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Promising results found for treatment of melanoma in the brain

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Researchers at the University of North Carolina Lineberger Comprehensive Cancer Center are helping to make strides in the treatment of metastatic melanoma that has spread to the brain.

At the American Society of Clinical Oncology Annual Meeting 2017 in Chicago, researchers presented promising data for two different investigational drug regimens used to treat melanoma that has spread to the brain, a common and deadly complication of this cancer. The two trials, COMBI-MB and Checkmate 204, tested combinations of drugs that had been previously approved by the U.S. Food and Drug Administration for treatment of metastatic melanoma. No studies have examined their impact in patients with untreated metastases to the brain.

UNC Lineberger's Stergios Moschos, MD, a clinical associate professor in the UNC School of Medicine and co-investigator in both of these international, multi-center studies, said the two strategies could represent a major shift in the first line treatment of metastatic melanoma that has spread to the brain, and could potentially spare some patients from requiring radiation or surgery right away.

"These findings mean that some people may have a durable response to these drugs, and therefore, they can potentially be spared radiation and surgery for some time," Moschos said. "Now, patients have a choice."

The trials were conducted through the UNC Brain Metastases Specialty Clinic at UNC Lineberger. The clinic combines the expertise of neuro-

oncology, radiation oncology, and other disciplines to offer investigational therapeutic strategies for patients with cancer that has spread to the brain. In addition, physician-scientist are also working to understand the biology of brain metastases. A challenge that researchers face in identifying treatments for brain metastasis is the blood-brain barrier, which can prevent treatments from reaching high enough concentrations in order to be effective.

In the Checkmate 204 trial, which is an ongoing phase II trial sponsored by Bristol-Meyers Squibb, researchers tested a combination of immunotherapy treatments, nivolumab and ipilimumab, for a select group of patients. These "checkpoint inhibitors" release the brakes on the immune system, thereby helping the body's own defense system to attack the cancer. Patients on the trial did not have any neurologic symptoms or any history of steroid use, and had melanoma brain lesions limited to between 0.5 and 3 centimeters in size.

Researchers reported results for 75 patients from centers around the United States and Europe, including the N.C. Cancer Hospital, at the ASCO Annual Meeting. They found that 56 percent of patients had intracranial response, and 19 percent had a complete response to the treatment. At the time that physicians gathered the data, which was nine months after treatment, most patients were still responding, Moschos said. There were no serious neurologic toxicities observed, except for headaches. One patient died of myocarditis.

While most treatments typically must be able to cross the blood-brain barrier, Moschos said, to reach high enough concentrations in order to be effective, the Checkmate 204 trial showed that the treatments can activate the immune system outside of the brain. Moschos said this may be sufficient to induce responses in the brain without treatment actually reaching the brain site.

The responses to these immunotherapy treatments were impressive, said Carey Anders, MD, UNC Lineberger member, associate professor in the UNC School of Medicine, and co-director of Brain Metastases Specialty Clinic.

"I look forward to future studies evaluating this approach in breast cancer brain metastases as well," Anders added.

In the second multi-center phase II trial, researchers tested two targeted treatments for metastatic melanoma. The trial findings were presented at ASCO and published simultaneously in the journal *Lancet Oncology*. The study investigated the combination of dabrafenib and trametinib, which target BRAFV600 mutations that occur in a large share of melanoma patients.

Researchers reported statistically significant results for a group of 76 patients out of a total of 125 who participated in the trial. This subgroup had BRAFV600 mutations, no symptoms, and no prior local brain treatment. Of this group, 58 percent of patients had an intracranial response to the treatment. For the remaining patients, the findings were only considered hypothesis-generating due to their limited sample sizes. In the group overall, the preliminary overall survival result was more than 10 months. While the overall survival result was smaller than what had been reported in trials testing the same regimen in patients without brain metastases, Moschos said it was an improvement compared to historic outcomes for treatment of for patients with melanoma metastases to the brain. Similar to the Checkmate 204, there were no neurologic symptoms reported for patients.

The two strategies may offer the possibility that certain patients with melanoma metastases to the brain could get system-wide treatments prior to radiation or surgery. Moschos said this could help patients get treatment faster that attacks the cancer throughout their bodies. Patients

may be able to delay potential long-term side effects seen with radiation treatment to the brain – an important factor since patients with both treatment types are now living longer.

"Clinicians should no longer be hesitant to depart from the standard paradigm of 'you have brain metastases, you have to see the radiation oncologist to do radiation before you do any systemic treatment,'" Moschos said. "However, the management of these patients remains challenging and discussion among the multidisciplinary team of radiation oncologists, experienced medical oncologists in the treatment of this disease, and neurosurgeons should always occur first. Local treatments such as radiation and surgery remain the main treatment in relapsed disease."

Moschos also was first author of two additional abstracts presented at ASCO. One study tested an investigational compound that could be paired with standard targeted treatments, dabrafenib and trametinib, that are used in the treatment of metastatic melanoma. The addition of the investigational compound, AMG23, was designed to activate a normal cell death program driven by p53 to kill cancer cells.

"This compound is designed to pair with targeted treatments that arrest growth, rather than kill cells, in order to kill cancer cells and prevent relapse," Moschos said.

The researchers reported that the compound was "tolerable" up to a dose of 180 milligrams, and had early antitumor activity.

More information: COMBI-MB: A phase II study of combination dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600–mutant (mut) melanoma brain metastases (MBM). abstracts.asco.org/199/AbstView_199_180699.html

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