Cancer therapy that boosts immune system ready for wider testing

2 June 2012

Two clinical trials led by Johns Hopkins Kimmel Cancer Center researchers in collaboration with other medical centers, testing experimental drugs aimed at restoring the immune system's ability to spot and attack cancer, have shown promising early results in patients with advanced non-small cell lung cancer, melanoma, and kidney cancer. More than 500 patients were treated in the studies of two drugs that target the same immune-suppressive pathway, and the investigators say there is enough evidence to support wider testing in larger groups of patients.

Results of the Phase I clinical trials will be published online June 2 in the New England Journal of Medicine and presented at the 2012 Annual Meeting of the American Society of Clinical Oncology (Abstracts #2509 and #2510).

"Based on the positive response rates to these drugs and longevity of many of these responses, we believe that new clinical trials should move forward," says Suzanne Topalian, M.D., professor of surgery and oncology at Johns Hopkins. Preliminary analysis shows that, among responding patients who were followed for more than one year, responses were maintained for more than one year in two-thirds of those treated on one trial and in half of those in the other trial.

The immune-based therapies tested in the two clinical trials, both made by Bristol-Myers Squibb, aim not to kill cancer cells directly, but to block a pathway that shields tumor cells from immune system components able and poised to fight cancer.

The pathway includes two proteins called programmed death-1 (PD-1), expressed on the surface of immune cells, and programmed death ligand-1 (PD-L1), expressed on cancer cells. When PD-1 and PD-L1 join together, they form a biochemical "shield" protecting tumor cells from being destroyed by the immune system. Another protein involved in the pathway and also expressed by cells in the immune system, programmed death ligand -2 (PD-L2), was originally discovered by Johns Hopkins investigators.

To make cancer cells more vulnerable to attack by the immune system, investigators tested each of two drugs -- BMS-936558, which blocks PD-1, and BMS-936559, which blocks PD-L1 -- in separate clinical trials conducted at multiple U.S. hospitals. The drugs are given intravenously in an outpatient clinic every two weeks, and patients can remain on the treatment for up to two years.

The PD-1 blocking drug was tested in 296 patients with various advanced cancers who had not responded to standard therapies. Of those patients receiving the anti-PD-1 therapy, 240 who started treatment by July 2011 were analyzed for tumor response. Significant tumor shrinkage was seen in 14 of 76 (18 percent) non-small cell lung cancer patients, 26 of 94 (28 percent) melanoma patients and nine of 33 (27 percent) kidney cancer patients.

In this trial, some patients experienced stable disease for six months or more, including five of 76 (seven percent) lung cancer patients, six of 94 (six percent) melanoma patients and nine of 33 (27 percent) kidney cancer patients. The investigators say that additional clinical studies will be needed to determine the drug's potential impact on survival.

"This level of response in patients with advanced lung cancer, which is typically not responsive to immune-based therapies, was unexpected and notable," says Julie Brahmer, M.D., associate professor of oncology at Johns Hopkins.

The anti-PD-L1 therapy also showed responses among 207 treated patients. Five of 49 (10 percent) non-small cell lung cancer patients, nine of 52 (17 percent) melanoma patients, and two of 17 (12 percent) kidney cancer patients responded.

"The positive results from both drugs give us a good indication that the PD-L1/PD-1 pathway is an important target for cancer therapy," says Topalian.

The anti-PD1 therapy caused serious toxicities in 41 of 296 (14 percent) patients. Many of the toxicities were immune-related, including colon inflammation, thyroid abnormalities and three deaths from pneumonitis (lung inflammation). The investigators say they are working with colleagues across the country to develop better methods for early detection and effective treatment of pneumonitis. Other less severe toxicities included fatigue, itching and rash. The anti-PD-L1 therapy caused nine percent serious toxicities and no deaths.

Among patients receiving anti-PD-1, tumor samples collected from 42 study patients before they received the experimental therapy were evaluated at Johns Hopkins Medicine for molecular markers that may correlate with clinical response. The investigators found PD-L1, the partner protein to PD-1, in 25 of the 42 samples. Nine of the 25 patients with PD-L1-positive tumors experienced tumor shrinkage as compared with none of the patients with PD-L1 negative tumors.

"These early results indicate that PD-L1 expression in pretreatment tumor biopsies may correlate with clinical response to anti-PD-1 therapy, but more work needs to be done to confirm this, " says Brahmer.

The two therapies targeting the PD-1/PD-L1 pathway are in the same class of so-called "antibody therapies," which are made of proteins that target and bind to certain molecules on the cell surface. Other antibody therapies include such drugs as Erbitux, Herceptin, and Rituxan.

"We have just scratched the surface of laboratory and clinical research on these drugs," says Topalian.

Ultimately, they envision boosting the effectiveness of the therapy by combining it with other anti-cancer agents, including cancer vaccines.

Provided by Johns Hopkins University School of Medicine