events included: diarrhea, 20%; neutropenia, 11%; acne-like rash (grade 3 only), 9%. No grade 3/4 infusion-related reactions (IRRs) were reported.
Conclusions: The overall confirmed RR of 27% observed in this heavily pretreated population fully met the expectations for the primary endpoint of this study. LABEL confirmed the activity and safety of cetuximab plus irinotecan seen in previous studies.

3056 POSTER

XPA, XPD, ERCC1 and XPG/ERCC5 single nucleotide polymorphisme (SNPs) in oxaliplatin-treated colorectal cancer (CRC)

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Background: Oxaliplatin damages DNA, leading to apoptosis. XPA, XPD, ERCC1 and XPG/ERCC5 are involved in DNA repair, and polymorphic variant in these genes can influence the efficacy of oxaliplatin. We analysed SNPs in these genes and correlated the results with toxicity, time to progression and overall survival and response to oxaliplatin in advanced CRC.
Methods: 42 CRC patients (pts) recruited between April 2002 and May 2005 were treated with oxaliplatin as first line chemotherapy combined with fluoropyrimidine [Moreno I et al. Ann Oncol 2006; 17(Suppl 6): 75 (P-178)]. Update march 2007. DNA was obtained from peripheral blood cells at baseline, and allelic discrimination assay with ABI Prism 7700 was used to analyze SNPs at XPA 5′utr A/G, XPD Lys751 Gln, ERCC1 Thr/Lys and XPG/ERCC5 C/T
Results: Patients characteristics: 21 males/21 females, median age 66 yr (range, 44−79), PS 0−2. Pts with XPA genotype A/A showed lower emesis toxicity (12%) than those with A/G and G/G (20%) ($p = 0.010$). Pts with XPG C/C shower better objective response (74%), than those with C/T and T/T (35%) ($p = 0.03$). Pts with XPG C/C achieved longer time to progression (15.8 months) than those with C/T and T/T (7.5 moths) ($p = 0.009$). Pts with XPG C/C achieved better median survival (33 moths) than those with C/T and T/T (13.9 months) ($p = 0.000$). Pts with XPG C/C and XPA A/G or G/G achieved better time to progression and median survival (21.8 moths and 43.3 moths, respectively) than those others patients (7.5 months and 15.5 months, respectively) ($p = 0.000$). Cox multivariate analysis showed that gender (male), PS (<2), and genotypes XPG C/C and XPA A/G or G/G, were favourable predictive factors.
Conclusion: XPG C/C may be a predictive marker of response and genetic profile XPG C/C and XPA A/G or G/G may be a predictive marker of time to progression and overall survival in oxaliplatin CRC pts. Studies with a larger number of patients should be carried out to confirm these results.

3057 POSTER

Neoadjuvant chemoradiation for locally advanced rectal cancer. Analysis of clinical outcomes

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Background: During the past few decades, significant progress has been achieved in the management of rectal cancer with the introduction of total mesorectal excision.Preoperative radiotherapy appears more effective in terms of local control and toxicity compared to postoperative therapy. Several recent studies show that 5-FU-based chemotherapy enhances tumour response to radiotherapy and preoperative chemoradiotherapy is being increasingly used for stage II and III disease.
Our prospective cohort study will evaluate the impact of neoadjuvant radiochemotherapy at first on toxicity, surgical morbidity and pCR rate and then the local and distant recurrence rates.
Patients and Methods: From 1998 to 2006, 188 consecutive patients, with a tumour with an average distance from the anal verge of 6.5 cm, were treated with neoadjuvant radiochemotherapy. 89 of them (47.4%) had the tumour localized in lower rectum, 82 (43.6%) in the middle one and 17 (9%) to the upper rectum. All the patients were studied by EUS, MR and CT to establish the clinical stage and so decide the therapeutical strategy. These patients, staged as II and III, were submitted to a “long-course” radiochemotherapy. After 4−6 weeks from the end of the neoadjuvant therapy, all the patients were submitted once again to EUS and MR and then operated on.
Results: 164 patients showed a clinical stage III and 24 a clinical stage II. No major complications related to therapy were observed and all the patients have completed the course of therapy. A complete or partial response was observed in 70.7% of the patients and pCR was found in 13.8%. We observed a significant clinical down-staging ($p < .004$). Surgical procedures (112/188 [60%] laparoscopic) carried out were: 156 AR (83.9%), 24 APR (12.9%) and 4 TEM (2.2%). We observer clinical anastomotic leak in 6.3%. Mean nodal-sampling was 14.9. Concerning yTNM, 26/188 patients (13.8%) were in stage 0, 42/188 (22.3%) in stage I, 66/188 (35.2%) in stage II and 54/188 (28.7%) in stage III. Five-years overall-survival and disease-free-survival were respectively 73% and 60%. Pre-treatment clinical stage had no prognostic significance ($p = 0.9321$). On the contrary, postoperative yTNM was significant ($p = 0.0090$) for yT ($p < 0.001$) and yN ($p < .00024$). Non-responder patients had the worse prognosis (5-years survival 30%). The variable with higher prognostic significance was yN ($p < .0003$), especially if we distinguish N1 by N2 ($p < .00022$). With a mean follow-up of 36 months, local recurrence rate was 5.7%.
Conclusions: Our data showed that neoadjuvant chemotherapy in well tolerated and don’t improve the postoperative complication. The post operative stage play an important independent prognostic role in disease free and overall survival. Future neoadjuvat trials should evaluate, with modern molecular biology techniques, correlation between reresistence markers or other molecular markers to stratify patients besed on molecular markers instead of on biologic tumours response.

3058 POSTER

Administration of reduced glutathione in FOLFOX4 regimen in advanced colorectal cancer: effect on oxaliplatin pharmacokinetics and on Pt-DNA adducts formation

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Background: Neurotoxicity is the most common oxaliplatin (OXA) toxicity in FOLFOX4 regimen for patients with advanced colorectal cancer. Recently, Cascinu et al. (JCO 2002; 20: 3478–3483) provided evidence that reduced glutathione (GSH) reduces the OXA-induced neurotoxicity, but GSH influence on the formation of Pt-DNA adducts still remains unknown. This study evaluated the effect of GSH addition on OXA pharmacokinetics(pk) and on Pt-DNA adducts formation
Materials and Methods: 28 patients were given twelve FOLFOX4 courses and randomized to receive either GSH 1,500 mg/m^2 ornormal saline solution (placebo) before OXA. OXA pk and Pt-DNA adducts formation were evaluated at cycles 5, 9 and 12. Total and ultrafiltered platinum were analyzed by atomic adsorption, Pt-DNA adducts in leukocytes (as model for tumour tissue) by adsorptive stripping voltammetry. Pk analysis were done by non-compartmental analysis, statistical analysis by non-parametric Mann-Whitney test
Results: Median total and ultrafiltered platinum pk parameters were comparable to previously reported ones, only median total AUC_{tot} show statistically significant difference being higher in the placebo arm. On the other side, ultrafiltered platinum pk parameters show no statistically significant differences The formation of Pt-DNA adducts was more pronounced in GSH arm (median value at the end of infusion 4.52 Pt atoms/10^6 nucleotides vs. 4.25 Pt atoms/10^6 nucleotides), though not statistically significant.

	Total Pt			Ultrafiltered Pt		
	GSH-OXA	Placebo-OXA	p	GSH-OXA	Placebo-OXA	p
C_{max} (mg/l)	2.47	2.66	0.855	0.196	0.197	0.882
AUC_{tot} (mg*h/l)	127.5	166.9	0.036	4.49	4.43	0.982
Cl_{tot} (l/h)	1.08	0.97	0.385	31.1	33.2	0.235

Conclusions: The addition of GSH to FOLFOX4 regimen is able to reduce the OXA-induced neurotoxicity, without affecting either the OXA pk behaviour or the formation of Pt-DNA adducts, thus assuring that the well-known clinical efficacy is unmodified.

3059 POSTER

Prospective comparison of laparoscopic vs. open total mesorectal excision (TME) for rectal adenocarcinoma

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Background: The continue advancing of laparoscopic surgery has become possible to extend the mini invasive technique to Total Mesorectal Excision

(TME) for rectal cancer. The feasibility and efficacy of laparoscopic TME has been proved by several reports but oncologic outcomes remains unclear. The aim of this study was to define the oncologic outcomes of laparoscopic TME.

Patients and Methods: This prospective nonrandomized longitudinal cohort study conducted from January 1998 to August 2006 regards patients with histologically proven adenocarcinoma of the middle and low rectum. Those staged as II and III underwent a long course preoperative radio chemotherapy. Oncologic outcomes measures of the laparoscopic group (LTME) were compared with a computerized, case-matched open resection group (OTME), the matching variables being age, gender and TNM stage. The follow up was conducted prospectively.

We analysed in both groups the radicality of resection (quality of mesorectum, Circumferential Resection Margin [CRM], length of resection margins and lymph node's sampling) the local recurrence rate and overall survival.

Results: The LTME group consisted in 188 patients (mean age 63.9 years) The OTME group 188 (mean age 64.48 years). Mean follow up was 39.4 months (range 3−93). The TNM stage distribution was Stage 0 (7.1%), Stage I (22.1%), Stage II (35.0%), Stage III (27.0%) Stage IV (8.2%) tumours for LTME and 5 Stage 0 (2.3%), 38 Stage I (20.1%), 50 Stage II (26.6%), 71 Stage III (38.1%) 24 Stage IV (12.9%) tumours for OTME. Thirty-day mortality was 0.6% for LTME and 0.9% for OTME ($p = 0.433$). Early and late complication incidences were comparable ($p = 0.952$). Quality of mesorectum ($p = 0.534$), negative CRM ($p = 0.732$) and R1-rate ($p = 0.36$) were the same in both groups. The mean lymph node's sampling was 14.35 ± 5.7 for LTME and 13.33 ± 7.3 for OTME ($p = 0.822$). Local recurrence were observed in 12 patients (6.3%) in LTME and in 14 patients (7.4%) in OTME ($p = 0.31$). The Kaplan-Meier statistical analysis performed confirmed that TNM stage for stage overall survival was similar in the LTME and OTME group (log rank $p = 0.956$).

Conclusion: Notwithstanding the drawbacks of a non randomised study our results are consistent in showing that laparoscopic TME could potentially offer all benefits of a minimally approach and achieve short and long term results that compare favourably with conventional rectal surgery.

3060 POSTER

Final data from a large phase II trial of first-line bevacizumab plus classic or modified FOLFIRI in metastatic colorectal cancer (CRC)

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Background: Bevacizumab (Avastin®) significantly improves overall (OS) and progression-free (PFS) survival when combined with first-line irinotecan plus bolus 5-fluorouracil (5 FU) and leucovorin in patients with metastatic CRC. An ongoing, multicentre open-label trial is evaluating the efficacy and safety of first-line bevacizumab in combination with irinotecan and infusional 5-FU (FOLFIRI).

Methods: Eligibility criteria: metastatic CRC; no surgery within 28 days; ECOG PS 0/1, adequate organ function; no CNS metastases. Chemotherapy: a minimum of 6 two-weekly cycles of FOLFIRI; variations (modified FOLFIRI [mFOLFIRI], weekly regimen) were allowed. Bevacizumab 5 mg/kg was given on day 1 with chemotherapy, and then every 2 weeks until disease progression. The primary objective was PFS; secondary objectives included safety, overall response rate (ORR), duration of response (DOR) and OS.

Results: A total of 209 patients were enrolled at 31 centres between April 2005 and November 2005. Median patient age was 61.9 years (range 31–82) and 60% were male. Median followup was 13.3 (0.8−20.1) months. Median duration of treatment with bevacizumab was 9.2 months and approximately 6.5 months with FOLFIRI. 22% of patients discontinued study treatment for toxicity; 18% from chemotherapy discontinuation alone. The most common bevacizumab-associated adverse events were epistaxis (38%; grade $\geqslant$3, <1%), hypertension (26%; grade $\geqslant$3, 3.8%) and venous thromboembolic events (26%; grade $\geqslant$3, 19.6%). 78% of all patients had a dose modification; 63% interruption of bevacizumab (major reasons: neutropenia [30%], diarrhoea [5%], hypertension [5%]), 76% had modification of FOLFIRI (major reasons: neutropenia [41%], diarrhoea [13%], mucositis [7%], febrile neutropenia [5%]). Sixty (29%) deaths have been reported, the majority associated with progressive disease. Efficacy data are comparable with previous first-line bevacizumab studies (Table).

Conclusions: The safety profile of bevacizumab plus FOLFIRI is similar to that of bevacizumab and other chemotherapy combinations. Efficacy data indicate a promising benefit with regard to response rate and PFS. Bevacizumab plus FOLFIRI represents a safe and effective first-line therapy option for patients with metastatic CRC.

	Overall (n = 209)	Bevacizumab + FOLFIRI (n = 156)	Bevacizumab + mFOLFIRI (n = 53)
Median PFS, months	11.07	11.30	9.99
DOR, months	8.54	9.00	8.34
ORR, %			
CR	3.3	3.2	3.8
PR	49.8	50.0	49.1
SD	32.5	31.4	35.8
PD	7.2	7.1	7.5
Missing	7.2	8.3	3.8

3061 POSTER

Phase I/II study of novel oral fluoropyrimidine S-1 in combination with oxaliplatin (SOX) as first-line chemotherapy for metastatic colorectal cancer (mCRC)

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Background: An oral fluoropyrimidine, S-1 showed high activity for untreated mCRC with a response rate of 35%. It has shown good tolerability with the convenience of an oral administration schedule, which warranted further investigations particularly in combination with oxaliplatin (L-OHP) as an alternative to 5-FU and L-OHP (FOLFOX). The objectives of this study were to determine the maximum tolerated dose (MTD) and the recommended dose (RD) of SOX, and evaluate the efficacy and safety of SOX as first-line chemotherapy for mCRC.

Material and Methods: The inclusion criteria included histologically proven colorectal cancer with unresectable lesions, ECOG Performance Status (PS) of 0 or 1, patients (pts) aged 20 to 74 years with measurable lesions, adequate organ functions, and no prior history of chemotherapy. The chemotherapy consisted of a 2-hour infusion of L-OHP at escalating doses of 100 mg/m^2 (level 1) and 130 mg/m^2 (level 2) on day 1, and S-1 twice daily on days 1−14 at a dose of 80 mg/m^2/day, repeated every three weeks.

Results: A total of 32 pts were enrolled in the study between March 2005 and June 2006. Twenty three pts were male (72%) and the median age was 57 (range, 34−71) years. Twenty nine pts had an ECOG PS of 0. Median of 6 courses was administered (range, 2−11). Although a total of 9 pts were enrolled in phase I, no dose-limiting toxicities were observed and level 2 was determined as RD. A total of 29 pts received RD of L-OHP. Therefore, the median treatment courses actually administered were 6 (range, 2−11). Grade 3 and 4 major adverse reactions at RD were neutropenia (14%), thrombocytopenia (28%), and diarrhea (3%). Peripheral neuropathy was observed in all of 29 pts treated with RD, but none developed grade 3 peripheral neuropathy. Hand–foot syndrome was not observed. Pharmacokinetic profiles of L-OHP and S-1 were consistent with the data of both monotherapy studies reported previously. Two pts had complete responses and 13 had partial responses, hence the overall response rate was 54% (95% CI, 33.9−72.5) according to the RECIST. Two pts have continued to receive treatment with SOX for more than 11 courses. After a median follow-up time of 213 days, the median progression free survival was 189 days and median survival time has not yet been reached.

Conclusions: The SOX regimen demonstrated a promising activity with acceptable toxicity for the first-line treatment of mCRC, and the current data warrants further investigation.