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Point Mutation and Potential Biomarker of the Gene Coding for KRAS/RAS in Patients with Colorectal Carcinoma

Yasuna KOBAYASHI

Department of Pharmacology and Therapeutics, Niigata University of Pharmacy and Applied Life Sciences, 265-1 Higashijima, Akiha-ku, Niigata City, Niigata 956-8603, Japan (yasuna@nupals.ac.jp)

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Wisdom (Philosophical) Note:
As I was passing ...

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It is well-known that *KRAS* (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog*)/RAS* (rat sarcoma viral oncogene homolog) is an essential molecular target of the Ras/Raf/mitogen-activated protein kinase pathway. In chemotherapy treatment for patients with metastatic colorectal carcinoma, gene-coding for *KRAS/RAS* mutation(s) is known not only as a potential prognostic biomarker but also as a predictive factor for the efficacy of anti-epidermal growth factor receptors (EGFR) such as cetuximab. Although such phenomena are not observed in the treatment of anti-vascular endothelial growth factor receptor (VEGFR), the activation of Ras/Raf/mitogen mutation requires oncogenic mutations that produce a constitutively active protein. About 50-60% of Japanese metastatic colorectal cancer (MSC) patients do not have a KRAS/RAS mutation, and patients carrying the KRAS/RAS wild-type gene benefit from efficacy of anti-EGFR chemotherapy. In addition, the potential benefits from anti-EGFR chemotherapy (cetuximuab treatment) combined with FOLFOX and/or FOLFIRI in metastatic colorectal cancer patients with resectable stage-III are suggested by some findings that the three-year disease-free survival rate in patients with wild-type KRAS/RAS was significantly longer than that patients harboring KRAS/RAS mutations. In this respect, current pivotal two large world-wide clinical trials, FIRE-3 and CALGB/SWOG80405, have also clearly demonstrated and supported the observation that overall survival in MSC patients carrying KRAS/RAS wild-type lasts over 30 months, whereas those carrying KRAS/RAS mutation exhibit a shorter overall survival period. However, some clinical trials have demonstrated that KRAS/RAS mutations do not have a major prognostic biomarker regarding overall sur-

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vival and recurrence-free survival. Although in the treatment strategy of MSC, if the metastatic portion(s) is resectable, metastatectomy is strongly recommended because surgery is potentially the most effective approach for MSC control in these patients.

The most frequent mutations of the *KRAS/RAS* gene occur in Codons 12 and 13, and recent studies have demonstrated that MCS patients carrying KRAS G13D (Gly13Asp) mutation genes are most likely to respond better to cetuximab treatment when compared with those carrying other KRAS mutations. In addition to KRAS/RAS mutations, other point-mutations in the gene-coding for BRAF (v-Raf murine sarcoma viral oncogene homolog B), and PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase) are also known to be potential biomarkers in response to the anti-EGFR antibody therapy. Thus, point-mutation(s) in the signal pathway of cancer cells, such as KRAS/BRAF/PIK3CA, is reported to be an effective biomarker for anti-EGFR chemotherapy. Therefore, these gene-mutations should be checked before starting chemotherapy to improve the quality-of-life in colorectal cancer patients.