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Treatment of brain metastases in the modern genomic era

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ABSTRACT

Development of brain metastasis (BM) portends a dismal prognosis for patients with cancer. Melanomas and carcinomas of the lung, breast, and kidney are the most common malignancies to metastasize to the brain. Recent advances in molecular genetics have enabled the identification of actionable, clinically relevant genetic alterations within primary tumors and their corresponding metastases. Adoption of genotype-guided treatment strategies for the management of systemic malignancy has resulted in dramatic and durable responses. Unfortunately, despite these therapeutic advances, central nervous system (CNS) relapses are not uncommon. Although these relapses have historically been attributed to limited blood brain barrier penetration of anti-neoplastic agents, recent work has demonstrated genetic heterogeneity such that metastatic sites, including BM, harbor relevant genetic alterations that are not present in primary tumor biopsies. This improved insight into molecular mechanisms underlying site specific recurrences can inform strategies for targeting these oncogenic drivers. Thus, development of rational, genomically guided CNS-penetrant therapies is crucial for ongoing therapeutic success.

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1. Introduction

Brain metastases (BM) are the most common intracranial tumors in adults (Johnson & Young, 1996). Metastases from lung, breast, and melanoma primary malignancies account for 67–80% of BM (Schouten et al., 2002; Barnholtz-Sloan et al., 2004). Although metastases can also involve the cranium, leptomeninges, pituitary gland, pineal gland, or choroid plexus, most metastases arise within the brain parenchyma.

The annual incidence of BM is reported to be between 8.3 and 14.3 per 100,000 population (Percy et al., 1972; Walker et al., 1985; Counsell et al., 1996; Schouten et al., 2002). However, this estimation is likely to be an underestimation as it relies on data collected prior to the advent of modern imaging techniques. Indeed, some autopsy studies have reported BM in up to 25% of patients with cancer (Posner & Chernik, 1978; Nayak et al., 2012).

Survival after developing BM is dismal, with some patients dying within 3 to 4 months of diagnosis (Gaspar et al., 1997; Lagerwaard et al., 1999; Hall et al., 2000). Factors that predict for longer survival after the development of BM include younger age, higher performance status, low systemic tumor activity, site of primary, and the presence

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of an isolated CNS lesion (Gaspar et al., 1997; Hall et al., 2000; Sperduto et al., 2012). Traditionally, treatment approaches have primarily included surgical resection, radiation therapy, and adjunctive therapies directed towards symptom palliation. In patients with a high burden of BM, whole brain radiation therapy (WBRT) remains the standard approach. In contrast, surgical resection and stereotactic radiosurgery (SRS) are often used in patients with a limited number of BM. Randomized control trials have demonstrated improved survival, decreased local recurrence, and improved quality of life with surgical resection followed by adjuvant WBRT compared with WBRT alone (Patchell et al., 1990; Vecht et al., 1993; Noordijk et al., 1994).

As acute and delayed toxicities from WBRT can be substantial, current practice favors SRS to the resection cavity for patients with solitary BM who have undergone surgical resection (Chang et al., 2009; Brown et al., 2015; Habets et al., 2015). Although we are awaiting the results of the NCCTG N107C randomized controlled trial comparing SRS and WBRT following surgical resection (NCT01372774), published studies report a 1-year local control rate with SRS of 70 to 80% which is at least equivalent to WBRT, but is associated with far less neurotoxicity (Mathieu et al., 2008; Karlovits et al., 2009; Jensen et al., 2011; Brennan et al., 2014). Similarly, there are no reported prospective randomized controlled trials comparing definitive SRS to surgery. The local control rate with SRS alone in older studies, however, approaches 85% at 1 year (Flickinger et al., 1994; Alexander et al., 1995; Andrews et al., 2004; Aoyama et al., 2006).

Systemic therapy, particularly chemotherapy, has historically been inadequate in producing durable responses in patients with BM. Much of the difficulty in achieving adequate CNS disease control with chemotherapy has been attributed to limited blood brain barrier (BBB) penetration of chemotherapeutic agents (Lockman et al., 2010). Incorporation of targeted therapies into standard treatment paradigms has led to improvements in controlling both extra-cranial and CNS disease. Experience with these targeted agents has already reshaped treatment approaches, particularly the sequencing of local and systemic therapies. Lessons learned from the successes and failures of these new agents will likely inform the development of guidelines for incorporating genomic information into clinical decision making.

Undoubtedly, characterizing the genomic complexity and heterogeneity of BM will be of utmost importance in developing rational treatment strategies for patients with BM. Advances in molecular genomics and analytical approaches have led to increased appreciation of the often vast genetic heterogeneity between BM and corresponding primary tumors. A disproportionate distribution of oncogenic drivers resulting in detection of some drivers exclusively in BM has recently been reported (Brastianos et al., 2015). This heterogeneity likely contributes to disparities in extra-cranial and CNS responses to therapeutics. In this review, we discuss how knowledge of the genomic context within which cancers arise can inform rational drug selection, summarize the early clinical experience with newer targeted agents in patients with BM, and discuss the potential of large scale genomic studies of BMs to refine our approach to treatment of this unique patient population.

2. Lung cancer

Lung cancer, particularly nonsmall cell lung cancer (NSCLC), is the most common primary malignancy to metastasize to the brain (Nayak et al., 2012). Adenocarcinoma histology accounts for the majority of BM. At initial diagnosis of NSCLC, 45% of patients will have localized or locally advanced disease (Spiro et al., 2007). Even in patients presenting with resectable disease, risk of BM at the time of recurrence is reported as 11% at 5 years (Hubbs et al., 2010; Consonni et al., 2015). The risk of BM at relapse is increased for younger patients, patients presenting with larger tumors, tumors with lymphovascular invasion, higher grade tumors, and tumors presenting at a more advanced stage (Hubbs et al., 2010; Consonni et al., 2015). Approximately 30–50% of patients with NSCLC will develop BM during the course of their disease.

The genomic revolution over the last decade facilitated the discovery and characterization of several NSCLC oncogenic drivers. It is now generally accepted that NSCLC consists of several molecular subgroups characterized by unique clinicopathologic features and distinct outcomes. Prioritizing genotype-guided therapies over traditional chemotherapy has translated into improved survival in select patients (Kris et al., 2014). This success has fueled efforts to identify additional relevant NSCLC oncogenic drivers. While most efforts have focused on molecular characterization of primary lesions, a recent study comparing BM and associated lung adenocarcinomas reported enrichment for mutations involving the cyclin-dependent kinase pathway and the PI3K/AKT/mTOR axis in BM (Brastianos et al., 2015).

2.1. Epidermal growth factor receptor mutant lung cancer

Approximately 10–15% of patients with NSCLC in the United States will have an activating mutation in the epidermal growth factor receptor (EGFR) tyrosine kinase domain that confers sensitivity to EGFR tyrosine kinase inhibitors (TKIs). These mutations are particularly enriched in patients with adenocarcinomas who are never-smokers or light smokers and are of Asian ancestry (Pao et al., 2004; Rosell et al., 2009). Several large trials have demonstrated superiority of first generation EGFR TKIs compared with conventional chemotherapy in patients with EGFR-mutant lung cancer, with reported response rates of around 70% and median progression free survival (PFS) of approximately one year (Mok et al., 2009; Rosell et al., 2012). Similarly, recent trials have confirmed improved response rates and PFS with upfront use of the second generation EGFR inhibitor, afatinib, compared with chemotherapy (Sequist et al., 2013; Wu et al., 2014).

Prospective studies exploring the efficacy of EGFR TKIs in patients with BM are lacking. The limited data, however, suggests that EGFR TKIs have clinical activity in patients with BM. One prospective open-label single institution Phase 2 study reported an 83% objective response rate (ORR) in 28 patients with BM treated with gefitinib or erlotinib (Park et al., 2012). Notably, the response rate with first generation EGFR TKIs in this study is much higher than that reported from other groups (Porta et al., 2011; Heon et al., 2012). Reports indicate that the cerebrospinal fluid (CSF) concentration of erlotinib is significantly lower than that in the plasma (Broniscer et al., 2007; Togashi et al., 2010). Pulsed dosing has been proposed as a strategy to overcome this limitation. Unfortunately, however, pulse-dosed erlotinib may not appreciably increase TKI concentration in the CSF (Jackman et al., 2013).

Next-generation EGFR TKIs have shown promise as a treatment strategy for patients with BM. For example, a recent subgroup analysis of 81 patients with BM treated with upfront afatinib in the prospective LUX-Lung 3 and LUX-Lung 6 trials reported an ORR of 82% (Schuler et al., 2016). In a pooled analysis from these studies, compared with chemotherapy, treatment with afatinib improved median PFS and time to CNS progression from 5.4 months to 8.2 months and from 7 months to 15.2 months, respectively. Afatinib also appears to be an active agent in pretreated patients with BM. Indeed, a 35% intracranial ORR and 66% intracranial disease control rate were observed in 31 pretreated patients who received afatinib through a compassionate use protocol (Hoffknecht et al., 2015). Use of newer third-generation T790M-mutant specific EGFR TKIs has led to durable systemic responses for patients who have experienced disease progression on first- and second-generation EGFR TKIs (Jänne et al., 2015; Sequist et al., 2016). Additionally, the FDA-approved third-generation TKI osimertinib was recently shown to have preclinical activity in BM models and clinical activity against BM in patients with *EGFR*-mutant NSCLC (Ballard et al., 2016).

Several studies have examined the appropriate sequence of radiation therapy and TKIs in patients with sensitizing *EGFR* mutations. A retrospective analysis suggested that EGFR TKIs might have a role as