

Melanoma Central Nervous System Metastases

Current Approaches, Challenges and Opportunities

In December, 2015, the Melanoma Research Foundation convened a major scientific meeting to address the issue of patients who have melanoma metastases to the brain. That meeting resulted in a peer-reviewed publication. The following is a lay-level synopsis of that publication.

Melanoma has the highest risk of spreading to the brain among all common cancers, with 40-60% of patients developing brain metastases and up to 80% of melanoma patients having some kind of central nervous system (CNS) involvement. Not surprisingly, brain metastasis is the leading cause of death from melanoma.

Most CNS studies were done before the advent of the new drugs being used to treat melanoma, and conceivably we will see an increase in CNS involvement as patients survive longer with their non-CNS tumors being well managed.

Despite this prevalence, patients with melanoma brain metastases (MBM) are generally excluded from clinical trials. As a result, knowledge of how well the new drugs work against MBM is limited. New trials are now being done focusing specifically on this sub-class of patients.

Little is known about the specific characteristics of MBM. A growing body of evidence suggests that metastases in the brain have some key distinct features that separate them from primary tumor or metastases in other parts of the body. Certainly the tumor micro-environment in the brain is different. Significant pre-clinical work is needed to determine these differences and the impact they are likely to have on response to current therapies.

CLINICAL STUDIES

Targeted Therapy

Studies of targeted therapy in MBM suggest that this approach is superior to the older chemotherapy agent temozolomide. Although BRAF inhibitors do not effectively cross the blood-brain barrier (BBB) this drug does have significant impact on tumors in the brain. This suggests that the BBB is compromised by MBM.

While response rates to BRAF inhibition are good, tumors in the brain—like other tumors—become resistant to these drugs. A great deal of research has been done on extra-cranial metastases to determine the mechanisms by which this drug resistance occurs, but no similar studies have been done to see if those mechanisms are the same in MBM.

Other targeted therapy agents are being evaluated in MBM, which would make new treatments available for patients whose tumors do not have the BRAF mutation. Most of these studies involve blocking other steps along the same pathway that activates BRAF.

Another challenge is the lack of data around how much drug is actually getting to the brain. Higher systemic doses of these drugs might be required in order to achieve therapeutic levels in the brain. One way to determine this is by giving targeted therapy drugs prior to a planned surgery to remove tumor, then using the surgery as an opportunity gather tissue that will show how much drug is getting to the brain area.

MBM may have additional mutations that drive the growth of those tumors beyond those found in tumors outside the CNS. One study showed that tumors in the brain activated a different metabolic pathway from the one in which BRAF is found. This argues for MBM being treated with targeted therapies that impact both pathways simultaneously.

Immunotherapy

Based on what we know of the brain, immunotherapy should not be effective in treating MBM. The CNS does not typically respond to antigens such as cancer cells, and most immunotherapy drugs are antibodies that are too large to cross the BBB. Further, many patients with MBM require steroids to manage brain swelling, and these drugs counteract immunotherapy drugs.

Despite this, clinical practice has shown surprising benefit to MBM patients with immunotherapy. Some small studies suggest that response rates to tumors in the brain are comparable to those outside the brain. More work is being done in this area yet randomized trials are essential to determine how best to use these drugs.

A unique challenge for MBM patients on immunotherapy is the issue of swelling. Immunotherapy drugs often cause tumors to swell, resulting in a phenomenon called pseudo-progression. The tumor appears to get larger, but is actually only inflamed in response to the drugs. For MBM this swelling can result in increased intracranial pressure that is difficult to manage without administering steroids that offset the benefit of treatment.

Intrathecal Approaches

Sometimes melanoma spreads to meninges--the membranes covering the brain or spinal column—or to the spinal fluid. This phenomenon is known as leptomeningeal disease (LMD), and the prognosis for patients with this kind of metastasis is very poor.

One unique approach for LMD patients is to administer therapies directly into the intrathecal space, or the cavity around the spinal cord. Through this approach the drugs go straight to the spinal fluid rather than being diluted in the bloodstream.

Targeted therapy drugs cannot be given in this fashion as they are only in pill form. Small studies using immunotherapy drugs show little benefit. Some patients treated with IL-2 showed good response, but also significant side effects. In general, much more work needs to be done in this area.

Radiation Therapy

For a single brain metastasis the best outcomes are achieved by radiation followed by surgery. With multiple metastases, however, the best approach is less clear. Surgery is not an option in these situations and melanoma is relatively resistant to radiation.

The current approach is to combine high resolution imaging through MRI with focused, local radiation through stereotactic radiosurgery (SRS). Guidelines limit this to no more than four

relatively small tumors, but good results have also been reported in patients with more than four tumors. Research is needed to determine how far SRS can go in treating MBM.

Reports that patients on targeted therapy have stronger radiation-related side effects have resulted in stopping targeted therapy during radiation therapy. Comparable guidelines do not exist with immunotherapy. Some data shows that combining immunotherapy with radiation for tumors in other parts of the body increases response rates, but those studies have not looked at MBM. A solid prospective study is needed to determine the safety and efficacy of such combinations.

CNS Imaging and Response Assessment

Finding and tracking MBM is critical to managing the patient properly but also to contributing to the general understanding of how best to manage this disease. MRI is the most accurate method for assessing brain disease, but wide variations exist between types of equipment, the strength of the magnets used, slice thickness, and contrast media. The preferred imaging approach is to use closed field, strong magnets. At a minimum sequential MRI's should be taken using the same equipment, the same settings, and the same contrast medium so appropriate comparisons can be made over time.

Two issues related to imaging are only recently being resolved. First, having a common endpoint for clinical trials is critical. Trials are evaluated and patients are removed from trials based on response to the therapy. Without clear endpoints defining what "response" looks like in MRI the trials cannot be properly analyzed.

Second, only recently have criteria been developed to determine how to define response to therapy. Simply determining the size of the metastasis is inadequate when the treatment is immunotherapy. An immunotherapy induced "flair" might be mistaken for tumor progression. For this reason, patients who are doing well clinically should not be removed from immunotherapy simply because an MRI shows a larger tumor.

Clinical Trial Design

Current clinical trial practices create barriers to developing better clinical approaches for treating MBM. Data suggests that one metabolic pathway—the PI3K pathway—is more significant in brain metastases than in tumors in other parts of the body, yet under the current approach any drug targeting that pathway would need to be tested first in patients with no MBM. Not only does this exclude the patients who are most likely to benefit, it also means the drug is tested in a group of patients who are less likely to respond. In this scenario, a drug that could be useful for treating MBM would never be approved because it did not meet efficacy criteria.

More significantly, ways must be found to include patients with MBM in the broader clinical trial program. Data is clear that drugs which benefit patients with metastases outside the brain also benefit patients with MBM. While the level of benefit and ultimate outcomes may vary between these two groups, the benefit nevertheless exists. One simple solution would be to treat this group of patients as a sub-category within the larger trial.

In order to make clinical trials for brain metastases particularly beneficial, consistent criteria must be established regarding a number of aspects of the trials. Common criteria for who will and will not be enrolled in the trial should be established, and should include number and size of brain tumors. The use of steroids could be another factor, as could common understanding of how to determine response to therapy.

In particular, more specificity must be developed around how to define the endpoint of MBM trials. Generally this is using imaging to see if the brain tumors are responding, but imaging in brain metastases is challenged by a number of factors. The use of steroids can change images, as can hemorrhaging in the brain, the unique way that melanin reacts to magnetism, and the potential for swelling of tumors responding to immunotherapy. A sharper focus on overall survival might be required.

PRECLINICAL STUDIES

Molecular Determinants of Brain Metastases

A growing body of evidence suggests that MBM have unique characteristics that distinguish them from metastases to other parts of the body. For example, work with cell lines and clinical specimens has implicated a gene involved with brain development, and suggests that the activation of this gene helps tumors cross the BBB. This same gene may interact with the PI3K-AKT signaling pathway which, in turn, activates compounds known to help melanoma cells become more invasive into the brain.

Evidence also exists that the tumor microenvironment may be different for brain tumors. Implanting tumor cells in the brain of mice results in more than 1000 genes being reprogrammed, and this pattern is repeated across multiple tumor types. The pattern in these metastatic tumors is similar to that seen in primary brain tumors.

More work is needed to understand these cellular and tumor-level variations. Comparing cells from MBM to those from other metastases in the same patient might help identify the critical components that make the brain metastases so aggressive. These same samples can be used to understand better the basic biology of brain metastases as well as the impact of therapy on those cells.

Animal Models

Developing effective animal models is a critical step in understanding why melanoma metastasizes to the brain. Current efforts have involved injecting cells from cell lines into the brain of mice, but tumors that form from this approach behave very differently from what is observed in patients. Several labs are developing patient-derived xenograft (PDX) mice, in which tumor is removed from a patient and placed into a mouse. This is a more promising approach, as these human cells seem to behave more like real-world melanoma.

The mouse model must, however, also emulate the immune system so studies can be done evaluating how immunotherapy works in the brain. This will require further efforts to “humanize” the mouse with a human-like immune system.

Zebrafish have been used extensively in preclinical studies, including melanoma. Brain metastases rarely happen from melanoma in zebrafish, but can be created by injecting cells into the brain. This suggests that a number of factors are impacting the ability of melanoma cells to enter and flourish in the brain. Zebrafish are an excellent model for discovering those factors, and more research is essential. Identifying those factors might offer clues into how and why metastases occur in patients.

CONCLUSIONS

Key aspects of research and patient care that will result in better clinical outcomes include:

- Multi-disciplinary care: Addressing brain metastases requires a robust, collaborative team that includes not only the normal oncology team but also neurosurgeons, neurooncologists, neuroradiologists and others. A team approach across these disciplines is essential not only for optimal care, but also for understanding and addressing the impact of treatment on function and cognition.
- Clinical Trials: Patients with brain metastases need to be included in standard clinical trial protocols, and special trials are needed to address this particular population. Because brain metastases appear to be driven by specific metabolic pathways, studies are needed to determine if blocking those pathways will improve outcomes.
- Standardization of trial endpoints: Creating common criteria for defining response to a therapy will enable researchers to properly compare different studies across multiple institutions. This includes interpreting imaging in a way that is consistent across institutions, and also tailoring decisions about surgery and systemic therapy based on number, location, and size of the metastases.
- Leptomeningeal disease: LMD remains a major challenge, and the key to seeing progress is to have clinical trials for this subset of patients. Intrathecal therapies are showing promise, but more, and more robust, studies are required.
- Preclinical studies of the biology of melanoma brain metastases: Basic science and preclinical studies are necessary for advancement in understanding and treating brain metastases. At the core of this is development of relevant preclinical models.
- Establishment of multi-institutional collaborative specimen banks: Obtaining high-quality clinical specimens of brain tumors is challenging, so pooling such resources among multiple melanoma centers is important. Expanding this with warm autopsy samples may make this effort even more robust.
- Collaborations with physicians and scientists working on other CNS tumors: primary brain tumors and brain metastases from other cancers share many characteristics with MBM. Inter-disciplinary cooperation may help provide new insights and result in more rapid development of effective therapies.