Monitoring tumoral circulating DNA (ctDNA) plasma-derived from patients with metastatic colorectal cancer

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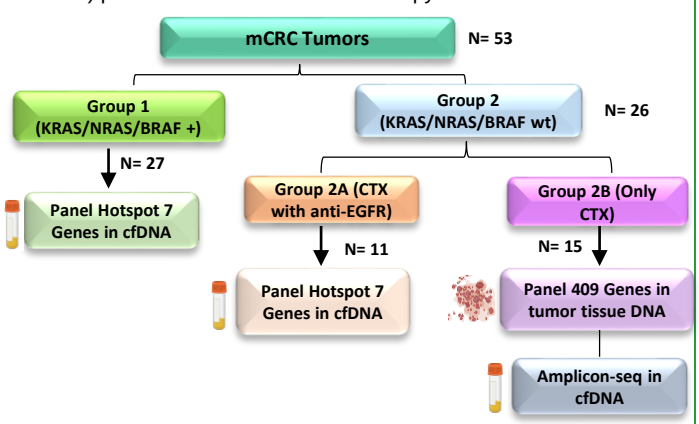
Introduction

Half of metastatic colorectal cancer (mCRC) harbors activated mutations in *KRAS/NRAS* that leads to the constitutive activation on MAP kinase pathway, which, in turn, is one of the mechanisms involved in anti-EGFR therapy resistance. Patients with wild type (WT) *KRAS/NRAS* tumors are eligible to anti-EGFR treatment while patients with mutated *KRAS/NRAS* tumors are not. Patients treated with anti-EGFR may show acquired resistance to EGFR inhibitors and one of the mechanisms involved is activated mutation in RAS genes. Circulating tumor DNA (ctDNA) has been widely used to monitor the treatment response and also to investigate mechanisms of resistance to therapy.

Objective: To evaluate the presence of specific-tumor mutations in cell-free DNA (cfDNA) in plasma of patients with mCRC under treatment.

Methods

The mCRC patients were divided in 2 groups: 1) tumors with KRAS/NRAS/BRAF activated mutations and 2) wild-type (WT) tumors. Patients of group 2 were divided in two groups: 2A) patients treated with anti-EGFR (Cetuximab) associate with chemotherapy and 2B) patients treated with chemotherapy.

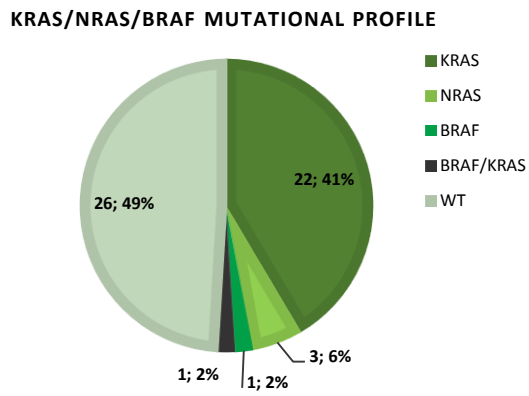


The ctDNA analysis was performed using a customized deep-amplicon sequencing approach using NGS (Next Generation Sequencing) in the Ion S5 platform (Thermo Fischer). The plasma samples were collected before initiation (baseline) and during treatment (monitoring).

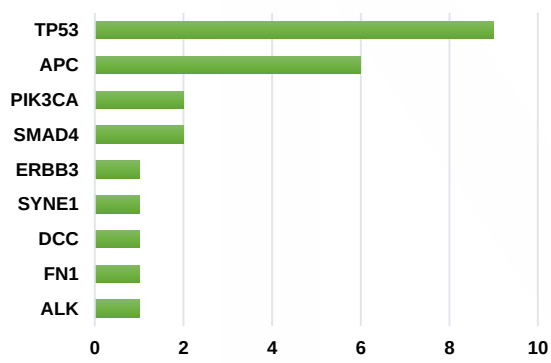
Results

A total of 53 patients were included in this study, 27 in the group 1 and 26 in the group 2. In the group 1, 81% (22/27) of tumor samples had activated mutation in *KRAS*, 11% *NRAS* (3/27), 4% in *BRAF* (1/27) and 4% in both *KRAS* and *BRAF* (1/27) genes. In the group 2 (WT-tumors), 11 and 15 patients were included in the 2A (treated with Cetuximab and chemotherapy) and 2B (treated with chemotherapy only), respectively.

Results



Regarding the tumor samples of the group 2B we used a somatic gene panel contaning 409 cancer genes and in 73% cases (11/15) at least a tumor specific mutation was detected. The most frequent gene was *TP53* found in 60% cases (9/15) followed by *APC* found in 40% (6/15), as shown in the figure below:



Regarding ctDNA analysis on baseline plasma samples, in the group 1 55% (15/27) of cases were ctDNA positive, while on the group 2B only 18% (2/11) was ctDNA positive. During monitoring period of treatment, in the interval from 3 to 6 months, in the group 1, positive ctDNA was detected in 36% (8/22) and in Group 2B in the 53% (7/13) of patients. In the interval from 9 to 15 months, in group 1, positive ctDNA was detected 73% (15/21) of patients while in group 2B positive ctDNA was detected 46% (6/13). Patients of group 2A in which RAS/RAF activated mutations were tracked as resistance mechanisms no positive ctDNA was found neither in the baseline plasma nor in both intervals.

Conclusions

Positive ctDNA was more frequent in mCRC patients with tumors with MAP kinase-activated tumors than in those with MAP kinase-non-activated tumors. No mCRC patients in the 2A group exhibited RAS mutations as a marker of acquired resistance to the anti-EGFR therapy in the period of 15 months in concordance with their clinical performance.

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