

# Drug Development for Brain Metastases

By Karen Kelly, MD, and Tianhong Li, MD, PhD

**Overview:** The incidence of brain metastases is rising as a result of improvements in local and distant therapies and increased detection. As more patients live long with their disease they become at increased risk for brain metastases. Systemic therapy for brain metastases has been a longstanding challenge with only a few active agents available. The major obstacle is limited drug delivery because of poor penetration through the blood-brain barrier (BBB). Animal models have shown the anatomic BBB is altered in the presences of brain metastases but remains highly functional. Numerous strategies to enhance drug delivery through the BBB are under investigation. One exciting new approach uses nanoparticle technology to carry drugs across the BBB. Nano-

particles are attractive because of their small size and ability for high drug loading. In a similar fashion, Trojan horse technology exploits the BBB endogenous carrier system to ferry drugs through the BBB. Novel agents are also showing promise. In particular, molecularly targeted agents that produce dramatically high response rates in extra central nervous system disease have shown encouraging results. Overall there has been a renewed enthusiasm for discovering active therapies for brain metastases. This review will summarize our current understanding of the challenges to systemic therapy for brain metastases, discuss current approaches to overcome them, and address their clinical evaluation.

**B**RAIN METASTASIS is an ominous complication for patients with cancer. In comparison to other sites of metastases, brain involvement is associated with a poorer prognosis, debilitating mental and physical impairment, and specialized treatment. In recent years an increase in the incidence of brain metastases has been observed. Two major factors account for this increase: 1) the widespread use of screening magnetic resonance imaging (MRI) or computed tomography (CT) scans; and 2) improvements in local and distal therapies. Patients with controlled extra central nervous system (CNS) disease are living longer only to be placed at high risk for brain metastases to which they will succumb. Radiation and/or surgery are highly effective local therapies for treating brain metastases but breakthroughs in the management of brain metastases will ultimately require a systemic approach. Despite decades of research, only a limited number of drugs are available to treat brain metastases highlighting the challenges we face in CNS drug development. Nonetheless, there is an urgent need to develop active systemic therapy for brain metastases. Fortunately there has been a significant improvement in experimental models of brain drug delivery, an increased knowledge of the biology of brain metastases, and a plethora of novel agents to evaluate that have reinvigorated our enthusiasm and likelihood for success. This review will discuss the challenges and recent advances in drug development for brain metastases.

## Barriers to Drug Delivery

A longstanding impediment to the successful development of systemic agents for brain metastases is the notorious BBB. The BBB is a highly specialized structure whose sole function is to protect the brain from exposure to harmful substances including cancer drugs. Drugs in the blood can only enter the brain by passive diffusion or active transport across the BBB. Its unique composition of brain capillaries with their continuous tight junctions, no fenestrations, and few pinocytotic vesicles that are insulated by a basal membrane, astrocyte footpads, and pericytes is a formidable barricade. In addition to this anatomic barrier, there are functional barriers including an active efflux transporter system and electrical resistance. Our understanding of the integrity of BBB in brain metastases is paramount to our drug development efforts. There is ongoing debate over the permeability of the BBB and its influence on drug delivery.

Is the BBB intact or compromised in patients with brain metastases? The contradictory clinical evidence suggests the answer is complicated. Emerging data from our laboratory colleagues have shed light onto this question. By using a new experimental animal model that establishes brain metastases from the systemic circulation via intracardiac injection of tumor cells rather than intracerebral injection of tumor cells, Lockman and colleagues evaluated the integrity of the BBB in more than 2,000 metastatic lesions.<sup>1</sup> The BBB showed partial permeability in 89% of the metastatic lesions but the permeability was markedly heterogeneous and was not associated with the size of the brain lesion. Treatment of the brain metastases with paclitaxel or doxorubicin revealed drug uptake was slightly higher in metastatic lesions than in the normal brain but cytotoxic concentrations could only be reached in 10% of most permeable tumors. This data clearly demonstrate that the BBB is impaired but remains sufficiently functional to prevent drug delivery.

The BBB's active efflux system further compounds brain drug delivery. Numerous transporters located on the apical side of the brain's endothelial cells are responsible for restricting drug uptake by actively pumping drugs back into the blood circulation.<sup>2</sup> Most transporters belong to the ATP-binding cassette (ABC) transporter family and include the well known P-glycoprotein, the multidrug resistance-associated proteins (MRPs), and the ABC sub-family G member 2 (ABCG2 or breast cancer-resistant protein, BCRP). Recently, organic anion and cation transporters (OATs and OCTs) were identified. They differ from ABC transporters in that they depend on energy from ionic or drug gradients for active transport.<sup>2</sup>

## Brain Drug Characteristics

Two major factors must be carefully considered when deciding to pursue an agent for the treatment of brain metastases: 1) its antitumor activity in the malignancy of interest; and 2) its ability to cross the BBB. Both features

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must be sufficiently high to proceed with testing. There is literature to suggest that objective tumor responses in the brain can occur at the same rate as that in other metastatic sites.<sup>3</sup> Thus agents with very high response rates in extra CNS disease should be considered for evaluation in brain metastases. Drug properties that are important in determining an agent's likelihood of penetrating the BBB are molecular weight (compounds < 400 daltons [D] that can passively diffuse through the BBB), lipid solubility (high lipid solubility assists in dissolving through the initial lipid membranes of the BBB), polarity (nonpolar compounds are undetected by the BBB's high electrical resistance), plasma protein binding (low plasma protein binding increases the availability of free drug to cross the BBB), half-life (drugs in the blood circulation for a longer period of time have more opportunity to enter the BBB), and known target of the BBB active efflux system (drugs that are targets of the efflux system should be avoided unless there is possibility that the drug can be modified).<sup>4</sup> Unfortunately, most anticancer agents, cytotoxics, and molecularly targeted agents exhibit one or more unfavorable characteristics. For example, frequently used chemotherapy agents such as docetaxel, gemcitabine, pemetrexed, and irinotecan have high plasma protein binding and are the targets of the BBB efflux system whereas small molecule tyrosine kinase inhibitors, imatinib, lapatinib, and erlotinib are substrates for efflux transporters.

## Other Challenges

### Neuropharmacokinetics

The lack of tools to evaluate pharmacokinetics (PKs) in the brain (i.e., neuropharmacokinetics) has hindered our ability to select the appropriate drug doses and schedules. Recently, investigators have taken advantage of an old technology used to study biochemical changes in acute brain injury known as intracerebral microdialysis (ICMD) and applied it to the study of drug concentrations. Nine patients with primary or metastatic brain tumors had a microdialysis catheter placed in peritumoral brain tissue at the time of surgical debulking to evaluate the PK of temozolomide.<sup>5</sup> They demonstrated that the use of ICMD was safe and feasible. Importantly, the neuropharmacokinetics data suggested that the temozolomide dosing may be suboptimal. ICMD appears to be a promising research tool that should be incorporated into the early investigation of new brain drugs.

### KEY POINTS

- The incidence of brain metastases is increasing.
- The blood–brain barrier is the major obstacle to brain drug delivery.
- New animal models of brain metastases have convincingly demonstrated that the blood–brain barrier exhibits increased permeability but remains highly functional, impeding drug delivery.
- Advances in drug formulation have led to novel approaches to penetrate the blood brain barrier.
- Molecularly targeted agents are showing promise in the treatment of brain metastases.

### Neuroimaging

MRI is the traditional imaging modality to assess anti-tumor response to drug therapy, but for early evaluation of new agents to assess drug delivery and drug targeting, alternative imaging is needed. An attractive initiative is to make drugs trackable by MRI or positive emission tomography. Animal studies using a positron emitter-labeled liposomes and multifunctional nanoparticles that can be tracked by MRI have shown success.<sup>6,7</sup>

### Strategies to Enhance Drug Delivery to the Brain

These new insights into the BBB plus advances in drug formulation have lead to several novel approaches to enhance drug delivery to the brain.

#### Carrier-mediated Drug Delivery Systems

**Nanoparticles.** Nanoparticle technology has emerged as an exciting new drug delivery strategy.<sup>8</sup> Nanoparticles are particularly attractive for enhancing drug delivery across the BBB because of their small size, typically ranging from 20 to 250 nm, high drug loading capability, and their hydrophilic outer shells or coatings. Once inside the BBB, the drug can be released and then passively or actively transported to the brain. Animal studies evaluating nanoparticle delivery to the brain have shown notably higher concentrations of several chemotherapeutic agents including doxorubicin, paclitaxel, and camptothecin in the brain when delivered by nanoparticles as compared with chemotherapy alone.<sup>9</sup> Researchers at the University of California, Davis have developed a nanoparticle formulation of lapatinib (Li, personal communication; January 2011). After further preclinical testing including evaluation in brain metastasis, a phase I clinical trial in breast cancer with brain metastasis is of high priority.

**BBB molecular Trojan horses.** The BBB molecular Trojan horse technology exploits the BBB endogenous receptor carrier system that ferry essential brain substances from the blood to the brain.<sup>10</sup> Trojan horses are endogenous peptides or peptidomimetic monoclonal antibodies (mAb) with specific characteristics. They must have high BBB receptor affinity and drug binding that is retained during transcytosis, high brain uptake, and in vivo CNS effects can be observed following systemic administration. Peptidomimetic mAbs to the insulin and transferrin receptors are two examples of Trojan horses. In animal models a mAb to the transferrin receptor conjugated with daunorubicin delivered considerably more drug to the brain than the drug alone.

**Substrate analogs.** Agents designed to mimic natural substrates of influx transporters conjugated to an active drug is another viable strategy under investigation. For example, the L-type amino acid transport 1 (LAT-1) is responsible for transporting melphalan to the brain.<sup>2</sup>

#### Efflux Transporter Inhibitors

Years ago, efflux transporters were found to be expressed on tumors cells and determined to be a major mechanism of chemotherapy resistance. In an attempt to overcome this mechanism of drug resistance efflux transporter inhibitors were developed. Several inhibitors to P-glycoprotein and MRPs were extensively evaluated in a variety of hematologic malignancies and solid tumors but produced disappointing results.<sup>2</sup> Although this history dampens the enthusiasm

for evaluating transporter inhibitors in the BBB, they are worthy of preliminary exploration. Recently investigators showed that erlotinib penetration into the brain was limited predominantly by the ABCG2 transporter and secondarily by P-glycoprotein.<sup>11</sup> The dual P-glycoprotein/ABCG2 inhibitor elacridar increased erlotinib cellular accumulation in *in vitro* experiments. Studies to delineate the effects of ABC transporter inhibitors on erlotinib delivery to the brain are planned.

### BBB Disruption

A unique technology to enhancing drug delivery to the brain is the concept of BBB disruption. Transient osmotic disruption of the BBB is achieved through intra-arterial infusion of mannitol, which is then followed by chemotherapy. This technique has been used extensively in patients with primary brain tumors and is associated with a low complication rate.<sup>4</sup> A few trials in metastatic disease are under consideration. A noninvasive approach uses ultrasound technology to disrupt the BBB. Several studies have shown that acoustical energy from focused ultrasound (FUS) can cause localized disruption of the BBB.<sup>12</sup> By using MRI-guided FUS BBB disruption, herceptin and doxorubicin have been successfully delivered to rodent brains.<sup>13,14</sup> The next steps are to assess the feasibility, safety, and neurotoxicity of serial FUS drug delivery.

### Promising Agents

#### Bevacizumab Monoclonal Antibody

The approval of bevacizumab in the treatment of recurrent glioblastoma has generated interest in its evaluation for the treatment for metastatic brain tumors. Bevacizumab, a mAb against vascular endothelial growth factor (VEGF), has an approximate molecular weight of 149 kD and a half-life of 20 days. The original rationale for evaluating bevacizumab in the treatment of glioblastoma was as a mechanism to increase chemotherapy delivery to tumors. Several retrospective case series and small prospective trials of bevacizumab plus chemotherapy such as irinotecan, temozolomide, and carboplatin, demonstrated antitumor activity.<sup>15</sup> However, increased toxicities primarily from chemotherapy lead to the evaluation of bevacizumab alone. Glioblastomas are very vascular tumors whose tumor growth is tightly associated with its blood supply. Thus, it is not surprising that glioblastomas produce high levels of VEGF. In the first pivotal study of bevacizumab monotherapy, an encouraging 6-month progression-free survival (PFS) rate of 29% was achieved in 48 patients.<sup>16</sup> The objective response rate was 35% and the median survival time was 31 weeks. Interestingly, half of the patients showed neurologic symptom improvement, a decrease in corticosteroid requirement, and a decrease in cerebral edema on MRI. In the larger study, 167 patients were randomly assigned to bevacizumab or bevacizumab plus irinotecan.<sup>17</sup> At 6 months the PFS rate was 42.6% and

50.3%, respectively, exceeding the 15% PFS seen in historic controls. Overall survival times were similar at 9.2 months and 8.7 months. The objective response rate was 28.2% for bevacizumab and 37.8% for the combination. This study also observed a trend toward lower or stable corticosteroid usage. Bevacizumab was well tolerated and safe in both studies. Bevacizumab continues to be evaluated in glioblastoma along with several angiokinases inhibitors.

In metastatic brain disease, large registry data have demonstrated that bevacizumab can be safely administered to patients with treated brain metastases without increased toxicity, especially hemorrhage.<sup>18</sup> Anecdotal case reports in patients with brain metastases from lung, breast, and colon cancers treated with bevacizumab do suggest activity with tumor shrinkage, improvement in neurologic symptoms, and reduced corticosteroid dependence.<sup>19-21</sup> Studies of bevacizumab and other antiangiogenesis inhibitors in brain metastases are warranted.

#### GSK2118436: Small Molecule Kinase Inhibitor

Most recently, results from a phase I/II trial of GSK2118436, an oral mutant BRAF kinase inhibitor, has captured our attention. Nine of 10 patients with melanoma with one or more asymptomatic, small, untreated brain lesions had a 20% to 100% reduction in the size of their brain metastases.<sup>22</sup> Ninety percent of patients had the V600E mutation in the *BRAF* gene. Tumor shrinkage in the brain correlated with shrinkage at other distant sites; however, responses were short lived. A phase II trial to determine the role of GSK2118436 as a treatment for brain metastases in melanoma is recruiting patients (NCT01266967). CNS delivery and pharmacokinetics of GSK2118436 will need to be further elucidated. Nonetheless, tumors that are driven by a single mutation tend to be exquisitely sensitive to their small molecule targeted inhibitor, therefore even a modest amount of drug crossing the BBB could have a dramatic effect. Case reports demonstrating the efficacy of erlotinib and gefitinib in the treatment of CNS metastases in patients with lung cancer with epidermal growth factor receptor mutations have been published.<sup>23,24</sup> This strategy of producing highly efficacious drugs for non-CNS metastatic disease will play an important role in developing drugs for treating brain metastases. Currently, there are many ongoing and planned early phase clinical trials using different novel molecularly targeted agents for the treatment of patients with brain metastases ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

### Conclusion

As the number of cancer survivors increase, the development of systemic therapy with activity against brain metastases must become a priority. In the past the major hurdle to brain drug therapy has been the BBB, but with significant advances in our understanding of this barrier several novel delivery platforms are showing promise. These recent discoveries coupled with an increasing number of active anti-cancer agents provide a solid framework for success.

# Authors' Disclosures of Potential Conflicts of Interest

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