Poster Discussions: Oral

GI: colo-rectal cancer

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Early recurrence and genetic alterations in colorectal cancer

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Introduction: Early recurrence (ER) in Colorectal Cancer (CRC) is not frequent when surgery has been performed correctly. The prognostic value of genetic alterations in CRC is controversial, both for overall survival and for early events like recurrence. We present the results of a study about this latter subject.

Objectives: To explore the prognostic value of clinical and pathological variables and genetic alterations for ER of CRC.

Patients and methods: Eligible patients were all consecutive diagnoses of CRC at our Hospital during the period from January 1996 to December 1998. Patients with disseminated disease or surgical margins invasion were excluded. ER was defined as local or systemic progressive disease during the first year after surgery. Clinical and pathological variables of interest were sex, age, tumour location, tumour size and nodal involvement, histological type and grade. Genetic alterations, determined with fresh tumour tissue available, were mutations in k-ras oncogene, p53 tumor suppresser gene and microsatellite instability (MI). Association of each variable with early recurrence was assessed with a two-sided Fisher's exact test. A logistic regression model was built to determine those independent prognostic factors.

Results: 561 patients were included during the study period. Mean age was 64 years (30-92) and 60.4% were male. 36.7% (206 patients) of all tumors were located in rectum and 63.3% (355) in colon. Tumor stages were A, 51 pts (9.1%); B1, 61 (10.87%); B2, 219 (39.03%); C1, 21 (3.74%); C2 209 (37.25%).

288/561 pts (51.3%) received postoperative chemotherapy and 135/561 (24.06%) pelvic radiotherapy. K-ras mutation was detected in 118/299 cases tested (39.5%). p53 mutation was detected in 65/124 (52.4%). MI was detected in 24/294 (8.2%). ER was observed in 55/561 (9.8%) pts. These were local in 8 pts (13.8%), systemic in 40 (69%) and local plus systemic in 10 (17.2%). ER was related to Stage (p=0.01), nodal involvement (p=0.002), lymphatic vessels invasion (p=0.002) and association of k-ras mutation and MI (p=0.05). Nodal involvement, lymphatic vessels invasion and having both k-ras mutation and MI (p=0.0455) remained statistically significant in a multivariate logistic regression model.

Conclusions: This analysis has shown that ER of CRC is mainly related to nodal involvement, lymphatic vessels invasion and the association of k-ras mutation and microsatellite instability.

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Phase III trial of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (MAYO) vs. weekly oxaliplatin (OXA) plus high dose 24h 5-FU infusion/FA in patients with advanced colorectal cancer (CRC)

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Rationale: 5-FU/FA plus Oxaliplatin (OXA) has shown to be superior to infusional 5-FU/FA in terms of response rate (RR) and progression free survival (PFS) in patients with advanced CRC. However, this combination has never been compared with bolus 5-FU/FA. After a phase II study which demonstrated encouraging activity and low toxicity in patients refractory to 5-FU/FA (ASCO 1998, abstr. 61), a randomized study was initiated comparing an OXA plus 5-FU/FA combination regimen (Arm B - OXA 2h infusion 50 mg/m2 + 5-FU 24h infusion 2000mg/m2/FA 500 mg/m2; d1,8,15,22, qd 36) with the standard Mayo Clinic protocol (Arm A).

Patients: 252 pts. (A 129, B 123) were randomized by 60 centers within 435 days. Both treatment arms were well balanced for main patient characteristics with the exception of previous adjuvant therapy (A 26%, B 14%).

Results: 229 pts are evaluable for toxicity (A 116, B 113; 1461 cycles) and 219 pts (A 110, B 109) for efficacy. Toxicity was comparable in both treatment arms with WHO °3/4 toxicity: neutropenia 7.9% vs. 1.7%, mucositis 1.8% vs. 0.6%, diarrhea 2.7% vs. 4.7%, vomiting 0.5% vs. 1.1%. WHO °3/4 cumulative sensory neuropathy occurred in 3.5% of pts, exclusively in Arm B. RR was significantly increased in Arm B with 51.4% vs. 21.5% (95% CI: 41.5 - 61.2% vs. 14.1 - 31.9%). After a median follow-up of 8.1 (A) and 8.8 (B) months, 62.7% (A) and 53.2% (B) of pts had progressive disease resulting in a significant difference in PFS of 5.6 (A) vs. 8.0 (B) months (p=0.0001). As of March 2001, 56.9% (A) and 73% (B) of pts are still alive, so that reliable data on overall survival cannot be calculated yet.

Conclusion: Weekly OXA plus 5-FU 24h/FA has superior anti-tumor activity compared with the Mayo Clinic protocol without enhanced toxicity except sensory neuropathy and could therefore serve as basis for the addition of other antineoplastic agents to further increase its efficacy. Updated data on RR and PFS as well as overall survival will be presented at the meeting.

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Intravenous (IV) vs intrahepatic arterial (IHA) 5fu/leucovorin for colorectal (CRC) liver metastases: preliminary results of the mrc cr05/eortc 40972 randomised trial

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IHA therapy should deliver higher doses of drug to the liver with reduced overall systemic exposure. An IHA regimen was designed which used the same drugs and schedule and achieved similar toxicity and steady-state venous 5FU levels as the standard de Gramont IV regimen. Patients with advanced CRC with metastases confined to the liver were randomised to either IV or IHA. On days 1 and 2 of a 2-week cycle, IV patients received LV 200 mg/m2 IV over 2 hours, 5FU 400 mg/m2 5-minute bolus and 600 mg/m2 IV 22-hour infusion, and IHA patients received LV 200 mg/m2 iv over 2 hours, 400 mg/m2 15-minute IHA infusion and 1.6g/m2 22-hour IHA infusion. The trial was closed in August 2000, when 290 patients had been entered from 16 centres in 6 years. Median age of patients was 61 years, 70% were male, 65% WHO PS grade 0, 68% had colon cancer, and these characteristics were well balanced between the two arms. Of the 145 IV patients, 15% did not receive any allocated therapy, but 77% received 6+ cycles of chemotherapy. Of the 145 IHA patients, 37% did not start, and only 35% received 6+ cycles. The additional problems in the IHA group were inability to insert the catheter, or infected, leaking, or blocked catheters. Clinicians reported similar levels of toxicity, and patients, completing the EORTC QLQ-C30 and HADS, reported similar quality of life, in both arms. There was no clear evidence of a difference in progression-free survival (HR 1.21 95% CIs 0.93-1.58, p=0.15) or overall survival (HR 0.97 95% CIs 0.73-1.29, p=0.82). From randomisation median and 2-year survival were 13.4 and 14.7 months, and 23% and 20% for IV and IHA respectively. This trial suggests there is no obvious role for this IHA regimen in the management of hepatic metastatic CRC.