GENETICS

TP53 mutations predict response to cetuximab

The use of anti-EGFR antibodies, such as cetuximab, has led to considerable improvements in the survival of patients with metastatic colorectal cancer in the past decade. Three principles are thought to underlie the effectiveness of anti-EGFR therapy. First, activation of the EGFR pathway mediates tumorigenesis, possibly as a result of overexpression of EGFR ligands, and so inhibition of this pathway would be an effective antitumor strategy. Second, the presence of *KRAS* mutations has been linked to cetuximab resistance, which suggests that activation of a downstream EGFR effector does not activate the EGFR pathway. Third, studies have shown that if the p53 protein is inactivated this can lead to malignant transformation via oncogenic activation of the EGFR pathway. These observations led Oden-Gangloff and coauthors to investigate the effect of *KRAS* and *TP53* status on response to cetuximab-based chemotherapy in patients with metastatic colorectal cancer. “One of the critical questions in the field of targeted therapies

used in metastatic colorectal cancer is the identification of markers of sensitivity or resistance. Since the validation of *KRAS* mutations as markers of resistance to anti-EGFR antibodies, the next challenge is the identification of markers of resistance in patients without *KRAS* mutations,” the authors said. They hypothesized that patients with *TP53* mutations but without *KRAS* mutations would be more sensitive to cetuximab therapy.

Oden-Gangloff and colleagues assessed tumor tissue from 64 patients with chemotherapy-refractory metastatic colorectal cancer who were treated with cetuximab-based chemotherapy. *KRAS* mutation analysis was performed on all samples from patients and direct sequencing was used to detect *TP53* mutations.

The results showed that 39 patients had controlled disease (defined as complete response, partial response or stable disease) and 25 had progressive disease after cetuximab-based chemotherapy. The median time to progression in patients with controlled disease was 24 weeks, compared with 12 weeks in patients with progressive disease ($P < 0.0001$). A total of 18 patients had a *KRAS* mutation, and none of the patients who had a complete or partial response to treatment had a *KRAS* mutation. A significant association between *KRAS* mutation in patients with progressive disease compared to those with stable disease was noted. Patients with *KRAS* mutations had a significantly lower median time to progression compared with patients with the wild-type gene ($P = 0.034$).

TP53 mutations were seen in 41 out of 64 patients. Of the 39 patients with controlled disease, a *TP53* mutation was detected in 29 patients. This mutation was detected in 12 of the 25 patients with progressive disease, which demonstrates a significant association between *TP53* mutational status and clinical outcome ($P = 0.037$). Furthermore, patients with a *TP53* mutation had a considerably increased median time to progression compared to those without such a mutation ($P = 0.004$).

“...*TP53* and *KRAS* mutational status were found to be independent predictive factors of time to progression.”

The investigators separately analyzed data from the 46 patients who did not have a *KRAS* mutation and found that 30 of these patients had a *TP53* mutation. In patients who did not have a *KRAS* mutation, patients with a *TP53* mutation had a significantly longer time to progression compared to those without the mutation (24 versus 12 weeks, $P = 0.0007$). When the investigators assessed the subgroup of patients with the *KRAS* mutation they found no difference in median time to progression between patients with or without the *TP53* mutation. On multivariate analysis, *TP53* and *KRAS* mutational status were found to be independent predictive factors of time to progression.

The authors commented, “the association that we report between *TP53* mutations and better clinical outcome may [seem] unexpected because in colorectal cancer most studies have shown that *TP53* mutations are associated with a worse prognosis in patients with stage II–III colorectal cancer.” The results of this study suggest that inactivation of *TP53* could be a means of *EGFR* activation and this relationship should be investigated further. *TP53* genotyping could have clinical applications to predict which patients with metastatic colorectal cancer who lack a *KRAS* mutation are most likely to benefit from anti-EGFR therapy. Further studies in larger groups of patients are needed to confirm these findings.

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