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Towards a Targeted Molecular Approach for Brain Metastases

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The most devastating statement a neuro-oncologist will ever make and a cancer patient will ever hear is, “Your cancer has spread to your brain” because based on the currently available treatments, that statement is likely to be followed by, “Even with surgery and radiation, you may only survive another six months.” Statistically, 40% of all cancer patients will have a conversation like this. With over 170,000 patients diagnosed with brain metastases each year, metastatic brain tumors are the greatest incidence of brain tumors, and these numbers are expected to rise as targeted therapies are better able to control the patients’ primary diseases. While the most common metastatic brain tumors originate from lung cancer, breast cancer, or melanoma, any primary cancer may have the potential to generate brain lesions [1]. As there are currently no biomarkers or laboratory tests able to predict which cancer patients will develop brain metastases, typically patients are not diagnosed until they have developed distressing neurological symptoms. The use of magnetic resonance imaging to routinely screen all cancer patients for brain metastases is not a viable option as the health care system would not be able to support the sheer numbers of scans that would be required, nor would it be able to bear the costs.

The current standard of care for brain metastases is surgical resection followed by stereotactic radiosurgery (for solitary lesions) or whole brain radiation therapy (for multiple lesions) [2]. There are no chemotherapeutic agents currently approved by the FDA for treatment of brain metastases. Despite remarkable advances in the treatment of primary cancers with targeted chemotherapies, these treatments, such as trastuzumab for breast cancer or crizotinib for non-small cell lung cancer, have been unsuccessful against metastatic brain tumors [3]. Published research seems to have focused on the idea that metastatic brain tumors will mimic the primary tumor from which they are derived, but the failure of standard chemotherapies argues that the biology of metastatic tumors varies from the primary, especially in light of the ‘leakiness’ of the blood-brain barrier in brain tumor patients [4] suggesting that inaccessibility of the brain lesion is not necessarily the limiting factor in drug action.

First put forth by Stephen Paget in the 19th century, the “seed and soil” hypothesis [4,5] is particularly appealing in the context of the ‘soil’ of the brain which is a complex milieu of cell signaling (neurochemicals, cytokines and hormones) and distinct cell types (neurons and

glia). The very idea that multiple dissimilar primary cancers are all capable of ‘seeding’ the brain with metastases suggests that there must be some common genetic anomalies that are conducive for tumor cell growth in the brain irrespective of the characteristics of the primary tumors.

A search of the literature reveals that the vast majority of studies of metastatic brain tumors focus on a single primary cancer with a lack of studies that have examined brain tumors from multiple primary cancers. This tunnel vision approach to metastatic brain tumor research is unlikely to yield any broadly efficacious chemotherapeutic agents or identify any predictive biomarkers.

In order to truly have an impact on this intractable clinical problem, future studies will need to include concurrent analyses of metastatic brain lesions from multiple primary cancer types. Ideally, once common genomic features in metastatic brain tumors are identified by high throughput assays such as whole genome sequencing or array comparative genomic hybridizations, attention can be turned to development of targeted therapies and, equally important, biomarkers that can be assayed from biopsy specimens of the primary cancer or patient blood to predict which patients will be most at risk of developing brain metastases. Even in the absence of new drug treatments, identifying the patients with high risk of brain metastases should allow for improved outcomes by the justified use of magnetic resonance imaging or more powerful positron emission tomography [6] to detect brain lesions before the occurrence of neurological symptoms in those high risk patients.

It should also be noted that while chemotherapeutic agents that can cross through the blood-brain barrier would still be preferred, drugs that may have difficulty passing through even a leaky blood-brain barrier but prove to be efficacious against the metastatic tumor cells would still warrant inclusion in clinical trials. Intrathecal delivery of such agents could obviate the need to focus solely on small molecules with properties amenable to passage through the blood-brain barrier.

In summary, despite the wealth of knowledge about primary cancers, metastatic brain tumors still remain a challenging clinical problem with limited treatment options for those afflicted patients. Historically, metastatic brain tumors have been considered as though they were an additional incidence of the primary cancer, without regard for the complexity of the microenvironment of the brain. New research directions including the collective study of metastatic tumors from multiple primary cancer types will provide the best hope of effective predictive testing and successful treatments.

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