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Oxaliplatin or irinotecan based chemotherapy for metastatic colorectal cancer in the elderly

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Background: Oxaliplatin and irinotecan are widely used in metastatic colorectal carcinoma. Their tolerance and efficacy are unknown in elderly patients (pts) over 75 years.

Methods: All consecutives pts over 74 years treated with oxaliplatin or irinotecan for metastatic colorectal cancer from January 1999 to June 2002 were retrospectively enrolled. Tumour response was assessed with CT examination every 2 to 3 months and toxicity was collected at each cure according to WHO criteria.

Results: Sixty-six pts were enrolled from 12 centres. Median age was 78 years (range: 75-88), 39 pts had no severe co-morbidity according to Charlson score. Forty four and 22 pts received oxaliplatin or irinotecan respectively, in combination with 5-fluororuracil +/- folinic acid or raltitrexed in 64 pts. A total of 545 chemotherapy cycles were administered in first (41%), second (51%) and third (8%) line. Dose reduction occurred more frequently in pts over 79 years (31 vs 48%, p2 (12 vs 44%, p=0.04). No treatment-related death occurred. Chemotherapy improved performance status and weight in 38 and 28% of pts, respectively.

Conclusion: In selected elderly patients, chemotherapy with oxaliplatin or irinotecan is well tolerated with comparable efficacy than in younger patients.

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The carcinoembryonic antigen (CEA)family: gene expression in colorectal tumor samples by real-time quantitative polymerase chain reaction (RT-QPCR)

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Background: The CEA family is composed of 7 proteins (CEACAM1, CEACAM3, CEACAM4, CEACAM5, CEACAM6, CEACAM7 and CEACAM8) which differ according to their C-terminal domain. CEACAM1, CEACAM3 and CEACAM4 have transmembrane and cytoplasmatic domains, while CEACAM5, CEACAM6, CEACAM7 and CEACAM8 are attached to the cell membrane via glycosyl phosphatidyl inositol. Immunohistochemistry and in situ hybridization have shown that CEACAM1, CEACAM5, CEACAM6 and CEACAM7 are expressed in normal tissue and in colorectal carcinoma, while CEACAM3, CEACAM7 and CEACAM8 are not expressed in epithelial tumors. To date, there is no clear correlation between the CEA family and clinicopathological factors. We assessed mRNA expression of CEA in normal tissue and in colorectal tumor samples by RT-QPCR and correlated results with clinicopathological characteristics.

Patients and Methods: mRNA was isolated from 16 surgery colorectal tumor samples and transformed into cDNA with RT-PCR. With probes marked for gene expression, mRNA expression was quantified (ABI Prims 7700) for CEACAM1, CEACAM3, CEACAM4, CEACAM5, CEACAM6, CEACAM7 and CEACAM8.

Results: The mRNA expression levels of CEA in tumor were different from levels in normal tissue: CEACAM1 (37.5%), CEACAM3 (31%), CEACAM4 (44%), CEACAM5 (63%), CEACAM6 (87%), CEACAM7 (37%) y CEACAM8 (44%). CEACAM3, CEACAM4 and CEACAM8 mRNA expression, which was not detected by immunohistochemistry, was observed in normal tissue.

CEACAM 5 was expressed in 5 of 7 (71%) stage II patients (pts), 2 of 3 (67%) stage III pts and 4 of 6 (67%) stage IV pts. CEACAM6 was detected in 7 of 7 (100%) stage II pts, 1 of 3 (33%) stage III pts, and 5 of 5 (100%) stage IV pts. CEACAM8 was detected in 6 of 7 (86%) stage II pts and 1 of 5 (17%) stage IV pts.

Conclusions: These preliminary data show that RT-QPCR is a sensitive method for CEACAM analysis. CEACAM5 and CEACAM6 are overexpressed in tumors and CEACAM7 is downregulated. The clinical significance of CEA family detection in surgery tumor samples by RT-QPCR needs further evaluation.

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The impact of microsatellite instability and its correlation with p53 expression in sporadic colorectal cancer (sCRC)

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Background. Inactivation of one of the mismatch repair (MMR) genes leads to microsatellite instability (MSI) implicated in the pathogenesis of 15-20% of sCRCs (mutator pathway). These cases constitute a particular group of sCRCs with distinct clinicopathological characteristics, different response to chemotherapy and better prognosis. On the contrary, p53 is implicated in loss of heterozygosity pathway (LOH) which leads to microsatellite stable carcinomas. Overexpression of p53 is usually correlated with worse prognosis.

We studied MSI via the expression of MLH1, MSH2-1 and MSH2-2 proteins and correlated them with p53 expression and other clinicopathological parameters.

Patients and Methods. 88 patients (pts) with sCRCs and a 5 to 10 year follow-up (M/F 51/35, mean age 61,4/60, 14 of them less than 50 years old) were included. The tumors, 26 of the right and 60 of the left colon, were staged according to Dukes classification as: 14 stage A, 29 B, and 43 stage C. Paraffin sections of tumor and adjacent normal mucosa were immunohistochemically studied for MSI, using monoclonal antibodies against MSH2-1, MSH2-2 and MLH1 proteins. Tumors with loss of at least one gene protein expression of were defined as MMR-. Expression of p53 was evaluated as the percentage of positive nuclei via an interactive morphometric image analysis program.

Results. Loss of at least one MMR protein expression was verified in 20 (22.2%) of sCRCs; MSH2-1 in 15/86 (17.4%), MSH2-2 in 10/86 (11.6%) and MLH1 in 5/86 (5.8%) of pts. The MMR-/MMR+ mean age of pts was 57.4/63.0 (p=0.055). MMR- pts were characterized by right-sided ($p<0.0001$), mucinous ($p<0.08$), partly mucinous ($p<0.05$) or low differentiated carcinomas ($p<0.005$). Survival rates were better for MMR+ pts. High expression of p53 was observed in MMR+ cases and correlated with worse survival ($p<0.005$). We noted minimal to nil percentage of p53 expression in MSH2-1-($p< 0,001$), MLH1-($p<0,05$) and MMR-($p< 0,0001$). No statistically significant difference was observed for MSH2-2- carcinomas. In multivariate analysis stage, p53 and MLH1 protein expression were shown to be independent prognostic factors.

Conclusions. MMR- sCRCs show distinct clinocopathological characteristics, better prognosis and absence or near absence of p53 expression. MLH1 expression seems to be an independent prognostic factor. p53 overexpression in MMR+ cases correlates with worse prognosis.

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Prognostic factors of survival after oxaliplatin therapy in colorectal cancer patients pretreated by irinotecan

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Background: Oxaliplatin (OHP) is effective as first and second line agent in metastatic colorectal cancer (CRC). The activities of OHP and irinotecan (CPT) alone or in combination with 5-fluorouracil (5FU) are comparable, but the data on the effectiveness of OHP in patients pretreated by CPT are limited.

Patients and Methods: The survival of 77 patients with metastatic or inoperable loco-regionally recurrent CRC treated with OHP after previous CPT therapy was analyzed retrospectively. 62 patients (81%) had liver metastases. 55 patients were treated by combination of OHP with 5FU, 25 patients were treated by OHP combined with raltitrexed (TOMOX), and 3 patients received sequentially OHP with 5FU and TOMOX. The impact of clinical and biological parameters on survival was analyzed by log-rank test. Multivariate analysis was performed by Cox regression method, and the results were expressed as hazard ratio (HR).

Results: The median survival of all patients was 10.6 months (1 year survival 43%). The median survival from the diagnosis of advanced/metastatic CRC was 34.3 months. On univariate analysis, the survival was not significantly affected by the line of the treatment, presence of lung metastases,

local recurrence, age, intraarterial administration, agents used in combination, previous radical surgery and platelet count, but significantly ($p < 0.05$) better in patients with only one site involved, hemoglobin (HGB) levels $\geq$ 125 g/l, peripheral blood leukocyte count (PBLC) $< 8 \times 10^9$/l, absence of liver metastases, and CEA < 100 µ g/l. Longer survival of borderline significance was observed in patients with duration of advanced/metastatic disease $\geq$ 21 months ($p = 0.13$) and interval from last CPT administration < 3 months ($p = 0.07$). These parameters were further examined by multivariate analysis, and HGB < 125 g/l (HR = 2.86), PBLC $< 8 \times 10^9$/l (HR = 0.45), duration of advanced/metastatic disease < 21 months (HR = 2.13), interval from last CPT administration < 3 months (HR = 0.42) and CEA < 100 µ g/l (HR = 0.49) were significantly ($p < 0.05$) associated with survival. HGB, PBLC, CEA and duration of advanced/metastatic disease, but not interval from last CPT administration retained statistical significance when the survival was measured from last CPT administration. Although the survival was similar among the 25 patients treated by TOMOX, there were 4 early deaths after this regimen.

Conclusions: More than 40% of patients pretreated by CPT survived 1 year after start of OHP therapy, and median survival from the diagnosis of advanced/metastatic disease in this selected group of patients was almost 3 years. The therapy was similarly effective as second or higher line of treatment. HGB, PBLC, CEA, and duration of advanced/metastatic disease were independent factors associated with survival. The number of early deaths observed after TOMOX is alarming.

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Patterns of failure after liver resection in patients receiving FOLFOX4 for metastatic colorectal cancer (MCRC) limited to the liver: a North Central Cancer Treatment Group (NCCTG) phase II study

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Background: Bismuth et al pioneered treatment of patients with non-optimally resectable liver limited MCRC with oxaliplatin/5-fluorouracil (OXAL/5-FU) regimens to allow resection. (Sem Oncol 1998). We have reported results on the response in 42 eligible patients (Proc Annu Meet ASCO 2003), enrolled in an NCCTG trial designed to confirm Bismuth's findings. We now report on patterns of failure.

Methods: Patients with liver only MCRC deemed not optimally resectable by a liver surgeon received biweekly OXAL 85 mg/m^2 on d1 followed by leucovorin (LV) 200 mg/m^2, 5-FU 400 mg/m^2 bolus IV, then 22-hour infusion 5-FU 600 mg/m^2 on d1; repeated d2 (FOLFOX 4). Responding patients were reassessed for resectability. Surgical response was classified as 1) completely resectable (S-CR), 2) partially resectable (S-PR), or 3) unresectable (S-UR). Study design specified accrual of 39 patients, with 2 or more S-CRs indicating promising activity. 43 patients were accrued with follow-up available on all patients.

Results: 26 patients (62%) had tumor reduction (1-CR, 21-PR, 4-REGR) by pre-operative imaging. 17 patients (41%, 65% of responders) have undergone surgery (14 S-CR, 1 S-PR, and 2 S-UR) after a median of 6 months of chemotherapy (range 3 - 17). With a median post-surgical follow-up of 14 months (range 6 ñ 27), 10 recurrences have occurred in S-CR and S-PR patients (67% of resected patients). 36 patients have had progression or recurrence which occurred most frequently in the liver (9/12 surgical patients, 19/23 non-surgical patients). Other sites included: lung, colon, abdomen, bone, neck, peritoneum, and a new primary. Of all patients, 25 have died. Median survival is 27.9 months (95% CI: 20 ñ 34).

Best Outcome	No Progression or Recurrence	Progression or Recurrence Site		
		Liver Only	Non-liver Only	Both
Surgical (N = 17)				
S-CR & S-PR	5	6	3	1
S-UR	0	0	2	1
PR/REGR	1	8	0	0
Stable	1	6	4	0
Progression	0	5	0	0
Too early	1	0	0	0

Conclusions: Our data suggest that OXAL/5FU/LV has a very high response rate in liver limited MCRC and allows for successful resection of initially not optimally resectable patients in many cases. However, a high recurrence rate (71%) after surgery was observed, of which 67% (8/12) involved hepatic disease. Our trial supports the findings of Bismuth (1998) and further trials are indicated to enhance the promising observed results. Novel therapies are now being explored to further reduce the rate of recurrence. Supported by NIH Grant CA25224-18 and Sanofi-Synthelabo.

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A phase II study of preoperative oxaliplatin, capecitabine, and external beam radiotherapy in patients with locally advanced rectal adenocarcinoma: the RadiOxCape study

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Local recurrence after surgery is a life-threatening problem in locally advanced rectal cancer. Preoperative radiotherapy is the standard of care for locally advanced tumors in many European countries and can decrease the local recurrence rate. Capecitabine and oxaliplatin are both active anticancer agents in the treatment of patients with advanced colorectal cancer and have radiosensitizing properties. Therefore, oxaliplatin and capecitabine may improve the effectiveness of preoperative radiotherapy in term of local control as well as prevention of distant metastases. This study was designed to investigate the efficacy (based on pathological response rate) and safety of preoperative chemoradiation in patients with locally advanced (clinical T3-T4 and/or N+) rectal cancer. Radiotherapy was administered for 5 weeks, 5 days a week (1.8 Gy/fraction, total dose 45 Gy, 3D conformation technique) in combination with oxaliplatin (50mg/m2 intravenously, weekly for 5 weeks) and capecitabine (825 mg/m2 orally, twice a day, each day of radiation). Since December 2002, 20 pts were accrued. Here, we report the preliminary data of acute toxicity during the administration of radiochemotherapy on the first 12 pts (ECOG 0-2; median age 55 y, ranging from 32 to 76; males/females 4/8). Radiotherapy was administered as planned to all patients. Grade III NCI-CTC toxicities were diarrhea (3 pts), vomiting (1 pt), and fever (1 pt). No grade IV toxicity was observed. One patient experienced grade 1 neurotoxicity. Dose adjustment had to be performed in only 3 pts. Oxaliplatin alone was reduced in 2 patients: total oxaliplatin dose received was 80% and 70% of the planned dose, respectively. Oxaliplatin and capecitabine were both reduced in the third patient: total doses administered of capecitabine and oxaliplatin were 86% and 90% of the planned dose, respectively. The main reasons to reduce chemotherapy dosages were grade III diarrhea and fever. These results demonstrate that preoperative oxaliplatin and capecitabine in combination with radiotherapy is feasible in patients with locally advanced rectal cancer. Updated data about safety will be presented at the meeting on 20 pts at least.

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Phase I dose-escalation study with Raltitrexed ('Tomudex') combined with UFT in metastatic colorectal cancer.

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Aims: Preclinical studies show synergism with Raltitrexed (Tomudex') given prior to 5-FU and preliminary clinical data indicate promising response rates. This study was initiated to determine the maximum tolerated dose, recommended dose and safety of this combination.

Patients and methods: Chemo-naive patients (pts) with metastatic, aged $\geq$ 18 years $\leq$ 75, WHO performance status score $\leq$ 2, satisfactory haematological, renal and hepatic function, life expectancy of at least 3 months, and at least one assessable or measurable lesion. Treatment schedule: patients received Raltitrexed (15-min iv infusion) every 3 weeks on days 1 and 21, and UFT (orally three times a day) on days 1 to 28, followed by 2 weeks' rest of a 6 weeks cycle. The dose limiting toxicity (DLT) was defined as: Diarrhoea grade III; mucositis grade III; platelets grade III; Leukocytes grade IV; Neutrophils gradeIV; Other Toxicity grade II, excluding alopecia or increase transaminases levels.

Results: Since December 1998 to September2000, 33 pts have been enrolled: median age 62.6 (range: 38-71) years; **WHO** performance status: