectal carcinomas and cell lines express CD97. The different epitopes of the molecule showed varying distributions within the tumours.

1093 POSTER

CPT-11 in combination with capecitabine as first line chemotherapy for metastatic colorectal cancer (MCRC): preliminary results of a phase I/II study

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CPT11, Campto (C) in combination with intravenous (iv) 5 Fluorouracil (5-FU) modulated by folinic acid (FA) is the reference treatment in first line MCRC. Capecitabine, Xeloda (X) is an oral fluoropyrimidine, which is converted to 5-FU predominantly at the tumour site by exploiting the higher activity of thymidine phosphorylase in malignant tissue. It has demonstrated superior activity and improved tolerability compared with iv bolus 5-FU/FA. The convenience of oral administration brings a new alternative to current iv therapy. C and X have different mechanisms of action and are synergistic. A phase I study was conducted to assess the maximum tolerated dose (MTD) and the recommended dose (RD) of the combination. Main eligibility criteria: measurable disease, WHO performance status ≤ 2, adequate haematological, hepatic and renal functions. Prior adjuvant chemotherapy with bolus 5-FU was allowed if the interval between the end of adjuvant and study entry was at least 6 months. C was given iv over 30 minutes, day 1, q 3 wks and X, per os twice daily 12 hours apart from d1 to d14, q 3 wks. Dose escalation (mg/m2): level 1 (3 patients, pts/18 cycles, cy) C 200, X 750; level 2 (6 pts/37 cy) C 250, X 750; level 3 (3 pts/24 cy) C 250, X 1000; level 4 (3 pts/20 cy) C 300, X 1000; level 5 (7 pts/25 cy) C 300, X 1250; level 6 C 350, X 1250. The MTD is reached at level 5 based on overall safety profile: grade (G)3 fatigue 2pts; G3 hand and foot syndrome 1pt; G3 diarrhoea 1pt; Febrile neutropenia 2pts. Recruitment in level 4 (RD) is ongoing. Efficacy is encouraging with responses observed at each dose level. A phase II and pharmacokinetic study is planned.

1094 POSTER

Results of a phase II study combining, weekly Irinotecan with pharmacokinetics (PK) adaptation of 5FU "Gamelin"schedule in first line in patients with metastatic colorectal cancer (MCRC)

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No standard schedule of 5FU/folinic acid (FA) is recommended in MCRC treatment. Infusion can be administered monthly, every 2 weeks or weekly. 'Gamelin' schedule associates FA 100mg/m2 bolus IV followed by 5FU over 7 hours (H); 5FU dose was individually calculated on PK samples, with a starting dose of 1300mg/m2. Our phase II study combines this schedule with weekly Irinotecan 80 mg/m2, H0-H1, given 6 weeks out of 7. The primary endpoint of this trial is the overall response rate (ORR).

Patients characteristics: 35 patients (pts) were included, 29 were analysed for safety and 28 for efficacy. Sex ratio M/F 17/12; PS O/1/2 19/6/3pts, median age 61y[43-75], primary tumor site colon 12pts (42%), rectum 13 (45%), rectosigmoid jonction 4pts(14%). Prior treatment: radiotherapy 8pts (27%), adjuvant chemotherapy 10pts (34.5%). Number of involved sites: one 16 pts (55%)/two 13pts (45%), liver metastasis 24pts(82%). 342 weekly infusions were given with a median of 12[2-24]. Treatment delay >7 days were observed in 10 pts (2 for hematological toxicity, 5 for diarrhea, 3 for other reasons). Safety (gr * per pt): diarrhea 6 pts (20.7%)/1 pt(3.4%) (4pts/7 had diarrhea at inclusion); asthenia 4 pt (13.8%)/0, neutropenia 2pts (3%)/0 without febrile neutropenia. One patient had drug interstitial pneumonitis with unknown causality. ORR: CR 1 pt(3.6%), PR 6 pt(21%), SD18 pt(64%) (9/18pts had only 1 evaluation, PR no confirmed), PD 3pt(11%). 2 pts had surgical resection of liver metastases.

Conclusion: Individually adaptation of 5fU allowed high dose escalation (up to 2480mg/m2/wk) combine with Irinotecan, without increase toxicities and with a good response rate.

1095 POSTER

Preoperative chemoradiation for rectal cancer. Toxicity, downstaging and complications in 114 patients

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Purpose: To define toxicity, surgical morbidity and downstaging in patients (pts) with rectal cancer treated with adjuvant radiochemotherapy followed by curative surgery.

Methods: From May 1993 to January 2001 114 pts (76 M, 38 F, median age 61 years, range 30-87) with a II-III TNM clinical stage adenocarcinoma of the middle-lower rectum received preoperative radiochemotherapy. Fifty-two pts received RT for a dose of 50.4 Gy in 28 fr. along with a continuous infusion (300 mg/m2/day) of 5-fluorouracil (5-FU) and a weekly bolus of Carboplatin (70 mg/m2/day). Sixty-two pts received RT for a dose of 45 Gy in 25 fr., while 5-FU (350 mg/m2/day) and LV (10 mg/m2/day) bolus were administered on days 1-5 and 29-33 during RT. Toxicity was scored according to the RTOG scale.

Results: Sixty-seven pts (58.7%) experienced gastrointestinal toxicity (grade 1-2 in 48 and gr. 3 in 19), 54 pts (47.3%) haematological toxicity (gr.

1-2 in 44, gr. 3 in 6 and gr. 4 in 4) and 34 pts (29.8%) cutaneous toxicity (gr. 1-2 in 29 and gr. 3 in 5). All patients underwent surgery after a median interval of 43 days from completion of adjuvant therapy. Surgical procedures were: low anterior resection in 92 (80.7%) and abdominoperineal resection in 22 (19.3%). Downstaging was obtained in 76 pts (66.6%) while complete pathological response was found in 18 (15.7%). No early mortality due to adjuvant or surgical treatment was found. Major postoperative complications occurred in 22 pts (19.3%): 7 clinical anastomotic leaks, 3 pelvic abscesses, 5 delayed perineal wound healing, 2 rectovaginal fistulas, 1 stoma ischemia and 4 postoperative ileus. After a median follow-up of 24 months (range 5-86), 4 (3.5%) local recurrences and 24 (21%) distance metastasis were observed. Eighty-eight pts were alive and disease free and 12 were alive with distance metastasis. Fourteen had died (12 of cancer related causes and 2 of other causes).

Conclusions: Local control compared favourably with recently published data. A high rate of downstaging and sphincter saving were obtained with acceptable toxicity, however a longer follow up is necessary to verify the impact on survival.

1096 POSTER

Relationship between high dose irinotecan (260mg/m2) and response rate, without increased toxicities in metastatic colorectal cancer (MCRC) combination with bi-weekly 5FU/FA in a phase II study

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The recommended dose of irinotecan with LV5FU2 is 180 mg/m2. In this phase I study the MTD was 300 mg/m2. In monotherapy, level 500 mg/m2 was safe in 2/3 patients(pts) with good response rate. The rationale of this study is to confirm safety and efficacy irinotecan 260 mg/m2 combined with LV5FU2 (group 1) then with LV5FU simplified regimen (group 2) after better safety published results of this schedule. The primary endpoint is the ORR.

Results: 34 pts with MCRC (10 had received adjuvant chemotherapy) were included for 1rst line, prophylactic G-CSF after hematological toxicity to maintain dose intensity; sex ratio (H/F)=20/14; median age 55y[41-73]; PS 0/1=16/18; number of sites involved 2[1-4].

	Group 1 (%cy/%pts)	Group 2 (%cy/%pts)
N cycles/N patients	209/20	46/14
Median cy/patients	8.0 [1-16]	5.0 [1-8]
Diarrhea G3/G4	(1.0/4.2)/(0/0)	0/0
Asthenia G3	1.5/13	4/10
Vomiting/Nausea G2	(2.5/17)/(5/21)	(6/20)/(10/30)
Neutropenia G3/G4	(15/58)/(2/21)	(17/60)/(0/0)
Febrile neutropenia	0.5/5	0/0
ORR (%RP-SD-PD)	(20 pts) 55*-35-10	Too early**

*3 pts with surgical resection of liver metastases. **Only one evaluation per patient.

Conclusion: Preliminary results, CPT-11 260mg/m2 demonstrates a good safety profile, more especially when combined with simplified LV5FU than LV5FU2, with an overall better efficacy when compared to 180 mg/m2.

1097 POSTER

Significance of different classes of p53 gene mutation in patients with colorectal cancer

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Purpose: The p53 tumor suppressor gene controls many critical processes related to tumor development and progression. Specific p53 mutations have been found to be associated with various clinical phenotypes. The clinical and pathological significance of p53 mutations in defined structural and functional domains were prospectively investigated in a large series of colorectal cancer patients.

Methods: Surgical specimens from 335 consecutive patients with stage I-IV colorectal adenocarcinoma were collected between 1991 and 1998. p53 gene mutations in exons 4 to 8 were searched for by PCR-SSCP analysis, followed by direct DNA sequencing. Comparison between groups was made using the Chi-square test. Survival analyses were carried out by the log-rank test and the Cox's proportional hazards model.

Results: p53 gene mutations were detected in 141/335 (42.1%) cases. The higher mutational frequencies were found in exons 5, 7 and 8 (37.6%, 24.8% and 29.1% respectively). p53 gene mutations were associated with left-sided tumors ($p<0.001$) and more advanced lesions (stage III and IV) ($p<0.01$). In particular, mutations located on exon 5 and in the L2 loop region were significantly associated with tumors in stage III and IV. At univariate analysis of survival, no significant differences were found in relation to p53 gene status. However, among cases with p53 gene mutations, those with alterations in exons 4 to 6 had a worse outcome than those with alterations in exons 7 and 8 ($p<0.02$). On the other hand, cases with L3 loop region mutations had a better outcome than cases with mutations in other sites of the gene ($p<0.05$). At multivariate analysis, the only factors which independently predicted survival were tumor site and stage.

Conclusion: Our results indicate that p53 gene mutation is not a prognostic marker in patients with colorectal cancer. Specific p53 gene mutations in defined structural and functional domains are associated with different clinical and pathological findings.

1098 POSTER

Colorectal cancer (CRC) patients surveillance with virtual computed tomography colonography(CTC): preliminary results

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Purpose: Which is the best follow-up schedule in colorectal cancer (CRC) patient is still controversial. The aim of our analysis was to asses the role of virtual computed tomography colonography (CTC) in the follow-up of patients who underwent surgery for colorectal cancer (CRC).

Methods: From January 1998 through March 2001, 35 CRC surgical treated patients (all adenocarcinoma, 18 female, 17 male, 14 rectum, 20 colon, 1 r-s junction, grading 2 G1, 23 G2, 3 G3, 7 GX, 8 Dukes A, 14 Dukes B, 13 Dukes C, mean age 63 years, age range 43-78), entered our surveillance program with CTC. Patients were following a schedule which consist in annual conventional colonoscopy, liver US and chest X-ray, physical examination and serum CEA every 3 months for the first 3 years from diagnosis, every 6 since 5th year. Bowel was regularly prepared with standard setting for traditional colonic exam and after air insufflate; multislice spiral CT (Somaton Plus 4 Volume Zoom, Siemens) examination of the abdomen and pelvis was performed. Patients were scanned in supine and prone position using the following parameters: 1 mm collimation, 1 mm reconstruction index, 8 mm/sec table speed, and mAs 80 with the patient in the prone position, and then after the injection of intravenous contrast medium (60 sec delay), with the patient in the supine position, using 120 mAs. Images were evaluated on a dedicated workstation.

Results: We consider as gold standard for virtual exam the conventional colonoscopy and related pathologic exam. Thirty patients were negative for any pathologic aspect. We checked only one false positive. We found: 3 patients with liver metastases confirmed by RMN, 1 patient with 2 basal pulmonary nodules, 5 patients with 6 polyps and 1 local anastomotic relapse.

Conclusions: We think that CTC is feasible and can offer, unlike conventional, the opportunity to have a complete TNM owing to liver scan with I.V. contrast, with low patient discomfort; it can also check extra-colonic findings. Our study is still ongoing to subsequently assess if CTC can be considered as first choice exam in the follow-up of patients surgically treated for CRC.

1099 POSTER

Tomudex + folinic acid + 5-fluorouracil (5FU) and preoperative concomitant radiotherapy for locally advanced rectal cancer(LARC): a phase I study

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Background and Purpose: Preoperative chemoradiation in rectal cancer (RC) is still investigational: improved resectability rates and sphincter preservation with low toxicity are reported. Prolonged venous infusion (PVI) of 5-FU concomitant with postoperative radiotherapy has shown good results in both local tumor control and survival. Nevertheless PVI 5-FU is cumbersone and expensive. Accurate preoperative evaluation by endoscopic ultrasound (EU) is mandatory for a careful selection of patients.