Two combination therapies shrink melanoma brain metastases in more than half of patients

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High response rates to a pair of combination therapies point to potentially new options for a group of metastatic melanoma patients who have been largely left out of recent treatment progress - those whose disease has spread to the brain.

A combination regimen of two immunotherapies and another of two targeted therapies each significantly shrank metastatic brain tumors in at least 50 percent of patients in separate multi-center clinical trials presented today at the 2017 ASCO Annual Meeting by principal investigators from The University of Texas MD Anderson Cancer Center.

"These encouraging results highlight the possibility of new treatment options, and new hope, for our patients with metastases to the brain, which are a leading cause of death from the disease," said Hussein Tawbi, M.D., Ph.D., associate professor of Melanoma Medical Oncology and leader of the immunotherapy trial.

Very often clinical trial protocols either exclude these patients or require them to first receive radiation treatment for their brain tumors before they can take experimental drugs, Tawbi said. The practical effect is virtual exclusion from participation in many promising investigational studies.

"The goal is to accelerate systemic treatments for these patients," Tawbi said. "These trials show you can have response in the brain without radiation first." About 70 percent of patients with stage IV, or metastatic, melanoma eventually develop brain metastases.

"In addition to showing that these combinations are safe and effective, these results demonstrate the overall feasibility of conducting clinical trials for melanoma patients with brain metastases, which ultimately will make more treatments available to these patients," said Michael Davies, M.D., Ph.D., associate professor of Melanoma Medical Oncology and co-leader of MD Anderson's Melanoma Moon Shot.

Davies and Tawbi are part of a team at MD Anderson intensely focused on improving treatment of melanoma brain metastases. They designed and led these clinical trials.

In the past six years, a wave of new drugs - including both immunotherapies and targeted therapies - have extended the lives of patients with metastatic melanoma. However, concerns about whether the drugs could reach tumors in the brain, coupled with the historically poor prognosis of these patients, led drug developers to exclude patients with untreated brain metastases from all of the clinical trials that resulted in U.S. Food and Drug Administration approval of these agents.

While overall median survival is climbing from a base of nine months for other patients, progress has been slower for patients with tumors that have spread to the brain, who historically have a median survival of 4-5 months.

Checkpoint inhibitors, durable responses

Tawbi reported the initial efficacy outcomes from the CHECKMATE-204 study. All patients were treated with ipilimumab,

which blocks the CTLA-4 checkpoint on T cells, in combination with nivolumab, which inhibits activation of the PD1 checkpoint. Both checkpoints otherwise shut down T cells and thus block the anti-tumor immune response. Both drugs are infusions of targeted antibodies.

Tawbi reported the unprecedented result that 41 of 75 patients (54 percent) of the patients treated to date in the trial had their brain tumors significantly shrink. Sixteen patients had a complete response—disappearance of all tumors. Importantly, at nine months of follow up, only one of the 41 responders developed disease progression, Tawbi noted, a strong sign of durable response, a hallmark of these drugs when they are effective in patients with metastatic melanoma.

A challenge to treating tumors in the brain has been getting drugs past the blood-brain barrier, a tight seal on blood vessels that protects the brain from leakage of blood-borne toxins. It appears that this treatment may work because immune checkpoint drugs treat T cells, which can get through the barrier, rather than the hit tumor directly.

Immunotherapy poses another potential risk in patients with brain tumors, Tawbi said. When checkpoint blockade works, tumors get inflamed by the immune response, and often swell up before shrinking.

"In the closed space of the brain, inflammation and swelling could cause additional neurological side effects," Tawbi said. "We saw no increase in neurological events in the combination trial, just the range of toxicities that we find in patients with no brain metastases."

Serious treatment-related side effects, grade 3 or 4 adverse events, occurred in 52 percent of patients and were safely managed, typical of melanoma patients receiving the combination. One patient died of cardiac inflammation related to treatment.

Targeted therapy 1-2 punch

Davies presented the results of the COMBI-MB clinical trial. All of the patients in the trial had metastatic melanoma with a BRAF V600 mutation, which is the most common oncogenic mutation in this cancer, occurring in about half of patients. Patients received dabrafenib, which targets the BRAF600 mutations, and trametinib, which binds to and inhibits MEK 1 and 2. Both BRAF and MEK are protein kinases in the RAS/RAF/MEK/ERK signaling pathway, which regulates cell growth. They are approved as oral single agents and in combination against metastatic or inoperable melanoma.

The trial included four different groups of patients, who varied in the specific types of BRAF mutations they had; whether or not they had received previous treatments for brain metastases; and whether the symptoms from the brain metastases were controlled or not. The largest group of patients in the trial had a BRAF V600E mutation, no prior treatments to their brain tumors, and symptoms caused by the brain metastases were under control.

Davies reported 44 of the 76 patients (58 percent) in that group had their brain tumors significantly shrink, and four had a complete response. Similar results were observed in the other three groups in the trials, although those groups were much smaller (16-17 patients per group).

While this response rate approached those previously observed in patients without brain metastases, the duration of brain tumor control was shorter. On average, responses lasted 6-7 months, in contrast to the average duration of about one year in previous trials of patients without brain metastases, and in contrast to the results with ipilimumab and nivolumab.

"Treatment with dabrafenib and trametinib had impressive initial activity

in the patients. The important question is how do we make the responses last longer," Davies said. Combining these drugs with other treatments, including radiation or drugs that block other pathways that have been identified specifically in brain metastases, is one potential approach. Higher doses of dabrafenib and trametinib could also be explored as a strategy to improve outcomes, Davies added.

The COMBI-MB trial results are published in *Lancet Oncology* online as of June 4.

Next Steps

Davies and Tawbi note additional follow up is necessary to more fully gauge the impact of these combinations on melanoma patients with brain metastases. However, these initial results strongly support the feasibility of conducting prospective clinical trials in this under-studied population- and reinforce the need for continued research to improve outcomes further.

The immunotherapy trial was sponsored by Bristol-Myers Squibb, which markets ipilimumab (Yervoy) and nivolumab (Opdivo). The targeted therapy trial was sponsored by Novartis Pharmaceuticals, which markets dabrafenib (Tafinlar) and trametinib (Mekinist).

Provided by University of Texas M. D. Anderson Cancer Center