cancer was detected in 6/17440 (0.0344%) cases, suspicion of hereditary CRC was detected in 11/17440 (0.063%) cases.
Conclusions: The role of the classical Amsterdam criteria in diagnosing HNPCC in CRC patients of Latvia is quite limited and diagnostic criteria for suspected HNPCC are the most effective to detected MMR gene mutation carriers. The frequency of constitutional mutations within the MMR genes is 1% of all newly diagnosed CRC cases. CHEK2(I157T) variant is associated with slightly increased risk of CRC, but difference is not statistically significant. Increased hereditary CRC risk group was observed in 1.3% of all adult population.

3025 POSTER

Impact of pre-medication on the frequency of infusion-related reactions (IRRs) and efficacy in patients (pts) treated with cetuximab plus irinotecan for metastatic colorectal cancer (mCRC): the MABEL study

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Background: Cetuximab (Erbitux®), an IgG1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR), is active alone and in combination with irinotecan in patients (pts) with mCRC failing prior irinotecan therapy. IRRs have been observed in a small number of pts especially at the first cetuximab infusion.
Methods: The primary objective of the MABEL study was to investigate the impact of cetuximab plus irinotecan on the progression free survival (PFS) rate at week (wk) 12 in pts with EGFR-detectable mCRC who had recently progressed on irinotecan-containing treatment. Secondary objectives included PFS time, overall survival (OS) time and rates, and cetuximab-related adverse events. Pts received cetuximab (initial dose 400 mg/m^2, then 250 mg/m^2 wkly) plus irinotecan as pre-study (125 mg/m^2 wkly for 4/6 wks; 180 mg/m^2 every 2 wks; 350 mg/m^2 every 3 wks). Data were retrospectively analyzed regarding the impact of prophylactic pre-medication (classified as antihistamine alone and antihistamine plus corticosteroid) on the frequency of IRRs and efficacy in terms of PFS and OS.
Results: Overall, 1147 pts were treated: median age 62 yrs [25–84]; KPS $\geqslant$ 70%; 64% pts male. 1122 pts were pre-treated with antihistamines. IRRs were less frequent in pts receiving antihistamine + corticosteroid as compared to antihistamine alone (9.6% vs 25.6% any grade, 1% vs 4.7% grade 3/4 IRRs). Efficacy results for PFS and OS (see table) by antihistamine alone vs antihistamine + corticosteroid groups suggest no apparent differences related to prophylactic pre-medication.

Efficacy results for PFS and OS

	Antihistamine alone (n = 422)	Antihistamine + corticosteroid (n = 700)	Total antihistamine pre-treated (n = 1122)
Median PFS, wks [95% CI]	13.1 [12.6, 16.0]	16.1 [13.0, 19.3]	14.3 [13.0, 17.1]
PFS rate, % [95% CI]			
12-wk	60 [56, 65]	61 [57, 65]	61 [58, 64]
24-wk	32 [27, 36]	35 [31, 39]	34 [31, 37]
36-wk	16 [12, 19]	18 [15, 21]	17 [14, 19]
48-wk	6 [3, 8]	6 [4, 8]	6 [4, 8]
Median OS, months [95% CI]	9.0 [8.3, 10.5]	9.2 [8.5, 10.0]	9.2 [8.5, 9.8]
Survival rate, % [95% CI]			
6-months	67 [63, 72]	68 [64, 71]	67 [65, 70]
12-months	39 [34, 44]	37 [33, 41]	38 [35, 41]
18-months	21 [16, 25]	19 [16, 22]	20 [17, 22]
24-months	7 [0, 15]	8 [3, 12]	8 [4, 21]

Conclusions: The data suggest a reduced incidence of IRRs when both antihistamine and corticosteroid pre-medication is given (grade 3/4 IRRs: 1% vs 4.7% for antihistamines alone). In addition, there is no apparent difference in PFS and OS between the analyzed pre-medication groups.

3026 POSTER

Loco-regional tumor control and normal tissue reactions after three different fractionation schedules of preoperative radiotherapy for rectal cancer

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Purpose: To evaluate the effectiveness and normal tissue reactions in three different fractionation schedules of preoperative radiotherapy for locally advanced rectal cancer.
Material and Methods: Between 1996 and 2002 168 patients with locally advanced rectal cancer were treated as follows: 53 patients received 25 Gy in 5 Gy per fraction (group A), 45 received 30 Gy in 3.0 Gy per fraction (group B), and 70 were treated with accelerated hyperfractionation 42 Gy, 1.5 Gy per fraction, given twice a day with an inter-fraction interval of 6 hours (group C). The clinical characteristics of the groups was comparable, the patients did not receive concurrent chemotherapy. A Cox regression method was used to analyze the factors which may influence loco-regional tumor control (LRC) and overall survival (OS). The evaluation of normal tissue reactions included the analysis of the incidence of surgical complications, as well as of acute and late radiation effects.
Results: The following variables significantly influenced LRC: fractionation scheme (5-year actuarial LRC 82%, 71%, and 93% in groups A, B, C respectively, p = 0.02), and hemoglobin concentration before radiotherapy (p = 0.026). The stage of disease, age and sex did not appear significant for LRC. The overall 5-year OS was 64%, 60% and 74% in groups A, B, C respectively (p = 0.08). The OS was significantly influenced by postoperative pathological nodal stage (p = 0.001). The most relevant acute radiation reaction was a mild/severe diarrhea which appeared in 7%, 4% and 12% of the patients (no significant differences between the groups A-C). The spastic ileus appeared in perioperative period in 4%, 2% and 1% of the patients. The median wound healing time in those who underwent abdomino-perineal resections was 6, 6 and 4 weeks, and the persistent fistulas appeared in 4%, 7% and 2% of the patients (groups A, B, C, respectively). Other reactions appeared less relevant.
Conclusions: While due to non-randomized character of the study the conclusions should be regarded as hypothesis-generating only, the analysis has shown an acceptable local effectiveness and tolerance of schedules A and C, and disappointing effectiveness of schedule B. The present study supports thus the data which suggest that the clinical effect of preoperative radiotherapy for rectal cancer is influenced not only by total radiation dose but also by overall radiation treatment time and dose per fraction.

3027 POSTER

High rate of TRG1–2, and prolonged RFS with OXA/TOM and FU/LFA during preoperative pelvic RT in patients with poor prognosis locally-advanced rectal cancer (LARC)

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Introduction: We have previously reported that 3 cycles of Oxaliplatin (OXA), Raltitrexed (TOMUDEX [TOM]) and 5-Fluorouracile (FU) + levofolinic acid (LFA) during pelvic RT had an acceptable toxicity and produced a complete (TRG1, 42%) or subtotal (TRG2, 29%) pathologic tumor regression in 71% of 31 pts with poor prognosis LARC (Avallone et al, Br J Cancer 2006). Here we report an expanded experience on such treatment.
Methods: We enrolled 62 eligible pts (M, 33; F, 29), with median age of 58 (27–79) yrs, and adenocarcinoma of the extraperitoneal rectum, with at least one of the following characteristics: cT4 (N pts), cN+ (N), cT3N0 with tumor location $\leqslant$5 cm from the anal verge and/or CRM +ve (assessed by MRI) (N). Pts received 3 biweekly courses of OXA 100 mg/sqm + TOM 2.5 mg/sqm on day 1, and LFA 250 mg/sqm + FU 900 mg/sqm (31 pts) or 800 mg/sqm (31 pts) on day 2, and concomitant pelvic RT (1.8 Gy/day in 25 fractions, total dose 45 Gy). Surgery with TME was planned 8 weeks after the end of treatment. Pathologic response was evaluated by tumor regression grading (TRG) according to Mandard's modified classification. Pts with cT4, pN+ and pCRM +ve received also 4 months of weekly FU/FA.
Results: All pts received full dose of RT, and 98% of the planned CT cycles. Neutropenia was the most common grade $\geqslant$3 toxicity (40%), while grade 3 diarrhea was seen in 19% of pts with FU 900 mg/sqm, and in only 6% of pts with FU 800 mg/sqm. All but 2 pts had a TME with R0 resection, and no treatment-related or perioperative death occurred. Median number of sampled lymph nodes was 36 (range, 10–80). 28 (45%) pts obtained a TRG1, and 17 (27%) pts a TRG2. Activity of the combined treatment was similar in all risk groups (N), regardless of FU dosage. On the whole series of 62 operated pts, 1 pt suffered a local recurrence (after 9 months), and 3 pts had distant metastases (after 22, 33, and 47 months). After a median follow-up of 34 (range 6–54) months, all pts are alive, and the estimated

34-month RFS was 95%. All pts achieving a TRG1, and all but one with TRG2 (pCRM +ve), were recurrence-free.
Conclusions: These data confirm the feasibility and activity of the whole treatment. A slight reduction of FU dosage appeared to improve the safety of this combination. Currently, we are now evaluating the addition of bevacizumab, 5 mg/kg every 2 weeks, before and during this concurrent

3028 POSTER

Induction of dihydropyrimidine dehydrogenase expression by Mitomycin C in colorectal cancer

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Background: Since thymidine phosphorylase (TP) is an essential enzyme for the activation of capecitabine to 5-fluorouracil (5-FU) in tumors, TP up-regulators should enhance the efficacy of capecitabine. Dihydropyrimidine dehydrogenase (DPD), on the other hand, is considered to be a key enzyme in the catabolism of 5-FU, and its high expression in a tumor is thought to reduce the efficacy of 5-FU against tumors. The aim of this study was to confirm whether or not mitomycin C (MMC) is a TP and/or DPD regulator.
Materials and Methods: Biopsy specimens were obtained from 62 colorectal cancer patients preoperatively by colonoscopy. After a biopsy, 33 patients received neoadjuvant chemotherapy with MMC and underwent operations after 1−13 days. Using biopsy and operative specimens, TP and DPD levels in the tumors were examined. Patients were divided into three groups; an MMC(−) group (no MMC), a Short group (operation within four days after MMC) and a Long group (operation over six days after MMC).
Results: In the MMC(−) and Short groups, no significant differences in DPD levels before and after MMC were observed. In the Long group, on the other hand, DPD levels were elevated ($p = 0.026$). As for TP, MMC did not raise the levels of TP in the MMC(−) and Short groups, but it tended to do so in the Long group ($p = 0.13$).
Conclusions: Although MMC appears to be a TP up-regulator, it is also a DPD up-regulator at appropriate intervals.

3029 POSTER

A Swiss multicentre phase II study of capecitabine plus oxaliplatin (CAPOX) in combination with preoperative pelvic radiotherapy in patients (pts) with locally advanced rectal cancer

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Background: This study evaluated the addition of capecitabine and oxaliplatin (CAPOX) to preoperative radiotherapy (RT) in patients with locally advanced rectal cancer (LARC).
Materials and Methods: Patients (pts) with T3/T4 rectal adenocarcinoma with or without nodal involvement staged by endorectal ultrasound were recruited. Treatment consisted of a full dose cycle with CAPOX (capecitabine 1000 mg/m^2 bid on days 1–14 and oxaliplatin 130 mg/m^2/d on day 1), followed by RT as 25 daily fractions of 1.8 Gy on 5 consecutive weeks in combination with capecitabine 825 mg/m^2 bid on days 22–35 and 43–56 and oxaliplatin 50 mg/m^2/d on days 22, 29, 43 and 50. Surgery was scheduled 5 weeks after completion of CAPOX-RT. Primary endpoint was pathological complete tumour response (pCR) prospectively defined as grade 3 or 4 in the histological grading of regression according to Dworak classification (DC). Secondary endpoints were rate of sphincter preservation, R0 resection in pts with T4 tumours, downstaging, pathological incomplete tumour response rate and safety. Second-opinion pathology review was performed in all tumours categorised as DC grade 2 or 3.
Results: 60 pts were enrolled from 6 cancer centres. Median tumour size was 50 mm. Nodal infiltration was diagnosed in 47 pts. Tumour location (from anal verge): $\leqslant$5 cm in 21 pts, 5–10 cm 22 pts, >10 cm 17 pts. 58 pts received CAPOX-RT and underwent surgery (49 TME, 9 abdominoperineal resection), 1 pt withdrew consent and refused further treatment, and 1 died during neoadjuvant CAPOX. R0 resection was achieved in 57 pts, including all 5 pts with T4 tumours. The pCR rate was 23% (95% CI, 13–36; DC 3: 7 pts, DC 4: 7 pts). Sphincter preservation was achieved in 84% of pts. Tumour downstaging (T and/or N) was observed in 65% of pts. Pathological incomplete response (DC 0/1/2) was observed in 1/20/23 pts. Main grade 3 adverse events were: diarrhoea 20%; thrombosis 3%; nausea, vomiting, proctitis, fatigue, hand–foot syndrome 2% each. No grade 3/4 haematological adverse events, except lymphocytopenia (43%), were observed.
Conclusions: Preoperative combined treatment with CAPOX and RT is feasible and resulted in encouraging high rates of pCR, R0 resection, sphincter preservation, and tumour downstaging in this group of pts with LARC.

3030 POSTER

Randomized strategical trial of chemotherapy in metastatic colorectal cancer (FFCD 2000−05): preliminary results

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Background: The survival benefit of using a combination therapy instead of keeping it for a second line (L2) has not been demonstrated in metastatic colorectal cancer. The purpose of this trial was to compare the efficacy of simplified LV5FU2 (s) followed by FOLFOX6 (arm A) to FOLFOX6 followed by FOLFIRI (arm B) on progression-free survival after two lines of chemotherapy. We present here preliminary results relating to toxicity, observance and overall survival.
Materials and Methods: Inclusion criteria: a) non resectable metastases of histologically proven colorectal adenocarcinoma, b) evaluable disease (WHO criteria), c) absence of previous chemotherapy other than adjuvant. Treatment was as follows: LV5FU2s = at day 1, folinic acid 400 mg/m^2, 5-FU bolus 400 mg/m^2 and continuous infusion over 46 hours 2400 mg/m^2/2 weeks; FOLFOX6 = LV5FU2s + oxaliplatin 100 mg/m^2 at day 1; FOLFIRI = LV5FU2s + irinotecan 180 mg/m^2 at day 1.
Results: 410 pts out of 570 initially planned (early stopping due to slow accrual and new treatments) were included from 02/2002 to 02/2006 (205 in each arm). Median follow-up was 25 months. The median number (range) of cycles (28 days) in first line (L1) was respectively 5 (1−24) and 6 (1−24) in the arms A and B ($p = 0.01$), and for L2 (152 and 144 pts in the arms A/B): 5 (1−17) and 3 (1−33) (NS). In the arms A and B, 74% and 70% of pts had L2. L1 was stopped for toxicity for 1% and 16% of the pts in arms A and B ($p < 0.0001$); L2 respectively for 15% and 2% pts ($p < 0.0001$). The percentages of pts presenting at least a grade 3−4 hematologic toxicity (mainly neutropenia) by arm were: 6% versus 37% ($p < 0.0001$) for L1 and 30% versus 27% (NS) for L2; grade 3−4 non hematological toxicity (grade 2−4 neurotoxicity): 26% (1%) versus 56% (64%)($p < 0.0001$; $p < 0.0001$) for L1 and 54% (60%) versus 46% (40%) of the pts for L2 (NS; $p < 0.01$). No toxic death was observed in the arm A against 5 in the arm B: 3 in L1 and 2 in L2. Overall survival medians were 17 and 16 months in arms A/B (logrank $p = 0.64$) (preliminary results, 291 observed deaths).
Conclusions: This trial does not show any substantial difference in treatment duration and overall survival between both arms and shows a more important toxicity in the arm with first line combined chemotherapy.

3031 POSTER

Significance of polymorphisms in biotransformation enzymes for colorectal carcinogenesis

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Background: Biotransformation enzymes play important role in metabolism of xenobiotics. Genetic polymorphisms in biotransformation enzymes may result in variations in detoxification capacity. Interaction