Gastrointestinal tumours

Mutations of KRAS/NRAS/BRAF in cetuximab-resistant metastatic CRC patients

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Aim/Background: Although patients with metastatic colorectal cancer (mCRC) bearing KRAS-exon2-wild-type could benefit from cetuximab treatment, ~45% of these patients were refractory to such a therapy. This study aims to identify additional genetic markers that can enhance the prediction of the cetuximab treatment response.

Methods: 53 mCRC patients with wild-type KRAS exon2 were treated with cetuximab/irinotecan-based chemotherapy in first-line or third-line setting. Formalin-fixed paraffin-embedded samples obtained from primary tumor of all subjects were analyzed for the mutational status of 10 genes in the EGFR pathway using next-generation sequencing technology.

Results: We detected KRAS (exon 3 and 4) mutations in 5 patients, NRAS mutations in 4 patients, and BRAF mutations in 6 patients. Except for 1 patient with an NRAS mutation who was a responder, all other patients harboring KRAS, NRAS, or BRAF mutations are non-responders, indicating the predictive role of these genetic mutations for poor cetuximab responsiveness. The Kaplan-Mirer analysis revealed that patients with KRAS or BRAF mutations have a significantly shorter progression-free survival.

Conclusions: Our results suggest that genetic testing for KRAS in combination with NRAS and BRAF provides a stronger predictive power and should be implemented to improve the response rate of cetuximab for mCRC patients.

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