MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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The Standard of Care for Brain Metastases in Melanoma

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H&O Why is it so important to have new treatments for patients with brain metastases in melanoma?

HT Melanoma is highly curable when it presents in its early stages, even if it has spread to local lymph nodes. It becomes much more difficult to treat when it metastasizes. The risk for the development of brain metastases is extremely high in melanoma; these are more likely to occur in melanoma than in any other common solid malignancy. Between 30% and 40% of patients with a diagnosis of metastatic melanoma have a brain metastasis at the time of diagnosis, and up to 80% of patients with metastatic melanoma have a brain metastasis at the time of death.

When tumors start growing in the brain, they can cause swelling and pressure that affect neurologic function. Headaches, numbness, weakness, or difficulty speaking or swallowing—symptoms similar to those of a stroke—may develop. The symptoms are quite debilitating and affect people's performance status significantly. If not treated properly, patients with melanoma and brain metastases have a median survival of just 4 to 5 months.

H&O What is the standard treatment for patients who have melanoma with brain metastases?

HT The usual standard of care for these patients is local treatment (surgery or radiation) followed by systemic therapy. Surgery is usually the best choice for large, symptomatic metastases, especially those that exhibit intratumoral hemorrhage. Stereotactic radiosurgery (SRS) is a highly effective form of radiation therapy that offers meaningful control of brain metastases. The main drawback of SRS is that it works only for the lesions that are targeted; it does not help with lesions elsewhere in the brain or those outside the brain. The vast majority of patients who present with brain metastases—approximately 90%—have disease both inside and outside the brain. As a result, most of them also receive systemic treatment consisting of immunotherapy, targeted therapy, other agents, or a combination.

Whole-brain radiation is sometimes used for patients with brain metastases in an effort to provide palliation, even though it produces cognitive decline. However, a recent Australian study by Hong and colleagues, published in the *Journal of Clinical Oncology* in 2019, found that whole-brain radiation does not produce clinical benefit in terms of distant intracranial control, survival, or preservation of performance status. These data, which were also presented at the 2019 annual meeting of the American Society of Clinical Oncology (ASCO), confirmed what many of us have thought for a long time.

H&O What experimental approaches are being used in patients with brain metastases?

HT Most of the clinical trials in melanoma conducted over the past 10 years specifically excluded patients with brain metastases unless they had previously received

surgery or radiation and had stable disease for at least 4 weeks. During the past few years, however, a few trials have been designed to look specifically at patients with brain metastases.

Several trials have looked at the use of targeted therapy with a single agent, such as the BRAF inhibitor dabrafenib (Tafinlar, Novartis) or vemurafenib (Zelboraf, Genentech/Daiichi Sankyo). These agents have been shown to shrink brain metastases in approximately 40% of patients, although they have not been shown to improve progression-free survival beyond 4 months. Combining these agents is even more effective. The COMBI-MB trial (Study to Evaluate Treatment of Dabrafenib Plus Trametinib in Subjects With BRAF Mutation-Positive Melanoma That Has Metastasized to the Brain) showed that the combination of dabrafenib and trametinib (Mekinist, Novartis) was able to shrink intracranial disease in 58% of patients with *BRAF* V600E–positive, asymptomatic melanoma brain metastases, no previous local brain therapy, and an Eastern Cooperative Oncology Group performance status of 0 or 1. This is quite impressive for drug treatment alone, with no radiation. One interesting finding was that progression-free survival among patients with disease in the brain was half (approximately 5 months) of what we are used to seeing among patients with disease outside the brain (approximately 10 months). This was concerning because we want to be able to do as good a job intracranially as extracranially.

An important finding that we saw in our study is that patients did not respond to immunotherapy if they were on corticosteroids at the time therapy was initiated.

Another approach that is being studied is immunotherapy. Studies have found that single-agent therapy with ipilimumab (Yervoy, Bristol-Myers Squibb), pembrolizumab (Keytruda, Merck), or nivolumab (Opdivo, Bristol-Myers Squibb) is safe for the brain, meaning that it does not cause increased brain swelling or major unexpected toxicity. The intracranial response rate in studies of these agents was approximately 20%. The nivolumab study, by Long and colleagues, included a group of patients who received nivolumab plus ipilimumab, and these patients had an intracranial response rate of 46%. In all cases, the patients who responded tended to have a very durable response.

In CheckMate 204 (An Investigational Immunotherapy Study to Evaluate Safety and Effectiveness in Patients With Melanoma That Has Spread to the Brain, Treated With Nivolumab in Combination With Ipilimumab, Followed by Nivolumab by Itself), a phase 2 study of combination immunotherapy with nivolumab plus ipilimumab that we published in the *New England Journal of Medicine* in 2018, we found a 57% rate of intracranial response and the same rate of extracranial response among 94 patients with metastatic melanoma after a median follow-up of 14 months. These responses were also durable. This research indicates that combination immunotherapy is the best systemic treatment we have now for patients with brain metastases.

H&O What makes the intracranial response so much better with combination immunotherapy than with single-agent immunotherapy?

HT That is something we are still working to understand. It is possible that the combination permits the generation of more T cells, which in turn are able to permeate the blood-brain barrier.

H&O Are certain patients with brain metastases more likely to benefit from immunotherapy?

HT We have found that patients with asymptomatic brain disease are the ones who do the best with immunotherapy. Patients whose tumors express programmed death ligand 1 (PD-L1) seem to have a slightly better response, but any difference is small. An important finding that we saw in our study is that patients did not respond to immunotherapy if they were on corticosteroids at the time therapy was initiated. In a subsequent follow-up of our study that I presented at the ASCO annual meeting in 2019, only 1 of 11 patients who were on corticosteroids responded to immunotherapy. We know that corticosteroids suppress the immune system, so that their effects are at odds with those of immunotherapy, but we were hoping that the combination of nivolumab and ipilimumab would be potent enough to overcome this problem. Unfortunately, that turned out not to be the case.

H&O What is the potential role of combining immunotherapy with radiation or SRS for brain metastases?

HT That is a field of very active investigation. I think that these combinations have the potential to provide a lot of value. All the evidence suggests that combining systemic treatment with radiation is a good idea. What we do not know are the optimal timing and the sequence. Should we start with immunotherapy and then add radiation, or should we start with radiation and then add immunotherapy? Some retrospective evidence suggests that administering immunotherapy first makes more sense, but we are still waiting for some prospective data. I understand that one group is working on this question, but results are not going to be available anytime soon.

H&O Is there a risk for radiation necrosis or other unique side effects with these treatments?

HT Some evidence from retrospective studies suggests that rates of radiation necrosis are slightly higher with immunotherapy combinations than without, but these data are highly conflicting. My group has published data showing no increased risk, whereas other groups have found the opposite. So I would say it's an unanswered question with immunotherapy. An increase in radiation necrosis does not seem to be an issue with targeted therapy.

We have not seen any other unique side effects with immunotherapy or targeted therapy plus radiation, such as increased neurologic toxicity. We know that brain edema can occur with immunotherapy, and we were concerned that we would see a very high rate of this in our combination study, but the rate ended up being less than 5%, and the brain edema was very easy to manage with corticosteroids. An important point is that treating patients with corticosteroids does not seem to detract from the efficacy of immunotherapy if the corticosteroids are used later in treatment, to address toxicity. The corticosteroids seem to affect results only if they are present at the time immunotherapy is initiated.

H&O How do you select the best treatment for patients with brain metastases and *BRAF* mutations?

HT I still think that dual immunotherapy is the best option for those patients. If disease progresses after this approach, you can fall back on targeted therapy as second-line treatment because the effects are less durable than those with immunotherapy. Also of note, we are now conducting trials with triplets consisting of immunotherapy plus targeted therapy. At the 2019 annual meeting of the European Society for Medical Oncology (ESMO), Elizabeth Burton from our group at MD Anderson reported on a phase 2 study called TRIDeNT (A Phase II Study of the TRIplet Combination of Dabrafenib, Nivolumab, and Trametinib in Patients With Metastatic Melanoma), in which we used a combination of nivolumab, dabrafenib, and trametinib in 26 patients *BRAF*-mutated, unresectable metastatic melanoma. We found that with this combination, patients who had brain metastases did just as well as patients who did not. We think that triplets might be a really good option for those patients.

H&O Have you ever seen an abscopal effect with radiation to the brain?

HT I have seen a couple of patients who had 1 or 2 lesions in the brain and were on immunotherapy, and when they underwent brain irradiation we saw extracranial disease respond—this is similar to an abscopal effect. It is not something that occurs often and we cannot plan on it happening, but we are happy when we see it.

> Regarding phase 3 trials, my hope is that pharmaceutical companies and investigators will start including patients with brain metastases up front, instead of conducting separate phase 2 and 3 studies for them.

H&O What additional studies are ongoing or planned?

HT Right now, we are following several lines of investigation. First, we are trying to maintain the efficacy seen with nivolumab and ipilimumab while reducing the toxicity; one approach is to use lower doses. Right now, we are studying a lower-dose combination of ipilimumab with pembrolizumab.

Second, we are studying combinations of targeted therapy and immunotherapy, as I just mentioned with TRIDeNT. One of the other combinations we are studying is nivolumab, encorafenib (Braftovi, Array BioPharma), and binimetinib (Mektovi, Array BioPharma).

Third, we are looking at new combinations of

targeted therapy. One trial that I am especially excited about is the POLARIS study (An Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With BRAFV600-Mutant Melanoma Brain Metastasis) of encorafenib and binimetinib. These agents are similar to dabrafenib and trametinib but are better tolerated, so we would like to see if pumping up the dose will be helpful in patients with brain metastases.

Fourth, we are still working to identify the best options for patients who are symptomatic and for those who are on corticosteroids.

Regarding phase 3 trials, my hope is that pharmaceutical companies and investigators will start including patients with brain metastases up front, instead of conducting separate phase 2 and 3 studies for them. All the evidence we have seen has been very convincing that it is safe to treat patients with brain metastases, and they can do just as well as patients who do not have brain metastases.

H&O Is there anything you would like to add?

HT There is still a lot of progress to be made for this population. We are presently at a place where we are just trying to confirm that the things that work outside the brain also work within the brain. One of our goals for the future is to be much more deliberate about targeting what is unique about the brain, rather than just showing that we can translate the extracranial benefit of various combinations to the brain. We want to develop studies that are specifically designed to target the brain-specific tumor microenvironment and potentially brain-specific pathways.

Disclosure

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Suggested Readings

Burton EM, Amaria RN, Glitza IC, et al. Safety and efficacy of TRIplet combination of nivolumab (N) with dabrafenib (D) and trametinib (T) [TRIDeNT] in patients (pts) with BRAF-mutated metastatic melanoma (MM): a single center phase II study [ESMO abstract 1312]. *Ann Oncol.* 2019;30(5)(suppl).

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