11(13%) patients and more than 90% necrosis was observed in additional 14 patients(18%). After a median follow-up of 36 months, survival and overall survival rates of the resected patients were 95%, 69% and 86% respectively.

Conclusion: The pre-operative chemo radiation regimen employed had a tolerable acute toxicity profile. It is a reasonable option in patients who have locally advanced or lower 1/3 rectal cancer and with low locoregional recurrence.

1134 POSTER

COX-2 expression in rectal cancer: immunohistochemical pattern and prognostic value

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Purpose: It is controversial whether COX-2 expression is a prognostic factor for rectal cancer with respect to other established prognostic parameters for local recurrence and/or survival in this disease.

Methods: To evaluate the impact of COX-2 on outcome of rectal cancer we reviewed data of 62 patients with adenocarcinoma of the rectum treated between 1995 and 1996, all patients in stage I-III were resected curatively. The samples were stained for COX-2 expression using a polyclonal antibody for human COX-2. According to the intensity and extend of positive reaction of tumor cells the labeling index of stained cells was calculated.

Results: The median labeling index was 0.58. The chi-square-test revealed no correlation between COX-2 and the established prognostic factors. In the univariate analysis COX-2 overexpression did not show a significancy according to the endpoints local recurrence ($p=0.41$) or disease specific survival ($p=0.28$). In contrast COX-2 was a significant prognostic factor for pulmonary metastasis ($p=0.04$).

Conclusion: The majority of specimens showed a mild or moderate immunoreactivity for COX-2 but there is a lack of significancy for COX-2 expression as a prognostic factor for local control and survival. However, there is evidence that COX-2 overexpression might be linked to an increased risk for hematogenous metastatic spread.

1135 POSTER

Irinotecan (CPT-11) plus oxaliplatin (LOHP) plus infusional 5-fluorouracil (5-FU) and leukovorin (LV) as first line treatment for metastatic colorectal cancer (MCC): A phase II trial

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Background: A phase II study was conducted in order to evaluate the toxicity and efficacy of the combination of CPT-11 plus LOHP plus infusional 5-FU/LV in MCC.

Patients and Methods: Thirty-five chemotherapy-naïve patients were enrolled. The median age was 60 y; male/female: 21/14; PS (WHO) 0/1/2: 16/14/5; prior surgery 24 pts; adjuvant chemotherapy: 18 pts; adjuvant RT: 3 pts; Number of metastatic sites 1/2/≥3: 13/12/10. CPT-11 was administered on d_1 at the dose of 150 mg/m^2 over a 90 min infusion, LOHP on d_2 at the dose of 65 mg/m^2 over a 2 h infusion, simultaneously but in different lines with LV (200 mg/m^2 on days 2 and 3) followed by 5-FU administration as bolus iv infusion at dose of 400 mg/m^2/d and as 22 h continuous infusion at the dose of 600 mg/m^2/d on days 2 and 3. The regiment was repeated every 2 weeks.

Results: All patients were evaluable for toxicity and 28 (5 too early, 2 not evaluable) for response. CR was achieved in 2 pts (7.1%) and PR in 14 pts (50%) (ORR: 57.10%; 95 ci: 39,12%–82.64%); 9 pts (32.1%) had SD and 3 (10.7%) PD. The median duration of response was 4.5 m; the median TTP and OS have not yet been reached, after a median follow up period of 11 months. Grade 3 and 4 neutropenia occurred in 12 pts (34.29%), febrile neutropenia in 2 pts (5.7%), anemia grade 2 in 5 pts (19%), while thrombocytopenia didn't exceed grade 1. Diarrhea grade 3/4 was observed in 10 pts (28.5%), neurotoxicity grade 3/4 in 3 pts (8.5%), asthenia grade 3 in 2 pts (8.5%). No treatment related death occurred.

Conclusions: The combination of 5-FU/LV + CPT-11 + LOHP is an active and well-tolerated regiment as front-line treatment in MCC and merits further evaluation in prospective randomized trials.

1136 POSTER

Joint United States of America (USA)/Japan study of UFT (uracil and tegafur) plus leucovorin (LV) in patients (pts) with metastatic colorectal cancer (CRC)

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Introduction: UFT is a 5-FU prodrug developed as a single agent against various solid tumors in Japan. Based on the extensive use of LV with 5-FU in the West, UFT was combined with LV for the treatment of CRC in the USA and European countries. Two large phase III study demonstrated equivalency between intravenous 5-FU/LV and UFT/LV among Western patients with CRC (Pazdur R., and Carmichael J., ASCO 1999). Although different doses and schedules of UFT in CRC have been tried in Japan, there is no study with the combination of UFT plus leucovorin in that Country.

Methods: To evaluate the applicability of the results of the large Western trials to the Japanese population we decided to compare the response rates, the PK, and the type, frequency, and severity of side effects in American and Japanese pts with metastatic CRC.

Results: A total of 99 pts (45 in USA; 44 in Japan) has been enrolled; all are evaluable for toxicity and 98 pts are evaluable for response. Both groups were well matched for gender, age, performance, and prior adjuvant treatment. As of now, results show a comparable response rate of 36% and 34% in Japan and the USA, respectively. Diarrhea was the main toxicity in both groups and severe diarrhea was seen significantly less often among Japanese pts (9% versus 22% in the USA). Hematological toxicity was very mild and not significantly different in both groups. There were no other significant differences in toxicity. This indicates that UFT/LV is equally active in both ethnic groups but potentially more toxic among Western pts. Although AUC and Cmax of FT, 5-FU and Uracil were slight higher in Japanese pts than in the USA, when the results are adjusted for BSA, the parameters are similar.

Conclusion: The present study indicated that UFT/LV therapy is an equally efficient and reasonably well-tolerated treatment for American and Japanese pts with metastatic CRC. This data indicates that an extrapolation of clinical data from the West to the East is reasonable.

1137 POSTER

Serum concentration of soluble adhesion molecules and cytokines in patients with colorectal cancer

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Purpose: Human colorectal cancer cells express sialyl Lewis (a)(CA 19-9), which acts as a ligand for E-selectin, an adhesion molecule involved in the binding of colorectal cancer cells to endothelial cells. Circulating levels of inflammatory cytokines have been associated with the disease status of cancer patients. Moreover, IL-6 has been associated with CA 19-9 levels in patients with colorectal cancer. Therefore, this study was aimed to verify whether tumor marker levels correlate with blood concentrations of cytokines and adhesion molecules involved in the haematogenous spread of colorectal cancer cells.

Methods: Serum tumor markers (CEA, CA 19-9, CA 72-4), cytokines (TNF-alpha, IL-6, IL-1beta) and soluble adhesion molecules (sP- and sE-selectins, sVCAM) levels were measured in serum samples from 76 patients with primary (Stages: A=6, B=34, C=19, D=2) or recurrent (local=3, distant=12) colorectal cancer.

Results: Median cytokine levels were higher in cancer patients (TNF: 13.8 pg/ml; IL-1: 0.5 pg/ml; IL-6: 2.4 pg/ml) compared to controls (TNF: 0.3 pg/ml; IL-1: 0.1 pg/ml; IL-6: 0.2 pg/ml) (all $p<0.001$). Moreover, mean (SD) sE-selectin and sVCAM levels were higher in cancer patients [sE-selectin: 56.2 (32.5) ng/ml; sVCAM: 985 (509) ng/ml] compared to controls [sE-selectin: 39.3 (14.8) ng/ml, $p<0.01$; sVCAM: 478 (239) ng/ml, $p<0.001$]. Plasma sP-selectin levels did not show any significant difference. IL-6 levels directly correlated with sE-selectin ($r=0.40$, $p<0.01$) and sVCAM ($r=0.48$, $p<0.002$), and sE-selectin directly correlated with sVCAM ($r=0.43$, $p<0.006$). Patients with sE-selectin >70 ng/ml [mean (2SD) of controls] also had higher levels of CA 19-9 ($p<0.0005$), CEA ($p<0.002$) or CA 72-4 ($p<0.02$). IL-6 and sE-selectin levels were higher in patients with metastasis (median IL-6=5.5 pg/ml; median sE-selectin=71.5 ng/ml) than

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.