CPG ISLAND METHYLATOR PHENOTYPE IS ASSOCIATED WITH THE EFFICACY OF CHEMOTHERAPY IN PATIENTS WITH METASTATIC COLORECTAL CANCER

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Aim: The CpG island methylator phenotype (CIMP) with multiple promoter methylated loci has been widely observed in human colorectal cancer (CRC). However, the effect of CIMP status on the efficacy of standard chemotherapy is not fully known. Although CIMP-positive status is known to be associated with BRAF mutation, the relationship between CIMP and mutations in other genes in the epidermal growth factor receptor (EGFR) associated signal transduction such as PIK3CA, NRAS, and AKT1 have not been clarified. Then, we analyzed the relationship among CIMP, EGFR related gene mutation, and the response to chemotherapies.

Methods: In 125 metastatic colorectal cancer (mCRC) patients, we analyzed the relationship between CIMP status detected by methylaton-specific PCR in the five locus (CACNAG, IGF2, NEUROG1, RUNX3, and SOCS1) and clinical outcome of the standard chemotherapies, genetic status in 5 EGFR-related genes (KRAS, BRAF, PIK3CA, NRAS, and AKT1) detected by direct sequencing in the hotspot mutation regions.

Results: CIMP-positive status was significantly associated with proximal tumor location, lung and peritoneum metastasis (all p values < 0.05). The progression free survival (PFS) of the sequential first- and second-line therapy with irinotecan-based regimen followed by FOLFOX (median = 15.2 months) was superior to the reverse sequence; FOLFIRI followed by irinotecan - based regimen (median = 6.6 months) in CIMP - positive tumors (p = 0.043). However, the PFS of irinotecan-based regimen followed by FOLFOX and the reverse sequence in CIMP-negative tumors have not shown any significant difference (median: 16.1 months vs. 16.3 months, p = 0.69).

Furthermore, CIMP-positive tumors showed higher frequency of mutation in any of 5 genes related EGFR signal transduction (74.9%) than CIMP-negative tumors (48.0%)

Conclusions: Sequential irinotecan-based regimen followed by FOLFOX is more favorable for CIMP-positive tumors than the reverse sequence. However, the sequential order of chemotherapies did not make difference in CIMP-negative tumors. In addition, CIMP-positive tumors have high frequency of mutation in EGFR related genes.

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