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

for 14 days and Oxaliplatin was administered as a 2-hours infusion on day 1, every 3 weeks. Six dose levels were explored, ranging from 1650 to 2500 mg/m*/d and from 100 to 130 mg/m* and MTD was reached at 2500 mg/m*/d and 120 mg/m* for Capecitabine and Oxaliplatin, respectively. Eleven further chemotherapy-naive pts were enrolled in a Phase II trial which is ongoing.

Results: Twenty-five pts were assessable for toxicity in the dose-finding trial and DLTs were diarrhoea (Gr 3/4: 27%) and stomatitis (Gr 3/4: 9%) at dose level VI. Dose level V (Capecitabine 2500 mg/m* and Oxaliplatin 120 mg/m*) was found to be the MTD. Hematological toxicity was minimal, overall neurotoxicity (Gr.1-4) was 27% with 1% Gr3-4. A global response rate was 17% (95% CI 2-32%) and the median overall survival was 12 months. Based on these results 11 additional pts not chemotherapy pretreated received the combination at MTD: to date, 36 cycles were administered with a median of 3 cycles per patient (range 1-7); major toxicity was diarrhoea (Gr. 3/4: 27%). Six pts are evaluable for response: 1 pt with multiple liver metastasis achieved a CR and 2 a PR for a global response rate in untreated ACRC pts of 50%.

Conclusion: Capecitabine/Oxaliplatin combination seems to be an active and safe regimen; the ease of administration of this schedule makes it acceptable in the treatment of pts with ACRC although the high proportion of gastrointestinal toxicity. Further data on toxicity and response to treatment will be presented.

1146 POSTER

Raltitrexed combined with 5-Fluorouracil continuous infusion: a Phase I/II dose-escalation trial in advanced solid tumors

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Background: Increasing use of combination chemotherapy for Advanced Colorectal Cancer (ACRC). Raltitrexed (R) and 5-FU are each active as single agents in the treatment of ACRC. They are Thimydilate Synthetase inhibitors but via different mechanisms. They have non-overlapping toxicities profiles. Preclinical studies have shown synergism when R given prior to 5-FU and preclinical data indicate promising activity as higher response rates than each drug in monotherapy.

Purpose: To determine the maximum tolerated dose (MTD), recomended dose and safety using 5-FU as continuous infusion (c.i.)over 48 hours in a weekly basis (TTD group schedule) combined with R every three weeks. To test activity of this combination in ACRC.

Study design: Treatment schedule consists of 5-FU (48 hours iv c.i.)at the 1st week; R(15 min i.v. infusion) followed 15 minutes later by 5-FU c.i. at the 2nd week; 5-FU c.i. at the 3rd and 4th weeks and both drugs at the 5th week; treatment was repeated every 6 weeks. The study was planned for R to be escalated from 2 mg/m2 to 3.5 mg/m2 and for a 5-FU fixed dose of 3000 mg/m2.Dose-limiting toxicity (DLT) was defined as (CTC criteria): any grade 4 hematologic toxicity and/or non-hematologic toxicity >/= grade 3 except alopecia and increase in transaminases.16 patients (p) were initially enrolled. M/F: 14/2. Median age 61 (range 41-78); ECOG PS 0/1/2: 4/9/1. P with advanced solid tumors were included in Phase I part of the study (1 gastric, 1 non-small-cell-lung, 1 renal, 1 head-neck, 1 gallbladder and 11 ACR). The prevalent metastatic sites were: liver (10 p), lung (5 p), peritoneal nodes (5 p). 7 p had one single metastatic site and 9 p had more than one metastatic sites.

Results: 15 p had received at least 1 cycle and are evaluable for toxicity.

Level	N° P	Raltitrexed Dose	5-FU Dose	Grade 3-4 Toxicity
1	6	2	3000	2 x Neutropenia G3 Diarrhoea G3
2	4	2.5	3000	None
3	6	3	3000	Diarrhoea G3
4		3.5	3000	

Conclusions: Diarrhoea G3 and Neutropenia G4 were DLT. The MTD is not yet achieved. 4 p are now receiving the 3rd level of treatment. Three confirmed partial responses (2 colon and 1 gastric carcinoma) and two stable diseases were observed. Phase II study will be further initiated for ACRC.

Other gastro-instestinal tumours

1147 POSTER

Radiotherapy (± chemotherapy) in the curative treatment of anal canal carcinoma (ACC). Lyon experience in 252 patients (pts)

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Purpose: Retrospective analysis of a consecutive series of patients treated with curative intent by radiotherapy (RXT) in a single department. Study of prognostic factors.

Methods: Between 1980–1998, 252 patients were treated for A.C.C (in LYON SUD hospital). Median age: 65 years, female/male ratio: 8/1, histology: squamous cell carcinoma: 226, basaloid: 20, adenocarcinoma: 6. Tumor stage: T1: 37, T2: 132, T3: 52, T4: 31, N0: 157, N1: 69, N2: 21, N3: 5. Treatment: radiotherapy was given with external beam radiotherapy (EBRT) with Cobalt direct perineal field (181 pts) a more recently with 3 fixed field (63 pts). Concurrent chemotherapy was given to 161 pts usually with 5 FU-CDDP (122 pts). A boost was delivered with Iridium brachytherapy (IB) in 218 pts.

Results: Median follow up time was 6 years. Local pelvic failure was seen in 51 pts (20%). After salvage surgery ultimate control rate was 86%. Inguinal failure was seen in 8.3% of cases and distantmetastases in 6%. Overall 5 and 10 year survival rate were 73% and 57%. Grade 3 anal necroses occurred in 5% of pts. Sphincter preservation was possible in 205 pts and anal sphincter function was scored as good of excellent in 79% of these pts. Factors having positive influence an overall 5 year survival were, early stage, no involvement of anal margin, use of chemotherapy and Iridium brachytherapy.

Conclusion: These results confirm that radiotherapy can provide high rate of local control, survival and sphincter preservation in A.C.C. Use of concurrent chemotherapy with FU-CDDP and Iridium Brachytherapy seems to improve the results.

1148 POSTER

Herceptin and gemcitabine for metastatic pancreatic cancers that overexpress HER-2/neu

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HER-2/neu expression was evaluated by immunohistochemistry (IHC) in 154 patients with pancreatic adenocarcinoma at four Brown University teaching hospitals: 32 (21%) had HER-2/neu overexpression. At initial diagnosis, 16% of resectable cancers, 17% of locally advanced cancers and 26% of metastatic cancers had HER-2/neu overexpression. Therefore, we initiated a multi-institutional phase II study of Herceptin and gemcitabine for patients with metastatic pancreatic adenocarcinomas with 2-3+ HER-2/neu overexpression by the DAKO IHC assay. Patients received gemcitabine 1gm/m2/week for 7 of 8 weeks followed by 3 of every 4 weeks and Herceptin 2mg/kg/week following an initial Herceptin loading dose of 4mg/kg. Twenty-three patients have been entered. The median age was 67 years (range 46-80 years). The ECOG performance status was 0 in six patients (26%), 1 in 14 patients (61%), and 2 in three patients (13%). Fifteen (65%) had 2+ overexpression, four (17%) had 2-3+ overexpression, and four (17%) had 3+ overexpression. Two patients were unevaluable for response or toxicity after study removal following one week of treatment due to a surgical complication (1) and a rapid decline in performance status (1). Of 21 patients, grade 3/4 toxicities include neutropenia (n=3), thrombocytopenia (n=1), and decline in LVEF (n=1). Five patients (24%) had partial radiographic responses and 10 of 21 (47%) have had either partial radiographic responses or greater than 50% reduction in CA19-9. The median survival of all 23 patients is 7.5 months. The 1 year survival is 24%.

Conclusions: The combination of Herceptin and gemcitabine is well tolerated and has promising activity in an important subset of patients with metastatic pancreatic adenocarcinomas that overexpress HER-2/neu.