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The recovery of circulating dendritic cells during anti-VEGF treatment is related to clinical outcome in advanced colorectal cancer patients

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Background: The proved clinical efficacy of Bevacizumab (BEV) in metastatic colorectal cancer (mCRC) could be related not only to its well-established effect on tumor neoangiogenesis but also to a counteraction of VEGF-mediated dendritic cell (DC) abnormalities. BEV addiction to chemotherapy (CT) may improve the number and function of blood DCs in cancer pts. We have focused on the correlation between this immunological favourable effect and the clinical efficacy of a multicyclic BEV-based, 1st-line treatment for mCRC.
Material and Methods: Starting from January 2007 we performed a flow cytometric analysis of PB lymphocytes and DC subsets (DC1 and DC2) in 53 mCRC pts who had not received prior CT for metastatic disease or for whom 6 months had relapsed since adjuvant CT (M/F: 31/22, median age: 59 yrs; range 32−75; ECOG PS <2), before and every 3 courses of a BEV+CT (5-FU± CPT11± Oxaliplatin) program. Biological data of the 42 evaluable pts that received all the planned treatment were correlated to both tumor response (OR) and progression free survival (PFS).
Results: During treatment, DCs and their subsets showed a progressive, significant increase in absolute number, with respect to baseline, both in responder (CR, PR, SD) (67%) and in non responder pts; only responder pts keep this immunological effect at the moment of clinico-radiological revaluation, performed at 3 weeks since the last course administration. The DC and DC1 absolute number of pts with PFS > 15 months (58%) increased more evidently during antiangiogenetic-therapy and was significantly higher after therapy completion with respect to DC of pts with shorter PFS ($p < 0.02$).
Conclusions: First-line BEV-based therapy in mCRC pts improves the number of blood DCs, pointing out a potential additional anticancer mechanism of this drug. The recovery of DC does not influence OR but correlates with longer PFS. This suggests that BEV can influence tumor regrowth by contributing to overcome the impairment of the host immune surveillance induced by VEGF.

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Clinicopathologic significance of nuclear factor kappa B, hypoxia-inducible factor 1 alfa, and vascular endothelial growth factor expression in stage III colorectal cancer

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Background: Activation of transcription factor nuclear factor-κB (NF-κB) has a role in cell proliferation, invasion and angiogenesis. Hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF) are involved in tumor growth and metastases. The aim of this study was to evaluate the prognostic significances of the expressions of NF-κB, HIF-1α, and VEGF in stage III colorectal cancer.
Materials and Methods: The tumor tissues of 148 patients with stage III colorectal carcinoma that underwent potentially curative resection followed by postoperative adjuvant therapy were investigated immunohistochemically using monoclonal antibodies against NF-κB, HIF-1α, and VEGF. Clinical information, including tumor size, grades, vessel invasion, number of involved lymph nodes, carcinoembryonic antigen (CEA) levels, and disease-free survival and overall survival were evaluated with respect to the expressions of NF-κB, HIF-1α, and VEGF.
Results: Median follow-up duration was 53.2 months, and median patient age was 60±11 years (range 22−82). Positivity rates of NF-κB, HIF-1α, and VEGF were 52.7%, 47.3%, and 61.5%, respectively. NF-κB expression in tumor tissue was found to be significantly correlated with the expression of HIF-1α ($P < 0.001$), VEGF ($P = 0.044$), and presence of vessel invasion ($P = 0.013$). No relationships were found between the expressions of HIF-1α or VEGF and clinicopathologic variables. Univariate analysis showed that NF-κB expression was associated with poor 5-year overall survival (55.8 months vs. 76.9 months, $P = 0.012$). Multivariate analysis confirmed that NF-κB was independently associated with an adverse outcome (Relative risk: 1.59, $P = 0.049$). However, HIF-1α and VEGF were not found to be related to clinical outcome.
Conclusion: NF-κB expression in tumor tissue is associated with angiogenesis and a poor 5-year overall survival in stage III colorectal cancer patients.

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IVS10+12A>G polymorphism in hMSH2 gene associated with prognosis for patients with colorectal cancer

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Background: The polymorphisms in DNA repair genes may contribute to a variation in the DNA repair capacity, thereby affecting the risk of carcinogenesis and prognosis of colorectal cancer. Accordingly, the present study analyzed 14 polymorphisms in DNA repair genes and their impact on the prognosis for patients with colorectal cancer.
Materials and Methods: Three hundred and ninety-seven consecutive patients with curatively resected colorectal adenocarcinoma were enrolled in the present study. The genomic DNA was extracted from fresh colorectal tissue and 14 polymorphisms of DNA repair genes (XRCC1, hMSH2, ERCC2, ERCC4, VARS2[rs2074511, rs2249459], XPA, XPC, POLR2A, POLR2B, RFC1, RFC4, XAB2, DNMT3B) determined using a real-time PCR genotyping assay.
Results: The median age of the patients was 63 years (range, 21−85), and 218 (54.9%) patients had colon cancer, while 179 (45.1%) patients had rectal cancer. The pathologic stages after surgery were as follows: stage 0/I (n = 86, 21.7%), stage II (n = 146, 36.8%), stage III (n = 145, 36.5%), and stage IV (n = 20, 5.0%). A multivariate survival analysis, including age, differentiation, CEA level, and stage, revealed a better survival for the patients with the combined IVS10+12AG and GG genotype than for the patients with the IVS10+12AA genotype (disease-free survival [DFS]: hazard ratio [HR] = 0.47, 95% confidence interval [CI], 0.30−0.75, P = 0.002; overall survival [OS]: HR = 0.50, 95% CI, 0.26−0.98, P = 0.042). None of the other polymorphisms was associated with survival.
Conclusions: The IVS10+12A>G polymorphism in the *hMSH2* gene was found to be an independent prognostic marker for patients with colorectal cancer. Accordingly, in addition to the pathologic stage, an analysis of the IVS10+12A>G polymorphism in the *hMSH2* gene could help identify patient subgroups with a high risk of a poor disease outcome.

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S-1 enhances radiosensitivity in a mouse xenograft model of human colon cancer

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Background: Preoperative radiation therapy (XRT) with concurrent protracted venous infusion (PVI) 5-fluorouracil (5-FU) has become the standard of care for patients with locally advanced rectal cancer (LARC). Oral fluoropyrimidines have been developed as a therapeutic alternative to PVI 5-FU. S-1, a novel oral fluoropyrimidine, has demonstrated comparable therapeutic efficacy with UFT plus leucovorin (LV) in advanced colorectal cancer. In the present study, we compared the radiosensitization by S-1 with UFT or UFT/LV in a mouse xenograft model of human colon cancer.
Material and Methods: KM20C, human colon cancer cells, were implanted in the right hind leg of female BALC/cA-nu mice (N = 10 each group). Fractionated daily dose of 2 Gy was given to tumors on days 1−4 by 6MV X-rays locally. S-1 (5.7 mg/kg/day), UFT (13.9 mg/kg/day) and UFT (13.9 mg/kg/day)/LV (10 mg/kg/day) were administered orally 1 hr before irradiation for 2 consecutive weeks. Equitoxic doses of S-1 and UFT were selected. Tumor response to the treatment was assessed by calculating the tumor growth time (TGT), defined as the time required for the initial tumor volume to grow 5-fold after treatment. The growth delay (GD) was calculated by the formula: GD of each tumor = TGT (treated) of each tumor − average TGT (untreated). Synergy ratio was calculated by the following formula: (GD induced by combination treatment)/[(GD by chemotherapy) + (GD by XRT)]. A result greater than 1 indicates a greater than additive response. The GD produced by each treatment was analyzed by Mann-Whitney's U test. $P < 0.05$ was considered to denote statistical significance.
Results: With regard to GD by chemotherapy alone, there was no significant difference between S-1 and UFT/LV, although UFT/LV was demonstrated significantly greater GD than UFT. The GD by S-1+XRT was significantly greater than that by UFT/LV+XRT, but there was no significant difference between the GD by UFT/LV+XRT and that by UFT+XRT. The combination of S-1 plus XRT demonstrated a greater than additive