予期せぬMEK1変異はメラノーマの薬剤耐性の原因ではない

BRAF変異メラノーマはMEK1変異が共存していてもBRAF阻害薬が有効であった

Patients with BRAF-mutant melanomas responded to BRAF inhibitor despite a concurrent MEK1 mutation

BRAF変異メラノーマの治療を受ける患者においてMEK1の遺伝子変異は、この遺伝子変異が治療抵抗性の原因である可能性があるとの現在の見解に反し、BRAF阻害薬の有効性を阻害しない。この革新的な研究は2012年AACR学会で発表されCancer Discoveryプリント版に先立ちオンラインで掲載された。BRAF変異はメラノーマの50%以上において認められる。BRAF阻害薬は約60%の患者において抗腫瘍反応を誘発し得る。したがって一部の腫瘍は初期の時点で薬剤耐性であり、最初は薬剤が有効であった患者でも薬剤耐性を獲得し得る。研究者らは、メラノーマを有しBRAF阻害薬で治療されている31人の腫瘍標本を分析した。これらのうち、16%が治療前から腫瘍内にBRAFとMEK1変異の両者を有していた。2重にBRAF/MEK1変異を有する患者の5人中3人の腫瘍はBRAF阻害薬が有効である。研究者らは、実験室で培養したメラノーマの細胞株を使用してこの結果を実証した。BRAF変異メラノーマおよびBRAFとMEK1の変異を有するメラノーマはBRAF阻害薬またはBRAF阻害薬とMEK1阻害薬の併用の有効性が同等であり得る、と筆者らは結論付けている。

Full Text

A genetic mutation in MEK1 does not prevent response to BRAF inhibitors in patients undergoing treatment for BRAF-mutated melanomas, contrary to current thought that the gene mutations might have been a cause of resistance.

This groundbreaking research was presented at the AACR Annual Meeting 2012 and published online ahead of print in Cancer Discovery.

BRAF mutations are found in more than 50 percent of melanomas. BRAF inhibitors can induce an antitumor response in about 60 percent of patients. Thus, a subset of tumors is drug resistant at the outset, and those patients who first responded can go on to develop resistance to the drugs.

“Another gene, known as MEK1, is rarely mutated in cancers, but in this study, we found to our surprise that mutated MEK1 was frequently associated with BRAF mutations,” said Roger S. Lo, M.D., Ph.D., assistant professor of medicine/dermatology at University of California, Los Angeles Jonsson Comprehensive Cancer Center in Los Angeles, Calif.

To explore the association between MEK1 and BRAF, Lo and colleagues analyzed tumor samples from 31 patients with melanoma treated with a BRAF inhibitor. Of these patients, 16 percent carried both BRAF and MEK1 mutations in tumors before drug treatment.

“Based on the current state of knowledge, the presence of both mutated MEK1 and mutated BRAF is thought to be a biomarker for BRAF inhibitor resistance in melanomas,” Lo said. “However, we were surprised again when we found that patients with double BRAF/MEK1-mutated melanomas can respond to BRAF inhibitors as well as patients with single BRAF-mutated melanomas.”

Specifically, three of five patients with double BRAF/MEK1-mutated melanomas had a tumor response to the BRAF inhibitors. Lo and colleagues further verified these conclusions using melanoma cell lines grown in the laboratory.

“These findings tell oncologists that these two groups of patients — those patients with BRAF-mutated melanomas and those with BRAF and MEK1-mutated melanomas — can be expected to respond similarly well to BRAF inhibitors or the combination of BRAF inhibitors plus MEK inhibitors,” Lo said.

Despite the fact that MEK1 is not a cause of BRAF inhibitor resistance, Lo and colleagues will continue to explore why BRAF and MEK mutations coexist in the same tumor to find novel ways to weaken tumors with both mutations. In addition, other possible causes for ongoing BRAF inhibitor resistance still need to be uncovered.

“We are pushing forward to uncover biomarkers of BRAF inhibitor sensitivity or resistance and hope to use them as a guide to formulate therapeutic strategies,” Lo said.

The research was funded by Stand Up To Cancer and exemplifies Stand Up To Cancer’s unique research model, according to Lo.

“It places strong emphasis on the study of human cancer tissues, on knowledge generation that will help patients with cancer today and on the power of collaboration that can accelerate both aforementioned points,” he said.

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