ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Intrathecal Immunotherapy in Patients Who Have Melanoma With Leptomeningeal Disease

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H&O What is the rationale behind the use of immunotherapy for intrathecal treatment of leptomeningeal disease (LMD)?

ICG When we talk about treatments before the new era of options that have become available over the last decade, it is important to remember that the only treatment options that we formerly had for metastatic melanoma were standard intravenous chemotherapy and interleukin 2 (IL-2). For LMD, we really had nothing. That began to change in the 1990s, when Dr Nicholas Papadopoulos (my mentor) and others tried using IL-2 intrathecally.[1] The rationale was that because IL-2 worked for a subset of patients when given intravenously, administering it directly into the spinal fluid might benefit patients with LMD.

Early research showed that intrathecal IL-2 produced significant inflammation in the intrathecal space, which is very different from what we tend to see with current drugs. We hoped that this inflammation would "pull" more immune cells into the space, and that the immune cells might kill cancerous cells indirectly. We found that although this approach did kill cancer cells in a subset of patients, it also caused severe toxicity.[2]

When checkpoint inhibitors were first introduced, they represented a significant improvement over intravenous IL-2 for patients with metastatic melanoma, with better efficacy and much better tolerability. This led to the question of whether we could realize the same benefits of improved efficacy and fewer side effects by using the same checkpoint inhibitors intrathecally. The logic was sound because we conducted a study in our laboratory in which we were able to identify expression of programmed death 1 (PD-1) target on immune cells within the cerebrospinal fluid (CSF). Published research showed that monoclonal antibodies such as rituximab and trastuzumab could improve the outcome of patients with LMD secondary to other cancers when given intrathecally after disease progression with intravenous treatment alone.[3-5] Later on, researchers found that levels of checkpoint inhibitors are up to 300 times higher in the blood than in the CSF, which provides a rationale for intensifying the dose right where we need it.[6]

H&O Could you discuss your research looking at the use of intrathecal immunotherapy?

ICG Our first-in-human phase 1/1b study was designed to examine the use of nivolumab (Opdivo, Bristol Myers Squibb) as an intrathecal treatment, building on our experience with intrathecal IL-2. One important aspect of our study is that we allowed patients with pretty much any subtype of melanoma to enroll. We were not treating only cutaneous melanomas, which historically have been more sensitive to immunotherapy. This study included patients with uveal melanoma, mucosal melanoma, acral lentiginous melanoma, and melanoma of unknown primary. Some patients had *BRAF* mutations, the majority had a history of or concurrent brain metastases, and some

had concurrent extracranial disease. Most patients in the study had previously undergone treatment with checkpoint inhibitors and experienced progression.

The dose escalation phase of the trial, which enrolled patients with LMD related to melanoma, tested 4 dose levels of intrathecal nivolumab: 5, 10, 20, and 50 mg every 2 weeks for up to 19 cycles, in addition to intravenous nivolumab at the standard dose of 240 mg on the same schedule.[7] After that time, patients proceeded to monthly administration. It should be noted that we still struggle a bit with assessing response in LMD. Response to treatment can be difficult to measure with just magnetic resonance imaging, so we also consider the patient's symptoms and their CSF analysis findings. Therefore, our primary endpoints were determination of safety and the recommended dose of intrathecal nivolumab, and our secondary endpoint was overall survival (OS). The OS endpoint has been used in other studies of LMD.[8,9]

> NCCN guidelines include intrathecal nivolumab as a treatment that is "useful in certain circumstances" for patients with leptomeningeal metastases related to melanoma.

In our interim results, we saw no dose-limiting toxicities among our cohort of 25 patients. The 50-mg dose of intrathecal nivolumab proved to be very safe, so that is what we decided to use for the dose expansion phase. The median OS among these patients was 4.9 months at a median follow-up of 20 weeks, with a 44% OS rate at 26 weeks and a 26% OS rate at 52 weeks. Ultimately, a total of 50 patients were enrolled, including 2 patients with lung cancer. In an update that we presented at the 2024 European Society for Medical Oncology (ESMO) Annual Meeting, which included 50 patients, our longest survivor was out nearly 7 years. We hope to present final results of our trial by the end of 2025.

We are currently building on our phase 1/1b study with another arm—still listed under the same clinical trial number (NCT03025256)—to look at combination immunotherapy with nivolumab and relatlimab (Opdualag, Bristol Myers Squibb) in our current cohort of patients. We are actively enrolling patients in this trial at MD Anderson, with a target enrollment of 20 patients for this arm.

H&O What adverse effects did you see with intrathecal nivolumab?

ICG Overall, we have seen very few adverse effects with intrathecal nivolumab. We saw some fatigue, which is nearly universal in this population, as well as some vomiting, but very few grade 3 adverse effects. The agent was very well tolerated. When we did see an adverse effect, such as an elevation of liver enzymes, it was unclear whether this was caused by intrathecal nivolumab or the intravenous treatment, or the two combined.

H&O How widespread is the use of intrathecal nivolumab?

ICG We should see an increase in its use now that the National Comprehensive Cancer Network (NCCN) guidelines include intrathecal nivolumab as a treatment that is "useful in certain circumstances" for patients with leptomeningeal metastases related to melanoma.[10] This addition is exciting because it should make the approach accessible far beyond MD Anderson. The inclusion of intrathecal nivolumab in the guidelines should also make it easier for treatment to be reimbursed.

H&O What other studies of intrathecal administration are being conducted?

ICG Multiple studies are being conducted, which is exciting. One is a phase 1 study looking at the addition of intrathecal ipilimumab (Yervoy, Bristol Myers Squibb) and nivolumab to intravenous ipilimumab/nivolumab in patients with newly diagnosed LMD related to lung cancer or melanoma. This study is being conducted at the University of Zurich by Emilie Le Rhun and colleagues (NCT05598853). In addition, a phase 1/2 study of the intrathecal checkpoint inhibitors iparomlimab (a PD-1 inhibitor) and tuvonralimab (a cytotoxic T-lymphocyte–associated antigen 4 inhibitor) in patients with LMD (NCT06809530) is being conducted in Guangzhou, China, and our German colleagues are undertaking a phase 1 study of intrathecal nivolumab in Tübingen, Germany (NCT05112549).

H&O What research would you like to see happen in the next few years?

ICG More trials in patients with LMD are needed, and I am a big advocate of pushing companies to undertake these trials. This is a group of patients for whom hospice

has traditionally been the only option, but now we are seeing a subset of patients who are experiencing long-term survival with various treatments, including radiation. We need to continue to investigate and push the field forward.

Another approach to treatment involves non-intrathecal immunotherapy that is intrathecally based. For example, a phase 1 study from Plus Therapeutics, called ReSPECT-LM, is investigating the use of radioisotope therapy in LMD (NCT05034497). Adrienne Boire and colleagues at Memorial Sloan Kettering Cancer Center are investigating the use of an intrathecal ion chelator, deferoxamine, in LMD secondary to solid tumors (NCT05184816). The field is really evolving. We have treated 2 patients with intrathecal cellular therapy consisting of tumor-infiltrating lymphocytes, and I am hoping to begin a new trial of intrathecal cellular therapy.[11] I would like to see us able one day to use off-the-shelf cellular therapies.

H&O Which patients are most likely to benefit from intrathecal immunotherapy?

ICG It is hard to say at this point. We are examining CSF from many patients with LMD in an effort to identify which patients might be most likely to benefit from treatment. More collaboration among institutions is needed if we are to learn the answer to this question. We are in the process of analyzing the CSF and blood samples from the patients treated on this trial to understand how different the tumor microenvironment in the CSF is from that in the rest of the body, and if the dose levels of the checkpoints used in the CSF are associated with benefit.

Disclosures

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