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Treatment of Brain Metastases; an Interdisciplinary Approach to a Conundrum

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Metastatic brain tumors (MBTs) are the most common intracranial tumors in adults. These tumors occur in up to 40% of patients with certain cancer diagnoses. Also, 8.5% - 9.6% of cancer patients are diagnosed with brain metastasis in the course of their disease (1). In the United States, 200,000 patients are newly diagnosed each year with MBT (2).

Lung, breast, kidney, gastrointestinal tract, or skin cancers metastasize to the brain more commonly and with high probability; however, metastatic lesions in the brain may originate from any part of the body (2, 3). As an example, 10% to 30% of women with breast cancer will develop MBTs (4).

The estimated incidence rate for primary central nervous tumors was 6.4 per 100,000 (1, 5), while the metastatic brain tumors occur with an incidence rate of roughly 8.3 and 11.3 per 100,000, which supports the expected rising trend (1). More recent studies have demonstrated the rate of MBTs to occur as much as 10 times more frequently than primary tumors. This upward trend has also been predicted since 1987 by some Swedish cohort studies from 1987 to 2006 (6). Apart from general incidence information, a number of research outcomes indicated factors that predispose cancer patients for MBT development, namely, race, gender, and age (7).

The advent of novel imaging modalities and cancer therapies led patients to live longer due to earlier detection and better systemic therapies. Accordingly, the odds of developing brain metastases in patients raised over time (8). Hence, the prediction of greater frequency of metastatic brain cancer highlights the requirement for continued innovation in the therapeutic armamentarium.

Although brain metastases are generally considered a single disease entity, they are remarkably heterogeneous both clinically and pathologically, with a uniformly dismal outcome in patients (9).

Careful patient monitoring, earlier diagnosis of metastases, and improved local and systemic treatments have been achieved thanks to the recent progress in neuroimaging, neurosurgery, radiation oncology, medical oncology, and supportive care. Furthermore, the introduction of advanced strategies to alleviate potential complications has improved both the survival and quality of life (QOL) outcomes of patients with brain metastases. However, the remarkable heterogeneity of patients affected by brain metastases and their tumor microenvironments often give rise to a nihilistic approach in clinical management. Therefore, the complexity and controversy in the management of brain metastases necessitate a multidisciplinary approach (10).

Surgery, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and chemotherapy are currently used treatments for MBT. Currently, surgery and SRS are the standard treatment for MBTs, and both offer the best outcomes. The use of whole-brain radiotherapy has been restricted due to several acute adverse effects, serous otitis, alopecia, fatigue, skin erythema, and the altered sense of smell and taste (11). Moreover, some late-onset adverse effects, namely confusion, leukoencephalopathy, and memory loss often are health risks to patients and physicians. Thus, the use of this therapeutic modality has narrowed to patients with multiple brain metastases, for whom surgery or SRS is not recommended (10).

Patients with a single brain-metastatic lesion, a limited number of extracranial metastases, and a good KPS have a greater chance for enhanced survival outcomes with

surgery. Additionally, the removal of multiple brain metastases might be helpful for selected patients. Surgery might also be considered in cases of recurrent brain metastases (12). However, the probability of tumor cell dissemination, the difficulty of removing metastatic masses of an indistinct border, and the possibility of new or worsening neurological deficits always exist (13).

Novel approaches, such as immunotherapy (e.g., monoclonal antibodies against PD-1) and molecularly targeted therapy (small molecules, like osimertinib, dabrafenib, and lapatinib) are gradually being prescribed for the treatment of MBTs (10). Small molecules have shown some efficiency against metastatic brain tumors, especially in patients with some defined mutations (14, 15).

There are some positive reports of promising outcomes in patients with brain metastases from lung cancer and melanoma (16, 17). Nevertheless, based on the results of the multi-center phase II GETUG-AFU 26 NIVOREN study, patients with brain metastasis from renal cell carcinoma (RCC) under nivolumab treatment reached an intracranial response rate of only 12%. Also, patients with metastases > 1 cm in diameter or those with multiple lesions did not attain the objective responses (18). Furthermore, the desired treatment results may not be generalized to the patients with symptomatic brain metastases and under high-dose steroids as most of the patients recruited in these studies had asymptomatic brain metastases and were treating with low doses of or no concomitant steroids. Also, the combination of immune-checkpoint inhibitors with SRS, and in particular, the sequence of administering each intervention remains to be further investigated (10).

The advent of small molecules has enabled notable improvements in patient survival. These molecules selectively bind and hinder various irregularly activated signaling pathways and have shown greater efficacy in patients with melanoma (BRAF-muted patients), non-small cell lung cancer (NSCLC) (such as those with EGFR mutations or ALK-rearranged disease), and breast cancer (those with HER2 positive disease). However, the reports are somehow controversial; while some studies represent partial responses (14, 19) and a short median duration of response and several, others support ameliorated response rates, overall survival (OS), and progression-free survival (PFS) duration compared with controls (20). Also, a wealth of clinical trials are in progress (e.g., NCT03769103, NCT03535363, NCT03911869, NCT00981890, and NCT04434560), and their results might be propitious.

Traditional cytotoxic drugs are not common therapeutic options in MBTs for their inability to penetrate into the blood-brain barrier (BBB) and the existence of efflux pumps that lead to poor efficacy (21). Most studies investigating the use of systemic medicines in patients with brain metastases have failed to show impressive response rates (22). Accordingly, a combination of steroids, radiation (whole-brain and/or stereotactic), and surgery remain the mainstay of treatment.

Despite the introduction of new local therapeutic approaches, such as surgery and radiotherapy or systemic therapies to control extracranial disease, there is still increased demand for specific therapies to target brain metastases, particularly in breast cancer patients. Currently, there are several accurate therapeutic options from whole-brain radiotherapy and surgery to stereotactic radiosurgery, targeted therapies, and immunotherapies, which are often used in sequence or simultaneously. Nevertheless, there is still a long way to reach the desired treatment outcomes.

Recognition of brain metastasis generating cellular and molecular mechanisms is likely to pave the way for the prevention or treatment of such disease as well as raising our knowledge towards personalized treatment of each patient. It is not far-fetched that further cellular and molecular findings review could provide new therapeutic targets in this regard.

Footnotes

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