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.