Combination Therapy: Why Timing Might Be Everything

"This may be the solution to many problems," says researcher Rizwan Haq, MD, PhD.

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By Rachel Fischer, PhD, senior associate, Scientific Program and Grants Administration

About half of all melanomas have a mutated BRAF gene. This mutated gene makes an altered BRAF protein, which leads to the uncontrolled growth of melanoma cells. Drugs targeting these altered BRAF proteins, such as Vemurafenib and Dabrafenib have been approved for the treatment of BRAF+ melanoma. However, many melanomas quickly develop resistance to these drugs by increasing the activity of the protein MEK. To fight this, researchers added a drug that targets MEK to the BRAF inhibitors, creating what we call targeted therapy combinations, such as dabrafenib (Tafinlar) + trametinib (Mekinist), vemurafenib (Zelboraf) + cobimetinib (Cotellic), and encorafenib (Braftovi) + binimetinib (Mektovi). However, many patients experience only partial responses (shrinking or slowing the growth of tumors), or initially respond only to have their tumors develop resistance over time.

MRA funded investigator Rizwan Haq, MD, PhD, is working to understand how melanoma cells develop a resistance to BRAF/MEK inhibitors and to develop novel combinations of therapies to overcome resistance in patients. Haq is an assistant professor of medicine at Harvard Medical School, and principal investigator at the Dana-Farber Cancer Institute.

"My lab is very interested in understanding why current therapies stop working, when they do [work], and why they stop working in some patients but not others," said Haq. "BRAF/MEK inhibitors have shown tremendous success in the short term in controlling melanoma, but they [often] stop working after some period of time."

Researchers have observed that these drugs work by stopping melanoma cells from dividing—meaning they cannot continue to grow and create new cancerous cells. However, BRAF/MEK inhibitors generally do not do a good job of actually killing melanoma cells. Haq's research focuses on understanding why melanoma cells don't die after treatment with combination BRAF/MEK inhibition, in the hopes that this will help in developing more effective therapies.

Melanoma cells die through multiple cellular processes, each involving different proteins that each signal or regulate how and when a cell should die. The focus of Haq's most recent paper published

in Nature Communications is on understanding which specific gene or protein in a melanoma cell protects it from dying in response to treatment with combination targeted therapy. Haq and his team, along with collaborators at Massachusetts General Hospital, found that one particular protein, called MCL-1, is crucial for protecting melanoma cells from dying. Several early stage clinical trials are already underway to determine if MCL-1 inhibitors are effective in patients with blood cancers. However, MCL-1 inhibitors haven't proven particularly effective in killing solid tumors, such as melanoma, on their own, indicating a need for improved therapeutic combinations.

"When a cell is treated with a BRAF/MEK inhibitor, it generates a dependence on the MCL-1 protein," explained Haq. "Practically, what that means is that if you wanted to combine a BRAF/MEK inhibitor with an MCL-1 inhibitor, the ideal way of doing that would be to treat first with the BRAF/MEK inhibitor and after the melanoma cell becomes dependent on MCL-1, then treat with the MCL-1 inhibitor. When we do that in cells or mice, we very strongly see that the sequence of drug combinations is significantly better than the opposite [order], or [either of] the drugs alone."

The results of this research are very promising, and offer hope that dual BRAF/MEK combination therapy could be augmented with the addition of an MCL-1 inhibitor. In addition to the increased effectiveness of initial treatment, this combination also shows promise delaying the recurrence of tumors after discontinuing treatment.

In his study, mice with melanoma tumors who were treated with a BRAF inhibitor until they developed a dependence on the MCL-1 protein were then treated with an MCL-1 inhibitor for 14 days. This protocol successfully shrinks tumors and, in some cases, completely eradicated them. Haq continued to monitor the mice after the treatment was discontinued and, to his surprise, several mice had no tumor recurrence.

"One doesn't expect those kinds of durable responses with targeted therapies. In fact, that's one of the biggest limitations with using targeted therapies is that they [often] stop working after a period of time," said Haq.

Haq is currently working with several pharmaceutical companies who are already developing MCL-1 inhibitors to promote the concept of combining — in the proper sequence — MCL-1 inhibitors with other targeted therapies in early-stage clinical trials. He believes the biggest takeaway from his recent paper is that the timing of delivery of these drugs is critically important to their combined efficacy. He also believes this approach could be useful with other types of cancer based on early tests.

"This may be the solution to many problems. I hope that this paper has peaked the interest of pharmaceutical companies in thinking about MCL-1 inhibitors in melanoma and other solid tumors," says Haq.

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