MedicalXpress

# Researchers find potential solution to melanoma's resistance to vemurafenib

February 28 2012

Researchers at Moffitt Cancer Center in Tampa, Fla., and colleagues in California have found that the XL888 inhibitor can prevent resistance to the chemotherapy drug vemurafenib, commonly used for treating patients with melanoma.

Vemurafenib resistance is characterized by a diminished apoptosis (programmed cancer cell death) response. According to the researchers, the balance between apoptosis and cell survival is regulated by a family of proteins. The survival of melanoma cells is controlled, in part, by an anti-apoptotic protein (Mcl-1) that is regulated by a particular kind of inhibitor.

Their current findings, tested in six different models of vemurafenib resistance and in both test tube studies and in melanoma patients, demonstrated an induced apoptosis response and tumor regression when the XL888 inhibitor restored the effectiveness of vemurafenib.

The study appeared in a recent issue of Clinical Cancer Research, a publication of the American Association for Cancer Research.

"The impressive clinical response of melanoma patients to vemurafenib has been limited by drug resistance, a considerable challenge for which no management strategies previously existed," said study co-author Keiran S. M. Smalley, Ph.D., of Moffitt's departments of Molecular Oncology and Cutaneous Oncology. "However, we have demonstrated for the first time that the heat shock protein-90 (HSP90) inhibitor

XL888 overcomes resistance through a number of mechanisms."

The diversity of resistance mechanism has been expected to complicate the design of future clinical trials to prevent or treat resistance to inhibitors such as vemurafenib.

"That expectation led us to hypothesize that inhibitor resistance might best be managed through broadly targeted strategies that inhibit multiple pathways simultaneously," explained Smalley.

The HSP90 family was known to maintain cancer cells by regulating cancer cells, making it a good target for treatment. According to the authors, the combination of vemurafenib and XL888 overcame vemurafenib resistance by targeting HSP90 through multiple signaling pathways.

There was already evidence that HSP90 inhibitors could overcome multiple drug chemotherapy resistance mechanisms in a number of cancers, including non-small lung cancer and breast cancer. Because XL888 is a novel, orally available inhibitor of HSP90, the researchers hoped that it would arrest the cancer cell cycle in melanoma cell lines.

In their study, the inhibition of HSP90 led to the degradation of the anti-apoptopiuc Mcl-1 protein. The responses to XL888 were characterized as "highly durable with no resistant colonies emerging following four weeks of continuous drug treatment." In other studies not using XL888, resistant colonies "emerged in every case," they reported.

"We have shown for the first time that all of the signaling proteins implicated in vemurafenib resistance are 'clients' of HSP90 and that inhibition of HSP90 can restore sensitivity to vemurafenib," concluded Smalley and his colleagues. "Our study provides the rationale for the dual targeting of HSP90 with XL888 and vemurafenib in treating

melanoma patients in order to limit or prevent chemotherapy resistance."

Provided by H. Lee Moffitt Cancer Center & Research Institute