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.

Supported by ARTBC Int., Hôp.P. Brousse, Villejuif.

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