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Pathobiology and Emerging Targeted Therapies in Brain Metastases: Summary of Preusser et al, Acta Neuropathol 2012

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Background

Brain metastases of solid cancers are frequent and pose a major medical challenge, as they are associated with high morbidity and poor prognosis. The incidence of brain colonization strongly depends on the tumour type, in some cancers also on the molecular subtype [1]. Lung cancers (both small-cell and non-small-cell lung cancer), breast cancer (particularly HER2positive and triple-negative subtypes), kidney cancer, and melanoma metastasize to the CNS most frequently, while brain metastases from other common cancers, such as prostate or colorectal cancer, are rare. The incidence of brain metastases has been noted to be rising. The reasons are likely multifactorial and include an increasing incidence of lung cancer associated with tobacco consumption, generally longer survival times of cancer patients, and increased use of cranial magnetic resonance imaging in the upfront staging and follow-up. Furthermore, the advent of novel therapeutic compounds with good anti-neoplastic activity but inadequate penetration via the blood-brain barrier (eg, trastuzumab in HER2-positive breast cancer) may also contribute to an increase of brain metastases by "banishing tumour cells into the protected exile CNS". The therapy of brain metastases currently relies mainly on surgery and radiotherapy (whole-brain and stereotactic/ unfractionated radiotherapies). Systemic antineoplastic therapy has shown limited or no efficacy in brain metastases although comprehensive studies are almost lacking [2]. However, recent studies have elucidated some of the aspects of brain metastasis formation and an increasing understanding of the pathobiology of brain colonization supports the development of targeted agents that inhibit brain metastasis formation in high-risk cancer patients or that successfully treat manifest brain metastases [3].

Pathobiology

Metastatic brain colonization involves tumour cell dissemination from primary tumours or extracranial metastases through the blood circulation, attachment to brain endothelial cells, extravasation into the parenchyma, and interaction with the local microenvironment. According to the "seed and soil" concept, brain colonization is driven by a specific affinity of certain tumour cells for the milieu of certain organs. The specific reasons for the variable brain-tropism among tumour types remain unclear although a relation to molecular factors rather than just to the anatomy of blood perfusion has been postulated [4]. Circulating cancer cells attach to brain endothelial cells primarily at vascular branch points and transendothelial migration is probably mediated by interaction of tumour cell surface receptors and endothelial cell adhesion molecules like integrins, selectins, and chemokines. Platelets and leukocytes may support metastasis formation (or are exploited by tumour cells to do so) via selectin-dependent bonding of tumour and endothelial cells [3, 5].

After brain invasion, cancer cells degrade the local extracellular matrix (ECM) by production of heparanase and matrix metallo-proteases to facilitate migration and growth. Resident glial cells including astrocytes and microglia seem to exert not only anti-neoplastic effects like production of inflammatory tumouricidal molecules (eg, nitric oxide), but may also have pro-neoplastic functions. For example, astrocytes have been shown to protect tumour cells upon physical contact and exchange of calcium through gap junctions [6].

Angiogenesis is a major step in brain metastasis formation and involves activation of the vascular endothelial growth factor receptor (VEGF) pathway. Interestingly, the angiogenic potential seems to differ between tumour types. Some tumour types, eg, non-small-cell lung cancer, depend on early neoangiogenesis for successful brain metastasis formation, while others, such as melanoma, tend to spread along existing vessels (so-called "vascular cooption") [7].

Targeted Therapy Approaches

Effective targeted therapy approaches are emerging for patients with brain metastases. Among them, the most promising include anti-angiogenic drugs, inhibitors of v-RAF murine sarcoma viral oncogene homolog B1 (BRAF) for BRAF V600E mutated melanoma, and inhibitors of the epithelial growth factor receptor (EGFR) for non-small-cell lung cancer. For a long time, anti-angiogenic agents were not studied in brain tumour patients due to concerns of an increased risk for intracranial haemorrhages. However, large meta-analyses did not confirm these concerns and trials studying anti-angiogenic approaches in brain metastases have therefore been initiated. The blood-brain barrier-stabilizing effect of such drugs needs to be taken into account in such studies, as it has an impact on neuroradiological presentation and thus response evaluation. Based on preclinical data, the anti-angiogenic drug bevacizumab may be effective in preventing brain metastasis formation in non-small-cell lung cancer [7].

Mutations of BRAF, most frequently of the V600E type, occur in a broad range of tumour types and are most common in melanoma (approximately 60 % of cases). We could recently confirm that the mutation frequency in brain metastases is similar to the mutation frequencies in primary tumours. Furthermore, we detected that the mutation status is consistent in multiple tumour manifestations in individual patients. Emerging clinical data show that novel BRAF inhibitors are remarkably active against BRAF V600E-mutated melanoma including patients with brain metastases [8, 9]. Patient selection for treatment with BRAF inhibitors requires reliable identification of the mutation in tumour tissue samples, either with DNA-based (eg, with the FDA-approved Cobas 4800 BRAF V600 test, Roche) or immunohistochemical techniques. Recently, a monoclonal antibody has been generated, which detects the BRAF V600E mutated protein in routinely formalinfixed and paraffin-embedded tissue samples, even in cases with only small tumour content [10, 11].

In non-small-cell lung cancer, several case reports and small patient series suggest that inhibitors of epithelial growth factor receptor (EGFR) such as erlotinib and gefitinib are active in brain metastases, particularly in cases with activating EGFR mutations [12, 13]. Interestingly, a lower frequency of CNS progression has been observed in patients with advanced non-small-cell lung cancer after treatment with EGFR inhibitors [14].

Summary and Conclusions

Some aspects of the pathobiology of brain metastases have been elucidated, leading the way to effective prophylaxis and targeted therapy. BRAF inhibitors seem to be effective in patients with brain metastases of BRAF V600E-mutated melanoma, although definite clinical trials comparing this class of drugs to standard therapy are lacking so far. Anti-angiogenic drugs have shown promising results in preclinical studies and seem to be safe in patients with brain metastases, thus warranting the conduct of well-controlled clinical trials. The results of ongoing and future basic research projects will be necessary to inform patients of the further development of rational treatment of brain metastases based on individual tumour characteristics. The design of clinical trials needs to take into account the large diversity of cancer entities associated with brain metastases and should implement molecular stratification factors whenever possible. The choice of adequate endpoints warrants special attention, as novel drugs may be associated with unusual neuroradiological features. Also, the

status of extracranial disease needs to be considered and quality-of-life as well as neurocognitive measures should be included in trial protocols. The development of more effective strategies for the prevention and treatment of brain metastases will profit by the formation of strong interdisciplinary and international scientific collaborations.

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