Enhanced treatment, surveillance needed for certain melanoma patients to prevent secondary cancers

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Moffitt Cancer Center researchers suggest secondary cancers seen in melanoma patients who are being treated for a BRAF gene mutation may require new strategies, such as enhanced surveillance and combining BRAF-inhibitor therapy with other inhibitors, especially as they become more widely used. They discussed this topic in a review article that appears in the July issue of *Nature Reviews Clinical Oncology*.

The BRAF gene is mutated in about half of all cases of melanoma, as well as other cancers, and the mutant protein can be successfully deactivated by BRAF inhibitor drugs. The development and therapeutic use of BRAF inhibitors to treat patients in advanced stages of BRAF-mutant melanoma is a prime example of a successful targeted therapy. Inhibiting the mutant BRAF protein causes the tumor to shrink. FDA-approved BRAF inhibitors are widely used in metastatic melanoma with much success, and their use is expanding to other tumor types and is being tested in earlier stages of melanoma.

However, a type of cellular signaling caused by the BRAF inhibitors may leave patients susceptible to secondary malignancies, such as squamous cell carcinoma and RAS-mutant leukemia.

"These secondary cancers emerge because BRAF inhibitors can activate tumor growth pathways in cells with genetic changes," explained co-author Keiran S. Smalley, Ph.D., assistant member of the Cancer

Biology and Evolution Program at Moffitt. "When the BRAF inhibitor signaling activates a biological pathway called MAPK (mitogen-activated protein kinases), secondary cancers can emerge."

The researchers call the development of secondary cancers a case of paradoxical activation.

"The paradoxical activation of MAPK signaling was an unexpected observation that emerged as BRAF inhibitors were being developed," said co-author Geoffrey T. Gibney, M.D., assistant member of the Chemical Biology and Molecular Medicine Program at Moffitt. "Combination therapies using BRAF inhibitors and other inhibitors are being considered to prevent paradoxical activation of MAPK pathways."

A possible combination therapy to lessen the risk of paradoxical activation and the emergence of secondary malignancies is combining BRAF inhibitors with other inhibitors. One option is an MEK inhibitor, which inhibits the mitogen-activated protein kinase enzymes used to therapeutically affect the MAPK pathway that is often overactive in cancers. However, this combination does not eliminate all secondary cancers.

The researchers note that extended follow-up for patients showing long-term responses to BRAF inhibitors has often been lacking. They also added that BRAF-mutant melanoma patients with a family history of colorectal cancer may require more than the usual screening if BRAF-inhibitor therapy is necessary.

"Despite the concerns, the development of BRAF inhibitors is a major milestone in treating patients with BRAF-mutant melanoma," concluded study co-author Vernon K. Sondak, M.D., chair of the Cutaneous Oncology Program at Moffitt. "With surveillance and carefully designed drug combinations, the future for patients with BRAF-mutant melanoma

and other malignancies looks increasingly optimistic."

More information: www.nature.com/nrclinonc/journ … rclinonc.2013.83.pdf

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