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Left-sided microsatellite unstable colorectal cancers show less frequent methylation of hMLH1 and CpG island methylator phenotype than right-sided ones

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Background: MSI colorectal cancer occurs in 10 to 20% of unselected series of patients with colorectal cancer. Somatic hMLH1 promoter methylation is reported to cause MSI in sporadic cases. Many researchers report that MSI colorectal cancers are more frequently located in the right-side colon than MSS colorectal cancers. Though the number is very small, some MSI colorectal cancers are located in the left-side colorectum. We focused on the existence of left-sided MSI colorectal cancers and investigated whether they arise through hMLH1 methylation as they do in right-sided ones.
Materials and Methods: Thirty-eight sporadic MSI colorectal cancers were included in the study. The methylation status of hMLH1, p16, MINT1, 2 and 31 were examined and the proportions of methylated samples for each locus were compared.
Results: The left-sided group showed significantly less frequent methylation in hMLH1, p16, MINT1, 2 and 31. The frequency of CIMP+ samples in the left-sided group was significantly lower than the right-sided group.
Conclusions: Left-sided MSI colorectal cancers show significantly less frequent methylation of hMLH1. They also showed significantly less frequent occurrence of CIMP+ than right-sided ones. It is possible that left-sided MSI colorectal cancers differ from the right-sided ones in the way of acquiring MSI.

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Flow cytometric determination of circulating endothelial cells in advanced colorectal cancer patients treated with bevacizumab-based combination therapy

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Background: Antiangiogenetic therapy is a promising approach to cancer treatment but, to date, no pharmacodynamic marker for its efficacy, easy to detect in clinical setting, has been validated. The flow cytometric (FCM) evaluation of circulating endothelial cells (CECs) and their progenitors (CEPs) has been proposed as a surrogate biological marker of angiogenesis because the well-known correlation with tumor angiogenetic activity and growth. CECs and CEPs blood concentrations in untreated cancer pts are significantly increased in comparison to healthy subjects, correlating with the tumor progression. Recent data suggest that their modification during antiangiogenetic therapy have a potential role as prognostic markers in breast cancer pts (Mancuso P, Blood 2006). No data are available on the effect of Bevacizumab-based first-line therapy on blood concentration of distinct population of CECs and CEPs in metastatic colorectal cancer (mCRC).
Material and Methods: We analyzed blood levels of CECs (resting and activated) and CEPs by a 4-colour FCM in 15 normal donors (M/F: 10/5, median age 37 yrs), in 5 mCRC pts treated with first-line chemotherapy (CT) (M/F: 1/4, median age 67 yrs) and in 8 mCRC pts receiving a fist-line therapy including Bevacizumab (M/F: 4/4, median age 56 yrs). Resting CECs were defined as negative for CD45 and CD106 and positive for CD34 and CD146. Activated CECs were defined as CD45−, CD34+, CD146+ and CD 106+ cell. CEPs were depicted by the expression of the stem cell marker CD133.
Results: With respect to normal donors, mCRC pts treated with CT alone in first-line setting show a decrease of absolute number of the two CEC subsets and of the CEPs. At the same time, Bevacizumab-based therapy correlates with a trend toward the increase of CEPs and CECs, especially in activated subsets, in comparison to mCRC pts treated with CT alone. No statistically significant correlation was found between this trend and the number of antiangiogenetic treatment courses administered.
Conclusions: We suggest that the determination of CECs and CEPs by FCM could be an effective and rapid method for monitoring the clinical impact of antiangiogenetic therapies in mCRC pts.

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Optimal dose for an every 2 week (q2w) cetuximab (C) regimen in patients (pts) with metastatic colorectal cancer (mCRC): a phase I safety, pharmacokinetics (PK) and pharmacodynamics (PD) study of weekly (q1w) and q2w schedules

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Background: This study compared the safety, PK and PD of a q2w schedule of cetuximab (Erbitux®) with the approved q1w regimen in pts with EGFR-expressing mCRC.
Methods: C was given first-line to 13 pts in Group A (control; 400 mg/m^2 initial dose then 250 mg/m^2/week). In Group B (experimental), 38 pts received C q2w: 10 pts each at 400, 500, 600; 8 pts at 700 mg/m^2). Doses were escalated in the absence of dose-limiting toxicities (DLTs: Grade [Gr] 3/4 toxicities, except for hypersensitivity reactions, Gr3 skin toxicity, and/or <66% of the assigned dose due to toxicity). Complete PK profiles for 6w treatment with single-agent C were obtained for all groups. FOLFIRI (irinotecan/5-FU/FA) was then added. Skin and tumor biopsies obtained before therapy and on day 28 were analyzed for EGFR signaling, proliferation and apoptosis by IHC. Plasma samples and tumor biopsies were analyzed for protein and gene expression.
Preliminary results: 51 pts have been included. One DLT (Gr4 dyspnea) was reported at 700 mg/m^2. The safety profiles from all groups were similar. PK parameters ($t_{1/2}$, CL_{ss}) from the q2w (400–600 mg/m^2) regimens are in the range of data from the weekly group. Trough levels for 500 and 600 mg/m^2 q2w regimens and the weekly regimen are comparable, whereas levels for 700 mg/m^2 are considerably higher. PD data in skin show significant changes in pEGFR, pMAPK, Ki67, p27 and pSTAT3 with no major differences between the different C schedules. Biomarker analysis in tumor is ongoing.

Response

Cetuximab dose	Group A, control: weekly	Group B, experimental: every 2 weeks	
	250 mg/m^2 (n = 13)	400 mg/m^2 (n = 10)	500 mg/m^2 (n = 10)
Best overall response, n (%)			
Partial response (PR)	4 (31)	5 (50)	4 (40)
Stable disease (SD)	7 (54)	5 (50)	6 (60)
Progressive disease (PD)	2 (15)	0	0
Overall response rate (CR+PR), % [95% CI]	31 [9.1, 61.4]	50 [18.7, 81.3]	40 [12.2, 73.8]
Disease control rate (CR+PR+SD), % [95% CI]	85 [54.5, 98.1]	100 [69.2, 100]	100 [69.2, 100]

Response data for 600 mg/m^2 and 700 mg/m^2 groups are not yet available
Conclusions: Cetuximab can be safely administered in a q2w regimen from 400–700 mg/m^2. The MTD of q2w cetuximab has not been reached. Available overall response rates in the q2w regimens (400 and 500) and weekly are comparable. Trough level PK data for 500 and 600 mg/m^2 q2w regimens and the weekly regimen are in the same range, whereas levels for 700 mg/m^2 are considerably higher. Based on these data, cetuximab 500 mg/m^2 q2w may be an alternative and convenient dose and schedule of administration.

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Alpha(1,6)fucosyltransferase immunohistochemical expression and the survival of patients with colorectal cancer

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Increased levels of fucose residues and changes in fucosylation patterns, as a result of the different expression of various fucosyltransferases, act as specific markers in several tumour processes. For example, in human ovarian serous adenocarcinomas, both α(1,6)fucosyltransferase [α(1,6)FT]