Comparison of interphase fluorescence in situ hybridization and SNP array analysis for the assessment of ERBB family gene copy numbers in colorectal cancer

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The introduction of monoclonal antibodies (mAbs) against epidermal growth factor receptor (EGFR) in the therapy for metastatic colorectal cancer (CRC) prompted to search for predictive biomarkers. The lack of efficacy of anti-EGFR therapy in tumors bearing activating KRAS mutations has been well-demonstrated in clinical trials and the European Medicines Agency approved the use of mAbs against EGFR only in metastatic CRC patients with wild-type KRAS tumors. However, the absence of KRAS mutations is not sufficient to assure a clinical response and only a fraction of patients with wild-type KRAS show a good response to such therapies. Recent studies indicated that EGFR gene copy number could influence response to anti-EGFR mAbs therapy in CRC. In the majority of these studies EGFR genomic gain was assessed by fluorescence in situ hybridization (FISH). The introduction of SNP array technology for genome-wide analysis of tumor-associated cytogenetic abnormalities and the proposal of its routine use in CRC (Castorina et al. 2010) provide an alternative method for the determination of EGFR copy number and extend such analysis to all members of the ERBB family. Here we assessed copy number data for EGFR and ERBB2 gene in a series of 42 CRC by interphase FISH and SNP array analysis. 50% and 52% of the patients showed an increase of EGFR copy number by FISH analysis ($\geq$ 2.1 average hybridization signal per nucleus) and SNP array (log2ratio $\geq$2.2), respectively. As clarified by SNP array analysis, such increase was due to a polisomy of chromosome 7 (19 out of 42) or of its p arm (3 out of 42). 5 cases showed discrepant results between FISH and SNP array analysis (3 with increased copy number by SNP array not detected by FISH and 2 with EGFR genomic gain by FISH not detected by SNP array). A good correlation was also observed comparing the EFGR copy number values obtained with the two methods (r=0.67) which further increased by applying a correction values based on the percentage of tumoral cells in the samples used for SNP array analysis (r= 0.73). No amplification of EGFR genes was detected by FISH analysis (defined as a EGFR/CEN7 ratio >2), while only one case was detected by SNP array analysis (range 3.59-10.51 gene copies in different zones of the same tumor).

Reference

Castorina S et al. (2010) Recent advances in molecular diagnostics of colorectal cancer by genomic arrays: proposal for a procedural shift in biological sampling and pathological report. J. Anatomy (in press)