in those without (median IL-6=2.3 pg/ml $p<0.05$; median sE-selectin=42.0 ng/ml, $p<0.005$). Moreover 85% of patients without distant metastases had sE-selectin levels <70 ng/ml, whereas 50% of metastatic patients had sE-selectin levels >70 ng/ml (Chi-square: 5.8, $p<0.02$).

Conclusions: The results obtained showed that IL-6 and sE-selectin levels are associated with elevated CA 19-9 levels and the presence of metastatic disease, suggesting that these molecules may play an important role in the haematogenous metastasis of colorectal cancer.

1138 POSTER

Phase II evaluation of an alternated FOLFOX/FOLFIRI regimen in patients with resistant metastatic colorectal cancer (CRC)

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Oxaliplatin (LOHP), irinotecan (CPT 11) and 5 FU are active chemotherapeutic agents in patients with metastatic CRC. The use of LOHP is frequently limited by the occurrence of a cumulative neurotoxicity. Furthermore, CPT11 may interfere with DNA repair in tumor cells after exposure to oxaliplatin. To avoid the occurrence of the LOHP-related neurotoxicity, and to assess a potent synergy between LOHP and CPT11, we evaluated an alternated combination of FOLFOX and FOLFIRI regimens in patients with metastatic CRC after failure of a first line 5FU-leucovorin association. Patients alternatively received 4 courses of FOLFOX 6 (LOHP 100 mg/m2 d1 + simplified LV5FU2, repeated every 2 weeks) and 4 courses of FOLFIRI (CPT11 180 mg/m2 d1 + simplified LV5FU2, repeated every 2 weeks) until disease progression or limitant toxicity. Thirty eight patients were enrolled: M/F = 23/16, median age 64 (28-78), PS 0/1/2: 26/10/2. All patients were evaluable for toxicity, and 31 were evaluable for efficacy. Main results are presented here:

(1) Toxicity (grade 3-4) (NCI-CTC) (n = 38)
- Neurotoxicity*: 2 (5.2%)
- Neutropenia: 7 (18.4%)
- Febrile neutropenia: 0
- Diarrhea: 5 (13.1%)
- Alopecia 1 (2.6%)

(2) Efficacy (n = 33)
- OR/SD/PD (%) (WHO): 18 (54.5)/11 (33.3)/4 (12.1)
- Median TTP (months)**: 7.1
- Median survival (months)**: 14.4

*Specific scale, Levi et al. ** Current values, final results will be available at the meeting.

The evaluated alternated combination is well tolerated, specially with unfrequent neurotoxicity. Furthermore, the results suggest a potentiation between LOHP and CPT11, with interesting OR rate, TTP duration and survival.

1139 POSTER

Neo-adjuvant concomitant chemo-radiotherapy with dose intensification in UT3 rectal tumour

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The aim of the study is to evaluate the efficacy of an intensive neo-adjuvant chemo-radiotherapy schedule, in order to gain a better down-staging in staged uT3 rectal tumours.

From 4/99 to 3/01 65 patients (pts) entered the study. Median age was 61 yrs; the median distance from the anal verge was 4.6 cm; the gross tumours median extension was 5.1 cm. Pre-therapy clinical staging found out: 48% of cases uT3N-, 52% of cases uT3N+. All patients were staged also with endorectal ultrasonography The radiation therapy schedule delivered different doses at different volumes: 46-48 GY to posterior pelvis; 51 Gy to total mesorectal space, and 54 Gy to neoplastic volume. The concomitant chemotherapy was administrated with 5-Fluorouracil at dose of 300 mg/m2/day (7 days/week) by continuous infusion along 32 consecutively days. Surgery was performed 8 weeks after the end of chemo-radiation-therapy: 57 pts underwent surgical procedure, 8 pts are still waiting for intervention.

Pathological stage was: 40%, 18%, 12%, and 28% in stage 0, I, II and III, respectively; the global down-staging rate was 67.%. Pathologic complete remission (pCR) was obtained in 26% of cases; the rate of only microscopic disease (pTmic) was 16%. Gross tumour extension was correlated with pathological response: downstaging, pCR, and pTmic were, for tumours < 5 cm vs tumours = 5 cm, equal to 76% vs 62%; 40% vs 19%; 24% vs 13%, respectively. All pts were resecated, conservative surgery was possible in 78% of all cases; in 90% of pCR or pTmic pts. Gastro intestinal and haematological G3 (RTOG score) toxicity incidence was 4% and 7%, respectively. Peri-operative morbidity was joined in 16% of cases.

Neo-adjuvant concomitant chemo-radiotherapy with dose intensification (as proposed) may be efficacy in obtaining high rates (about 60%) of major pathologic responses (0-1 stages), with moderate toxicity.

The study is going on.

1140 POSTER

Topoisomerase-1 (topo-I) and thymidylate synthase (TS) primary tumor expression as prognostic and predictive factors for response to cpt-11 in advanced colorectal cancer (crc) patients

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CPT-11, a DNA topo-I inhibitor, has demonstrated antitumor activity in CRC patients in first-line therapy and after failure of 5-FU/LV- based chemotherapy. Previous reports suggest that TS expression could be considered a predictive factor for CPT-11 treatment (Saltz L. et al, ASCO 1998; 17:281a. In order to evaluate the clinical relevance of both Topo-I and TS, we analysed the primary tumor expression by IHC assay of Topo-I (NCL-Topo-I mAb) and TS (TS106 mAb) in a series of 50 patients with advanced CRC receiving CPT-11 based chemotherapy regimen. Thirty-two percent and 58% of cases were considered positive for Topo-I and TS expression, respectively. Patients with different Topo-I (32% vs 40%, respectively) and TS status (25% vs 42%, respectively; p: n.s.,) did not show a significant different probability of response to treatment. The best predictive pattern was demonstrated when TS and Topo-I tumor expression were considered together. In fact, while Topo-I -/TS - cases showed 28% of objective response rate (ORR), all the remaining subgroups showed an overall 41% of ORR. Moreover, while TTP resulted not related with the above bio-markers, OS resulted significantly associated with Topo-I tumor status ($p< 0.05$). The multivariate analysis confirmed for Topo-I tumor status a significant and indipendent role either on TTP or on OS ($p< 0.04$ and $p< 0.01$, respectively. In conclusion, our data suggest that Topo-I and TS primary tumor expressions could have clinical relevance prevalently on long term prognosis for CPT-11 treated patients with advanced CRC.

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1141 POSTER

Rectal cancer: quality of life during radiation therapy

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Purpose: The purpose of the study was to investigate whether health-related quality of life (QoL) was reduced during radiation therapy for rectal cancer.

Methods: This was a prospective study of 58 patients. Thirty-six patients received preoperative radiation therapy for locally advanced or recurrent rectal cancer. Twenty-two patients received postoperative adjuvant radiation therapy with concomitant chemotherapy (5-FU/leucovorin) for operable rectal cancer. All patients were treated with 2 or 3-field box technique, 50 Gy in 2 Gy fractions. QoL was assessed with the core questionnaire EORTC QLQ-C30 and the colorectal cancer module EORTC QLQ-CR38, scores were transformed to a scale from 0 to 100. A 5-day diary was also completed, including frequency of defecation and items from the common toxicity criteria (CTC). QoL and toxicity were assessed at start of treatment, end of treatment, and 4-6 weeks later.

Results: During radiation therapy, fatigue and diarrhoea were significantly increased, fatigue from 33 to 44 ($p<0,001$), and diarrhoea from 26 to 46 ($p=0,001$). Gastrointestinal problems increased from 18 to 26 ($p<0,001$). Overall QoL and several other scales showed significant, but small changes (less than 10 on a scale from 0 to 100). One month after completion of radiation therapy, QoL scores had returned to pre-treatment values. QoL scores during treatment will be related to CTC scores, and to the QoL of the general Norwegian population.

Conclusion: During radiation therapy, there is a transient reduction in QoL, most pronounced in the increase of fatigue and diarrhoea. One month after radiation therapy, QoL scores have returned to pre-treatment values.

1142 POSTER

A phase II study of leucovorin (LV)-modulated continuous infusion (CI) fluorouracil (DU) + CPT-11 alternating with LV-modulated CI FU + Oxaliplatin (L-OHP) in advanced colorectal cancer (CCR): high activity and low toxicity

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The addition of either CPT-11 or L-OHP to different FU regimens has resulted in higher activity/efficacy in multiple recent studies. Combining the three drugs is thus a logical step and alternating FU + CPT-11 to FU + L-OHP may result in less toxicity and delayed development of resistance compared to simultaneous administration of the three agents.

We have therefore developed a regimen consisting of CI FU (200 mg/m2/die, d 1-21) + CPT-11 (100 mg/m2 d 1, 8, 15) alternating with CI FU (same dose, d 28-49) + L-OHP (70 mg/m2 d 28, 35, 42). LV (20 mg/m2) was administered on the first day of each week of infusion. The cycles were repeated after a one-week rest (d 56).

Since April 2000, 35 patients with advanced CCR previously untreated for metastatic disease (males/females: 25/10, median age 60, range 46-78, years; median ECOG PS 0) were accrued in a phase II trial of this regimen at our Centre. The median number of the measured tumor lesions was 7. The median baseline tumor area and CEA level were 43.3 cm2 and 22 ng/ml, respectively. Twenty of 35 patients had multiple sites of disease.

Overall, 242 weeks of CI FU + CPT-11 and 219 weeks of CI FU + L-OHP were administered, corresponding to 74 full cycles of chemotherapy. 23/473 weekly courses were delayed (FU + CPT-11: 11; FU + L-OHP: 12) and 13 were administered at a reduced dose (FU + CPT-11: 9; FU + L-OHP: 4). Toxicity was mild with a prevalence of gastrointestinal and haematological toxicity in the CPT-11 part and neurotoxicity in the L-OHP part. No grade IV toxicity was reported. Grade III side-effects occurred in 8/242 courses of FU +CPT-11 (diarrhoea, n=3; neutropenia, n=4; stomatitis, n=1) and 2 of 219 courses of FU + L-OHP (neurotoxicity in all instances). Grade I and II neurotoxicity was observed in 72 and 4 of 219 courses of FU + OXA.

Two patients had the treatment discontinued before completing the first three weeks of chemotherapy due to cancer-related bowel obstruction. Eight patients are still receiving the first cycle. Among the 25 patients that have completed at least one cycle and are thus evaluable for response 1 CR, 14 PR, 3 MR and 5 SD were reported. Two patients progressed after the first cycle (RR: 60%, 95% CI: 79-41%). The response rate is likely to improve further as 3/3 patients with a MR and 4/5 with SD are still receiving chemotherapy.

These preliminary results suggest that alternating FU/CPT-11 and FU/L-OHP may enhance antitumor activity without increasing toxicity.

1143 POSTER

Pre-operative concomitant hyperfractionated radiotherapy and gemcitabine (gemzar®)(gem) for locally advanced rectal cancers: a phase I-II trial

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Purpose: Neoadjuvant radiation therapy (RT) is well recognized for diminishing the risk of loco-regional relapse in curatively resected locally advanced rectal adenocarcinoma (ARA). GEM has been shown to be a powerful radiosensitizer when administred concomitantly with RT. We launched a phase I-II trial to find primarely the optimal dose of GEM to be administrated concomitantly with preoperative RT for ARA, and to evaluate secondarely its efficacy.

Patients and methods: Patients (Pts) with stages II and III tumors assessed by echoendoscopy were enrolled and written consent was obtained. RT consisted in 50 Gy given in two daily fractions of 1.25 Gy in 4 weeks. GEM was given biweekly in a 30' IV perfusion at 10, 15, 20, 25, 30, 35, 40 and 45mg/m2. The tumor was resected 6 weeks after the end of RT. Response was assessed by extensive examination of the resected specimen. The absence of viable tumor was considered as pCR and the persistance microscopic tumoral remnants of <10mm as pPR.

Results: 23 Pts were enrolled so far into the study with 22 who have completed their treatment and are evaluable. Because no significant toxicity was observed with GEM from 10 to 30mg/m2, GEM was then increased directly to 45mg/m2 and 2 events of grade 3-4 rectitis were recorded among the 3 Pts treated. This was considered as dose limiting toxicity. GEM at 35 and 40mg/m2 is currently evaluated. Among 20 Pts already evaluated pathologically for response, 4 had a pCR and 9 a pPR.

Conclusion: GEM can be safely administred twice weekly concomitantly to preoperative RT for ARA with an encouraging pathological response rate. The recommended dose of GEM and the MTD should be available for the conference.

1144 POSTER

Chronomodulated (Chrono) irinotecan (CPT) versus standard (STD) infusion in patients (pts) with metastatic colorectal cancer (MCC), a randomized multicenter trial

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Background: CPT toxicity displayed a circadian rhythm in mice (Filipski, AACR 1997). A pilot study of chrono CPT suggested improved tolerability in 27 MCC patients (Giacchetti., ASCO 1999). The aim of the study was to evaluate graded toxicity over the 3 initial courses (c). Patients were randomised to receive 350 mg/m2 of CPT chrono (infusion from 02:00 to 08:00, peak at 05:00) or a 30 minute infusion (std) as 2nd to 4th line treatment. Secondary endpoints were CPT and metabolite SN-38 pharmacokinetics (PK) at 1st c, rest-activity cycle and quality of life (QoL) assessed by EORTC-QLQ-C30. Main pts characteristics (chrono vs std): 36 MCC patients were randomized (4 centers); colon/rectum: 16/1 vs 14/5; PS 0/1: 10/7 vs 10/9; 1/*2 M sites: 9/8 vs 13/6; 1/*2 prior chemotherapy: 8/9 vs 11/8. Preliminary results: Chrono 13 patients-34 c; std 14 patients-40 c. No toxic death and no grade 4 toxicity except grade 4 neutropenia are observed. Main toxicities: grade 3-4 neutropenia occurs in 54% chrono patients including 4 febrile for 1-3 days and in 43% std patients-no febrile-; 92% chrono patients and 57% std patients experience grade 2 diarrhea; no grade 3 diarrhea in chrono patients and 21% in std patients. Chrono decreases incidence of grade 2-3 asthenia (31% vs 64% patients) and grade 2-3 anorexia (8% vs 36% patients). PK results (15 chrono and 16 std patients): No schedule related differences observed for CPT exposure (AUC). Mean value and variability (sd) of CPT Cmax were reduced in chrono as compared to std (2.9 ± 0.5 vs 5.5 ± 2.0 μg/mL). Chrono slightly increased SN38 Cmax (0.054 ± 0.024 vs 0.044 ± 0.016 μg/mL) and AUC (0.65 ± 0.18 vs 0.53 ± 0.19 μg.h/mL). Metabolic ratio (SN38/CPT-11 AUC), was significantly increased after chrono administration ($p<0.01$) (2.5 ± 0.8 vs 1.9 ± 0.6%).

Conclusions: In this limited size population, chronomodulated CPT delivery decreases asthenia and anorexia and possibly downstages diarrhea. In addition, chrono increases the relative exposure to the active metabolite SN38 which might contribute to differences in clinical toxicity and/or efficacy.

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1145 POSTER

Oxaliplatin and capecitabine in advanced colorectal cancer: a pilot study

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Purpose: To determine the maximum-tolerated dose (MTD) and the dose-limiting toxicities (DLTs) of the Capecitabine plus Oxaliplatin combination regimen and to explore its safety and its activity in patients (pts) with advanced colo-rectal cancer (ACRC).

Patients and Methods: Thirty-seven pts with ACRC received the combination of Capecitabine and Oxaliplatin from November 1999 to April 2001. Twenty-five chemotherapy-pretreated patients were enrolled in a dose-finding study: Capecitabine was administered orally twice a day continously