Personalized medicine in brain metastases: a plea for more translational studies

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Central nervous system (CNS) metastases account for over half of intracranial tumors in adults. The prognosis for affected patients still remains poor, with a median survival of only 1–2 months for patients with untreated brain metastases [1] and 3–21 months with treated brain metastases [2]. The frequency of brain metastases is rising in light of advanced imaging techniques, as well as increased patient survival due to better surgical and radiation approaches and emerging targeted therapies for systemic disease. Despite this increased frequency, the extent of treatments available for patients with brain metastases is limited because clinical trials rarely focus on brain metastases specifically. Furthermore, the patients with brain metastasis are often excluded from most randomized Phase III clinical trials unless they have treated, stable intracranial disease.

Whole-brain radiation therapy (WBRT) has been the mainstay of treatment for patients with brain metastases for several decades [3], but this treatment modality has been shown to be associated with neurocognitive decline [4]. In a recent seminal study by Brown *et al.*, patients with one to three brain metastases were randomized to receive either stereotactic radiosurgery (SRS) alone or SRS plus WBRT in combination. This publication revealed that the fewer patients were affected by cognitive deterioration at 3 months after SRS alone (63.5% of patients) than in the cohort treated with SRS plus WBRT (91.7% of patients) [5].

Although the addition of WBRT to SRS has been shown to decrease distant brain failure, a definitive improvement in overall survival (OS) has not been demonstrated [6].

Targeted therapies are showing much promise. Thus far, the most common targetable genetic mutations in non-small-cell lung cancer (NSCLC) brain metastasis include *EGFR*-mutations [7], *ALK*-translocations, and amplifications [8], while *HER2*-amplifications and *BRAF*-mutations account for the current most common targets in the treatment of breast cancer and melanoma brain metastases, respectively. Agents with improved CNS penetration are in clinical development. For example, a recent Phase I trial showed promising results for the third-generation *EGFR*-tyrosine kinase inhibitor osimertinib and the reversible *EGFR*m-inhibitor AZD3759 in patients with brain metastasis from NSCLC harboring these activating mutations. Osimertinib also showed radiographic improvement in patients with leptomeningeal disease, which is the most lethal complication of CNS metastases [9]. Moreover, favorable intracranial response rates were observed in patients with *ALK*-rearranged NSCLC brain metastases who were treated with next-generation *ALK*-tyrosine kinase inhibitors such as ceritinib and alectinib [10,11]. The antibody-drug conjugate trastuzumab emtansine (T-DM1) showed promising responses in the patients with brain metastasis from *HER2*-positive breast cancer [12]. However, median progression-free survival in patients receiving this combination treatment was still less than 7 months. The Phase II BREAK-MB (*BRAF*-mutant melanoma metastatic to the brain) trial demonstrated an extended progression-free survival and OS and intracranial response rates of 31.4% of patients with V600E or V600K *BRAF*-mutant progressive melanoma brain metastases who were treated with dabrafenib [13]. Moreover, vemurafenib has been shown to be effective in terms of intracranial tumor control and OS in patients with previously untreated and previously treated *BRAF*-mutated melanoma brain metastases in a recent Phase II multicenter study [14].

In addition, immune checkpoint inhibitors targeting CTLA-4 and PD-1 such as ipilimumab, nivolumab and pembrolizumab have shown exciting results in patients with advanced melanoma [15–17]. An early analysis of an ongoing Phase II trial on patients with untreated, asymptomatic brain metastases from melanoma and NSCLC treated with pembrolizumab showed favorable intracranial response rates (22% in patients with melanoma brain metastases and 33% in patients with NSCLC brain metastases) [18]. However, the majority of patients did not respond, highlighting the urgent need to add more therapies to the armamentarium for brain metastases.

Recently, our knowledge of the underlying biology and additional genetic driver mutations in brain metastases has increased substantially. In the largest genomic study on brain metastases and matched primary tumors to date (104 paired cases in total, across multiple histologies), whole exome sequencing revealed branched evolution in all clonally related tumor samples; all primary tumors and associated metastasis in this analysis shared a common ancestral clone, but continued to evolve independently. As a result of this divergent evolution, in more than 50% of all analyzed samples, brain metastases harbored oncogenic alterations not detected in the underlying matched primary tumor. Thus, biopsies of primary sites in the setting of intracranial metastases may miss a substantial number of potentially clinically significant alterations. Intracranial metastases from the same patient were relatively homogeneous with respect to their genetic driver alterations, while lymph node metastases and other distant extracranial metastases were genetically divergent from the analyzed brain metastases. Genetic alterations of the PI3K-AKT-mTOR-pathway as well as alterations of the CDK-, EGFR- and Ras-Raf-MAPK-pathway were frequently observed among patients with brain metastases from lung adenocarcinoma, breast cancer and melanoma as well as in patients with renal cell carcinoma [19].

Although the blood–brain barrier (BBB) remains a major impediment for the administration of chemotherapy because of its active efflux transporters as well as due to its low passive permeability [20,21] our knowledge about the BBB and the blood–tumor barrier has increased substantially in recent years. The blood–tumor barrier permeability was found to be quite heterogeneous and associated with vascular remodeling [22]. These findings further highlight the need for more research on the efficacy and distribution of targeted agents that are able to cross the BBB.

Clinical trials evaluating inhibitors of the PI3K- and the CDK-pathway in patients with brain metastases harboring mutations of these pathways are now ongoing (NCT02896335, NCT01132664 and NCT02774681). New agents targeting these pathways are being developed, but there still is an urgent need for more preclinical as well as clinical studies to further evaluate the impact of these compounds on survival and tumor response in patients with brain metastases.

In recent years, we also have gained more insight in circulating biomarkers in liquid biopsies such as plasma and cerebrospinal fluid (CSF) in patients with brain metastases: Some early data using targeted gene panels from cell-free circulating tumor DNA in the CSF show that CSF harbors genetic changes that are detected in brain metastases more so than plasma [23,24]. However, more studies in this field are needed in order to assess the clinical impact of these biomarkers as well as correlations of these biomarkers pre- and post-treatment in order to evaluate their diagnostic value.

Therefore, it will be important to further refine our understanding of the genetic and molecular drivers of brain metastasis. Specifically, work should focus on identifying clinically actionable mutations in brain metastases. Agents with penetration into the CNS need to be developed that specifically target the driver mutations in brain metastases. In order to transfer preclinical findings to the daily clinical practice, it will be crucial to design randomized, controlled clinical trials that selectively focus on patients with brain metastases. Taken together, encouraging treatment options have been developed for patients with brain metastases in recent years, but response rates are still limited. Consequently, more translational studies are urgently needed to further improve therapeutic options for affected patients.

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