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Barriers to Effective Drug Treatment for Brain Metastases: A Multifactorial Problem in the Delivery of Precision Medicine

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Abstract

The treatment of metastatic lesions in the brain represents a serious unmet medical need in the field of neurooncology. Even though many effective compounds have demonstrated success in treating peripheral (non-CNS) tumors with targeted agents, one aspect of this lack of success in the brain may be related to poor delivery of otherwise effective compounds. Many factors can influence the brain delivery of these agents, but one key barrier is a heterogeneously “leaky” BBB that expresses efflux transporters that limit the BBB permeability for many targeted agents. Future success in therapeutics for brain metastases must take into account the adequate delivery of “active, free drug” to the target, and may include combinations of targeted drugs that are appropriate to address each individual patient’s tumor type. This review discusses some issues that are pertinent to precision medicine for brain metastases, using specific examples of tumor types that have a high incidence of brain metastases.

Keywords

blood-brain barrier; brain metastases; drug delivery; efflux transporters; metastasize; molecularly-targeted anti-cancer agents

INTRODUCTION

Metastatic spread of tumor cells from primary lesions to distant organs is a significant concern in the management of patients suffering from cancer (1,2). The formation of tumor metastases in vital organs, particularly the brain, can lead to a dismal quality of life and ultimately organ failure and death. Brain metastases are difficult to detect and diagnose, especially early in the disease course (3). Even after diagnosis, metastases to the brain are difficult to effectively treat due to various challenges associated with their treatment. While limited numbers of discrete metastases can be effectively treated with focal radiation and/or surgery, these patients have a high risk of subsequent metastases developing from pre-existing sub-clinical ‘micrometastases’ that are not detectable at the time of focal therapy. Patients with advanced brain disease (>10 metastases), or otherwise at high risk for

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micrometastases, are typically treated with whole brain irradiation, which is associated with an adverse effect on neuro-cognitive function (4,5). Thus, in light of the significant morbidity associated with radiation, efficacious small molecules that could effectively replace whole brain radiation therapy could have a significant positive impact on patients requiring treatment for brain metastases.

There has been important progress in the development of anti-cancer therapeutics, including molecularly-targeted agents (6–9) and novel immunotherapies (10). Both of these modalities are clearly efficacious towards tumors at the primary site (6–10), however, it remains a struggle to deliver these therapeutics across an intact BBB to many metastatic sites in the brain (11). The capillaries and associated cellular components in the brain have a highly specialized structure called the blood-brain-barrier (BBB) or neurovascular unit (NVU) that keeps many solutes, especially water-soluble solutes and large molecules, out of the brain (12). The tight junctions between the endothelial cells in the BBB in conjunction with multiple transport systems, both influx and efflux, regulate selective movement of molecules across the BBB into the brain (12) (Fig. 1 - a depiction of the NVU with transporters). Such mechanisms prevent the entry of various drugs, intended for the treatment of CNS diseases, into the brain. Specifically, many small molecule anti-cancer targeted agents have been shown to be substrates of active efflux transporters at the BBB, resulting in limited brain penetration of such therapies (Tables II, III, and IV) (13,14).

Another key issue for the treatment of brain metastases is the difference in gene expression profiles in tumor cells growing in the brain microenvironment compared to the peripheral (non-brain) lesions (15). The local tumor microenvironment between the brain and peripheral tumor lesions can potentially dictate that such differences will ultimately result in the development of resistance to therapies. This is a critical issue that needs to be tackled along with brain drug delivery to effectively treat tumors in the brain. While we recognize the importance of microenvironment in the context of resistance, the main focus of this review is to discuss aspects related to the delivery of targeted agents to the brain. We will give a brief overview on the clinical presentation of brain metastases as well as the currently available therapeutic options, before describing the difficulties encountered in the treatment of brain metastases.

Clinical Presentation of Brain Metastases

Brain metastases, a devastating complication of systemic malignancies, substantially raise the burden of cancer morbidity and mortality (1,2). They typically stem from hematogenous spread that seed at the distal fields of the main cerebral arteries (the “anatomic watershed areas”) (16). Consequently, approximately 80% of brain metastases are localized in the cerebral hemispheres (16). Initial symptoms at diagnosis range from headaches and seizures to focal neurological deficits and cognitive dysfunction; however asymptomatic brain metastases are also commonly found during initial staging exams. The symptoms presented by the patients often depend on the location of lesions and extent of metastatic disease burden (16).

Population studies underestimate the true incidence rates of brain metastases because of issues related to diagnosis and underreporting. The incidence of brain metastases, observed

in 8.5–9.6% of cancer patients, is estimated to be approximately ten times higher compared to primary brain tumors that represent 1.4% of cancer patients (17–20). Lung cancer, breast cancer, melanoma and renal cancer have a high propensity to metastasize to the brain and account for up to 80% of brain metastases (Table I and Fig. 2) (21). Patients with lung cancer are likely to develop brain metastases during the course of the disease (reported to be 16.3–19.9% of lung cancer patients (17,18)). This incidence can be as much as 50–60% in other reports, depending on individual study methods and analyses (22,23). Small cell lung cancer (SCLC) is known to be associated with a slightly higher occurrence of brain metastases than non-small cell lung cancer (NSCLC) at 5 years after the diagnosis, but the incidence rates of brain metastases for both subtypes tend increase over the course of the disease (22,23). The treatment of SCLC patients with prophylactic intracranial radiation following completion of definitive radio/chemotherapy markedly reduces subsequent risk of brain metastases and is associated with a survival benefit (24,25). Incidence of brain metastases from breast cancer is second to that of lung, even though only 5% breast cancer patients develop brain metastases, due to the high overall incidence of breast cancer (21,26,27). Autopsy series reveal brain metastases in about 30% of patients dying from breast cancer (28). Melanoma accounts for 6–11% of all metastatic brain lesions, and is the third most frequent cause of brain metastases. The observations from clinical and autopsy series estimate that the incidence of brain metastases in patients with malignant melanoma ranges from 10 to 70% (29–32). While lung cancer is reported to have the largest proportion of incidence of brain metastases, melanoma has the highest predilection to metastasize to the brain (21).

Several reasons contribute to the rising incidence of brain metastases. Advanced imaging techniques have improved the detection of occult brain metastases. Preliminary MRI screening for brain lesions is now routinely practiced for patients with newly diagnosis advanced lung cancer even in the absence of neurologic symptoms (21,24). Another possible reason for the increased incidence of brain metastases is that the median survival of patients with peripheral (non-brain) tumors is prolonged due to the novel therapeutic agents, that introduces the time it can take for the peripheral tumor cells to spread to the brain and thus, cause metastatic lesions in the brain (20,33). The restricted entry of systemically active therapeutic agents into the brain is another contributor to the increasing incidence of brain metastases because it creates pharmacological sanctuary that nurtures and protects the tumor cells to thrive in the brain (13,14). Thus, to advance drug therapies that are effective for controlling brain metastases, the field needs to consider that the BBB is likely intact in some regions of the tumor, especially in early non-contrast enhancing micrometastases, and can compromise the penetration of anti-cancer agents across the BBB (14,34,35).

Current Therapy for Brain Metastases

The initial treatment of brain metastases involves the management of acute symptoms. For instance, the use of glucocorticoids to alleviate symptoms secondary to brain edema, and anti-epileptic drugs (AEDs) to treat seizures. However, coadministration of AEDs and anti-cancer agents can increase the potential risk of clinically significant drug-drug interactions because of the shared metabolic pathways or transport systems across these different drug regimen (36,37). Some AEDs can modulate the hepatic cytochrome (P450) enzymes and/or

expression of drug transporters, causing an increase or decrease of systemic drug exposures, each of which can have consequences on resulting efficacy or toxicity. Such a complex interplay between transporters and drug-metabolizing enzymes (38,39), along with reduced drug delivery to the brain, can result in undesirable therapeutic outcomes in patients with brain metastases.

Surgical resection is the preferred treatment option, in part because as yet only surgery can drastically reduce the tumor mass in the brain (40) and improve survival outcome (Fig. 3. Treatment options). In cases where surgical resection is not feasible due to multiple low-volume metastases or inaccessible or eloquent locations where tumor cannot be surgically resected, alternative approaches such as stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT) are considered. SRS delivers high-dose of radiation to a specific region, whereas WBRT delivers to the whole brain. While surgery or SRS can provide a high rate of durable local tumor control, both of these strategies do not reduce the significant risk of developing additional brain metastases. In contrast, WBRT can reduce the risk of intracranial relapses, but the lower dose applied to the entire brain associated with this treatment failed to improve overall survival and is associated with a risk of neuro-cognitive impairment (41).

Systemic therapies have historically been considered ineffective against brain metastases. However, examples of limited success with systemic therapies have been reported in patients with brain metastases. For example, in patients with chemotherapy-naive brain metastases, the combination of cisplatin and etoposide achieved an overall objective response rate of 38% in breast cancer and 30% in NSCLC (42). Also, treatment with a combination of carboplatin and pemetrexed exhibited an overall response rate of 40% in patients with chemotherapy-naive brain metastases from NSCLC (43). In addition to these studies, several clinical trials also report limited efficacy from using a combination therapeutic approach in order to treat various types of cancer. The phase II LANDSCAPE trial, a combination therapy with lapatinib and capecitabine resulted in an objective partial response rate of 66% in patients with brain metastases from HER2-positive breast cancer (44). The phase II BREAK-MB study showed that in patients with V600E BRAF mutant melanoma meta-static to the brain, dabrafenib had an overall objective response rate of 39% in treatment naive patients, and 31% in patients that were previously treated (45). An open-label pilot study with vemurafenib reported an objective response rate of 42% in patients with non-resectable, symptomatic brain metastases from BRAFV600 mutation-positive melanoma that were previously treated (46). However, there were no overall survial benefit with these therapeutics, even though there have been partial responses. Lapatinib, dabrafenib and vemurafenib, are all substrates for both P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and the observed limited therapeutic responses might be in part due to transporter-mediated efflux and consequential restricted drug delivery to the brain metastases (Tables II, III, and IV). Transporter-mediated efflux and the consequential poor brain penetration across an intact BBB can severely limit the effectiveness of targeted therapies used in the treatment of brain tumors (13,14). Also, a heterogeneous brain-tumor barrier permeability can lead to non-uniform drug distribution in various sites of brain metastases adding another level of complexity in the treatment of brain metastases (11,47,48).

Barriers to Effective Treatment

Limitations in diagnostic imaging for early brain metastases are an obstacle for early detection and diagnosis of the disease. Magnetic resonance imaging (MRI), the most commonly used imaging method, utilizes a hydrophilic contrast dye, gadolinium diethylene-triamine-pentaacetate (Gd-DTPA). However, Gd-DTPA was reported to fail to visualize early-stage brain metastases that have little angiogenesis and BBB disruption, which will be problematic for early diagnosis of brain metastases (49), due to its poor distribution to the brain across an intact BBB. Moreover, a recent study has shown that repeated exposure to gadolinium-based contrast agents can lead to an increase in gadolinium deposition in the endothelium and neuropil even in the absence of intracranial abnormalities, that can significantly interfere with the MR signal (50,51). Therefore, it is difficult to rely on Gd-DTPA contrast enhancement to identify brain metastases, especially small-volume lesions, or “micro-metastases” (52).

The exclusion of brain tumor patients from clinical trials is yet another barrier to develop effective treatments for brain metastases. Since metastatic brain lesions may be difficult to control, associated with significant morbidity, and are associated with a dire prognosis, clinical trials often specifically exclude patients with known brain metastases. In a meta-analysis of 413 NSCLC clinical trials, only 31% of the industrysponsored and 16% of university/investigator-sponsored trials allowed inclusion of patients with diagnosed brain metastases (53). For cancer other than NSCLC, the majority of oncology clinical trials have excluded patients with brain metastases. Even those trials that enrolled this patient population, the outcome criteria have not always been clinically relevant. The recent review article by the Neuro-Oncology Brain Metastases (RANO-BM) working group reported in Lancet Oncology that many clinical trials for brain metastases utilized inconsistent endpoint criteria across trials that can limit interpretation across these studies (54). As a result, patients with brain metastases are often left with limited novel treatment options and are unable to participate in clinical trials testing potentially useful therapeutic treatments. The question that arises is: why are drugs that prove to be effective against peripheral metastases not as effective against brain metastases?

An important problem with regard to the pharmacological treatment of brain metastases is that many chemotherapeutic agents do not efficiently cross the blood-brain barrier (BBB) and blood-tumor barrier (BTB), and are unable to mount a pharmacodynamic impact on their target of interest (47,55). The structure of BTB is basically the BBB where the tumor exists, and can have “normal” BBB structure and function, especially in case of brain metastases that grow from small lesion at multiple locations, although the integrity of the barrier, i.e., the BTB, can be variable depending on the size and characteristics of tumor (11,47,56). The desired pharmacodynamic impact (efficacy) cannot be achieved without appropriate pharmacokinetic considerations (exposure). Inaccessibility of potentially effective anti-cancer agents to the parenchymal brain metastases can create a pharmacologic sanctuary where drugs that are otherwise effective against peripheral metastases fail to control brain metastases. Both the BBB and BTB in brain metastases have a unique anatomical barrier comprised of endothelial cells that establish robust tight junction between cells and express a variety of efflux transporters, which are absent in the peripheral

microvasculature. P-glycoprotein (P-gp) and Breast cancer resistant protein (BCRP), the two most highly expressed efflux transporters at the BBB, can efflux a wide range of drug molecules and restrict drug delivery to the brain. Numerous studies have shown that many compounds tested in clinical trials are substrates of P-gp and/or BCRP that have often failed to show clinical efficacy against brain metastases. As this discussion indicates, a thorough knowledge of the BBB and BTB in brain metastases, and how selected agents interact with these barriers, is critical in understanding the success or failure of pharmacological treatments that employ one or more of these targeted therapies.

Heterogeneous BBB and/or BTB integrity is a drug-delivery related challenge in terms of optimizing efficacy of targeted agents for the treatment of brain metastases. Several studies report variable intra-tumoral BBB permeability that results in non-uniform drug distribution and compromised drug efficacy (55). The study by Lockman *et al.* evaluated the pharmacodynamic effect resulting from heterogeneous intratumoral drug distribution of doxorubicin or paclitaxel in an experimental brain metastases of breast cancer (11,56). Each of these drugs reached a cytotoxic concentration (i.e., cleaved caspase-3 staining) in the "leaky" BTB regions, but significantly sub-therapeutic concentrations in the areas of intact BTB. In these models, there was no hindrance of drug delivery to the peripheral (non-brain) metastases with drug concentration more than 10-fold higher than the brain metastases. The overall outcome of non-uniform intratumoral distribution in the brain metastases was that each of these drugs failed to reduce tumor burden in *in vivo* animal studies (11).

Besides an anatomical barrier that is unique to the brain, treatment of brain metastases may be further complicated by the oncogenic footprints that are distinctive to the brain. Brain metastases, sharing a common ancestor with the primary tumor of origin, have evolved independently after reaching the brain, in part, because the brain has a different microenvironment than the rest of the body (15). A whole exome sequencing study by Brastianos *et al.* identified mutational signatures that are distinctive to brain metastases compared to their corresponding primary tumors, and 53% of the examined cases displayed such a phenomenon (15). In this context, analysis of peripheral tumor tissue biopsies could misguide the choice of molecularly-targeted therapies for the treatment of brain metastases. Moreover, a suboptimal drug concentration in the brain metastases could promote emergence of drug resistance, adding to the challenge of treating brain metastases. (Fig. 4).

Determination of brain drug exposure, especially in patients, is also challenging when choosing proper therapeutics for the treatment of brain metastases. Cerebral spinal fluid (CSF) is frequently thought to be surrogate of a concentration in the brain drug exposure. However, CSF concentration may not represent brain concentration for many molecularlytargeted agents that are substrates of efflux transporters, such as P-gp and/or BCRP. The CSF concentration is influenced by CSF turnover, extracellular fluid (ECF) bulk flow, and drug transporters at the blood-CSF barrier (BCSFB) (Fig. 5) (57–60). Specifically in contrast to the BBB, drug delivery across the BCSFB is unhindered by P-gp and BCRP, because the blood side of choroid epithelial cells lack P-gp and BCRP expression (61,62). For lipophilic compounds that readily diffuse across the choroid epithelial cells, the CSF concentration can overestimate the actual brain exposure (61). The study by Kodaira *et al.* showed that unbound CSF-to-brain concentration ratios of many compounds that are

substrates of P-gp and BCRP were lower in Mdr1a/1b(−/−)Bcrp (−/−) mice compared to the wild-type, indicating that there can be discrepancies between the unbound CSF concentration and the unbound brain concentration ($C_{u,brain}$) for P-gp and Bcrp substrates (61). Considering the structural and functional differences in the blood/brain versus the blood/CSF interface, CSF concentrations are often a poor predictor of brain drug exposure.

Microdialysis, a standard method to directly measure unbound brain interstitial fluid concentration ($C_{u,brain}$), currently has limited applications in patients (59,63–65). Many anticancer agents are often lipophilic, so that practical problems can rise with using microdialysis due to high nonspecific binding (59) and poor drug recovery (59). In an attempt to bypass such challenges, the brain homogenate and brain slice techniques have been developed to estimate the fraction unbound of drug in the brain. Each of these methods, used in combination with total brain concentrations, has demonstrated to be useful in obtaining surrogates of microdialysis $C_{u,brain}$. The study by Friden *et al.* showed that brain homogenate method predicted the $C_{u,brain}$ from microdialysis measurements within a 3-fold error for 10 out of 15 compounds (66). In the same study, the brain slice method predicted $C_{u,brain}$ for 14 out of 15 com pounds within a 3-fold error. These findings indicate that, for some compounds, either the brain slice or homogenate method can reasonably estimate the $C_{u,brain}$. Recently there was a development in expanding the analysis of the homogenate equilibrium dialysis method to determine unbound fraction of compounds, that might be useful for drug compounds with high protein binding (67). These techniques can allow determination of “active” free concentrations in different regions of the brain, including important regions of a growing brain tumor, such as the core of the tumor and the growing edge (68).

The application of the brain homogenate method has been readily employed in order to evaluate brain drug distribution in the CNS drug development. Traditionally, the brain-to-plasma ratio (Kp), which is the ratio of total brain concentration to total plasma concentration, has been considered to represent the degree of brain drug distribution. However, Kp,uu, the ratio of free brain concentration to free plasma concentration, has recently been introduced as a measurement of brain drug delivery that allows assessment of BBB transport mechanisms, separate from the influence of nonspecific binding in the brain (69). According to free drug hypothesis, only unbound drug concentration is considered to be a “pharmacologically active” concentration. The studies that examined brain penetration of molecularly-targeted agents have utilized both Kp and Kp,uu parameters (70,71), and are useful in assessing the effect of efflux transporters in brain drug delivery, but the latter allows differentiation of bound *vs.* unbound drug and may correlate better with efficacy. This has been recently discussed in the context of brain tumors by Heffron (72,73).

The evaluation of brain drug penetration has no single Kp or Kp,uu value that represents “optimal” brain penetration (69). The articles by Doran et al (2005) reported that a set of 32 commonly prescribed CNS drugs have a wide range of Kp (0.1 to 24), indicative that a compound having Kp of 0.1 can be still efficacious (69). This 240-fold difference in Kp indicates that Kp alone is inadequate to characterize brain drug delivery (69). On other hand, for the same set of CNS drugs, there is a 34-fold difference for Kp,uu (74), indicating that nonspecific tissue binding can affect assessment of Kp and brain drug penetration (69). Even

though there are limited studies that explore a direct relationship between Kp,uu and pharmacodynamic effect for the treatment of brain metastases, higher values of Kp and/or Kpuu often serve as parameters to indicate more advantageous delivery of drug across the blood-brain barrier (72,73).

Mechanisms that Limit Drug Delivery across the BBB

The blood-brain barrier (BBB) is a specialized structure of the cerebral microvasculature (Fig. 1), comprised of a complex network of cells, extracellular matrix, and proteins that regulate solute and xenobiotic transport into and out of the brain. Given this complexity, and the fact that the BBB is dependent on signaling from the neuronal environment, the BBB is now frequently referred to as the neurovascular unit (Fig. 1). The NVU contains numerous cell types, including vascular endothelial cells, pericytes, glial cells, and neurons (75,76). Pericytes mainly provide both structural and regulatory support of BBB and also contribute to the regulation of angiogenesis, neuroinflammation and stem cell activity (75). Astrocytes are cells that play an important role in regulation of BBB tight junctions, expression and localization of transporters and formation of specialized enzymes (77,78). Unlike the endothelium of many peripheral organs, the endothelial cells forming the capillaries of the brain are held together by tight junctions and adherens junctions that prevent the paracellular transport of most blood-borne substances to the brain (79). Adherens junctions are formed between vascular endothelial cadherins and initiate the contact between adjacent endothelial cells (79). Tight junctions are consisted of transmembrane proteins such as occludin, claudin, and junctional adhesion molecule (JAM) that interact with cytoskeletal proteins and recruit membrane-associated cytoplasmic proteins (12). Transporters at the BBB are important in maintaining the brain homeostasis and providing the brain with the necessary nutrients for normal function, while protecting the brain from toxic substances that may be in the systemic circulation (80). Solute carriers (SLCs) and ATP-binding cassette transporters (ABC transporters) are two major families of transporters at the BBB (81). These transporters play a crucial role in selectively moving specific substances (substrates) into or out of the brain depending on their physicochemical and structural properties, and often coordinate (80) with each other to efflux potentially toxic compounds out of the brain (82–84).

The SLC transporters are known to transport many polar compounds, including glucose and amino acids, that are essential nutrients for cell survival. However, this group of transporters is also involved in transporting organic anions (85). Organic anion transporters (OAT) and organic anion transporting polypeptides (OATP) are some members of this family, and are known to be present at the BBB (81). Transporters in this group can be unidirectional or bidirectional and are located in abluminal or luminal side of endothelial cells. Most of them have broad substrate specificity and some of substrates overlap with those of ABC transporters, which may indicate their coordinate function (86–88).

ABC transporters play a major role as active efflux pumps, consuming ATP, to limit the distribution of toxic substances in the CNS (83,84,89). P-gp and BCRP are the examples of efflux pumps which have broad substrate specificity and are able to actively transport substrates back into systemic circulation (80). In addition to P-gp and BCRP, multidrug

resistance-associate proteins (MRPs) can also be involved in actively limiting the brain delivery of certain drugs (90,91). In the treatment of brain tumors, the BBB often limits the brain distribution of therapeutic agents through the efflux activity of ATP binding cassette (ABC) transport proteins (70,80,92–100).

Impact of Transporters on the Treatment of Brain Metastases

The transport of a drug from the systemic circulation to the brain parenchyma is often depicted as a multi-step process. Initially, cerebral blood flow carries a drug compound to the brain and the drug is considered to be in equilibrium between the bound and unbound state in plasma, and the unbound drug is available to penetrate across the plasma-tissue barriers. Drug distribution to the brain at the blood-brain interface is regulated by the blood-brain barrier (BBB), blood-cerebrospinal fluid barrier (BCSFB), and other physiological systems in the brain (63,101). Upon successful drug delivery across the relevant anatomical barrier, the unbound (free) drug in the brain interacts with the target site and elicits pharmacological activities (59,61,63). Such unbound drug concentration in the brain interstitial fluid ($C_{u,brain}$) is assumed to represent a pharmacologically active concentration. However, if a drug compound has an affinity for efflux transporters, the drug can be "pumped" back into the vasculature before interacting with its intended target (Fig. 5) (63).

Many molecularly-targeted agents examined in clinical trials for brain cancer have been reported to be substrates of P-gp and/or BCRP (see Table II) (70,80,96–98,102,103). Even though there has been some discussion that class I compounds in the Biopharmaceutics Drug Disposition Classification System (BDDCS) that have high solubility and high permeability may be less affected by efflux transporters (104). These active efflux transporters at the BBB are known to prevent anticancer therapeutics from reaching parenchymal tumor cells, especially those from micro-metastases that may reside behind an intact BBB (72). Genetic knockout mice lacking transporters and transfected cell lines overexpressing transporters (MDCK-II cell line, or Madin-Darby Canine Kidney Epithelial cell line) are widely utilized *in vivo* and *in vitro* models to evaluate the substrate status of an investigational compound for P-gp and BCRP in the preclinical setting (70,96–98).

COMMON TYPES OF BRAIN METASTASES

Lung Cancer

Lung cancer, a prevalent tumor with about 222,500 new cases in 2017 in US, according to the American Cancer society's estimate, is the leading cause of brain metastases. Approximately 20% of lung cancer patients will eventually develop brain metastases (17). The epidermal growth factor receptor (EGFR) and the anaplastic lymphoma kinase (ALK) are the most well-known and well-developed drug targets to treat lung cancer, especially in non-small cell lung cancer (NSCLC) patients (105,106). Over 45% of the patients with EGFR+ or ALK+ have brain metastases at some stage of disease (107). The three most commonly-used and studied EGFR tyrosine kinase inhibitors (TKIs) are gefitinib, erlotinib, and afatinib. Gefitinib and erlotinib are first-generation EGFR TKIs and their CNS delivery is reported to be very limited (1.07–3.58% for gefitinib and 2.77% for erlotinib, see Table II) (108), mainly due to the efflux transporters, P-gp and BCRP (93,109–111). However, despite

this low brain penetration, these first-line TKIs seem to modestly reduce the risk of CNS progression when compared to standard chemotherapy (112). Therefore, erlotinib and gefitinib may have a prophylactic effect on brain metastases. Afatinib is a second generation inhibitor, which irreversibly blocks signaling from EGFR, HER2, ErbB3, and ErbB4 (113). While the CSF to plasma ratio of afatinib was reported to be extremely low in patients, less than 1%, due to active efflux by P-gp (114), a study showed that response rate to afatinib in the patients with or without CNS metastases were similarly efficacious, possibly due to the high potency of the compound (114). Osimertinib (AZD9291) is a recently approved drug to treat patients with T790 M resistant mutant NSCLC showed pre-clinical evidence that it can penetrate the BBB (115). Moreover, in a clinical trial, osimertinib has shown efficacy in patients with EGFR-driven NSCLC lung metastases in the CNS (116). Another EGFR inhibitor, AZD3759, has been specifically designed to penetrate the BBB (117), and efficacy in patients with NSCLC with brain metastases is under current clinical investigation (118).

ALK is another potent target that is constitutively active due to gene rearrangements in approximately 2 to 7% of lung cancer patients (119–121). Crizotinib, the first ALK targeted TKI, has been reported to have poor brain penetration based on a low CSF-to-plasma ratio (0.26%) in humans (122), mainly due to P-gp (100). It has been reported that the efficacy of crizotinib in the CNS seems to be limited, even though the overall objective response rate and the median duration of response were significantly improved with crizotinib treatment when compared to standard chemotherapy (123–125).

Alectinib and ceritinib are the second generation of ALK inhibitors that demonstrate their activity in crizotinib-resistant patients. Alectinib also inhibits RET, an oncogene involved in the development of several human cancers, including NSCLC (126). Several clinical studies that include patients with brain metastases at baseline have shown that alectinib has some efficacy in CNS tumors (127,128), possibly due to the fact that it is not a substrate of major efflux transporters (129). These efficacy results are in line with its high brain penetration in pre-clinical rat model (63–94%, Table II). However, the mean ratio of CSF concentration to the plasma concentration in patients was approximately 0.3% (128), which again suggests that concentration measured in CSF may not represent the concentration in brain or at the target site. (Fig. 5).

Ceritinib is another potent ALK inhibitor that showed some efficacy with intracranial metastases in a preclinical rat model with a brain to plasma ratio of 15% (130,131). This brain penetration may seem higher than expected considering ceritinib is a substrate of both P-gp and Bcrp. Nevertheless, the ASCEND study for advanced ALK-positive NSCLC has shown that ceritinib has efficacy against brain metastases, based on both the response and disease control rates (132).

Several other therapeutic agents are under clinical investigation to examine their efficacy in lung cancer patients with CNS metastases, including brigatinib, lorlatinib, entrectinib, cabozantinib, and tesevatinib. Brigatinib, a second generation ALK inhibitor, potently inhibits both ALK and EGFR.

According to a recently reported phase I/II clinical trial that included patients with CNS metastases, brigatinib has shown efficacy against brain disease (response rate 53% and PFS of 97 weeks).

Recently developed as third generation ALK inhibitors, lorlatinib and entrectinib are specifically designed to improve brain penetration, and a clinical trial is currently recruiting lung cancer patients for their first efficacy evaluation in patients. Lorlatinib is structurally designed to have a low affinity for P-gp (133). Based on an analysis to examine the influence of physicochemical properties on p-glycoprotein affinity, lorlatinib was intentionally designed to have logD range of 2–3 and minimal introduction of hydrogen bond donors (133). To minimize the hydrogen bond donors, intramolecular hydrogen bonds are introduced in the adjacent ether oxygen in the molecule. This chemical design aimed to have enhanced intrinsic permeability and to avoid efflux transporter liability, allowing lorlatinib to target brain metastases (133). Entrectinib has also been shown to have high brain penetration in nude mice (43% brain concentration to plasma concentration ratio) (134). While we await results from the clinical trials regarding improved efficacy, the fact that intentional structure-delivery efforts are being made bodes well for the development of compounds that will be efficacious against brain tumor cells that are behind an intact BBB.

Melanoma

Melanoma is a lethal form of skin cancer with a projected diagnosis of 87,110 patients in the United States for the year 2017, with close to 9730 deaths expected in the US (American Cancer Society 2017). The most common peripheral sites of melanoma metastases are lung, liver, bones and brain. Melanoma has the second highest prevalence of brain metastasis followed by lung cancer with an overall incidence of 5%–8% (135). Metastases in the brain have been identified in 55–75% of melanoma patients at autopsy, indicating a high tropism of melanoma to metastasize to the brain (31,32). Melanoma patients with metastatic disease that has spread to the brain are associated with a poor median overall survival of less than 6 months (136,137). Approximately 40–60% of melanoma patients have a mutation in the serine threonine kinase v-RAF murine sarcoma viral oncogene homolog B1 (BRAF-mu) (138). This oncogenic mutation results in sustained activation of the mitogen-activated protein kinase (MAPK) oncogenic signaling pathway (Fig. 6) (139–141). Therefore, the development of inhibitors specifically targeting BRAF-mu isoform was of significant interest in the treatment of melanoma. Vemurafenib, a FDA approved BRAF-mu inhibitor for the treatment of late-stage melanoma, showed an improvement in the 6-month overall survival rate by 20% when compared to dacarbazine chemotherapy with a response rate of approximately 50% (142,143). However, the results of preclinical studies show that the brain penetration of vemurafenib is limited due to active efflux by P-glycoprotein and Bcrp (141,144). A few patient case studies show that vemurafenib may have a potential efficacy to induce remission of brain metastases (46). This partial efficacy may be related to factors such as the size of the tumor and the degree of disruption of the BBB (145,146). A review of the clinical studies and case reports related to vemurafenib suggests that the effectiveness of vemurafenib seems to be limited in intracranial tumors, but it may provide successful therapeutic outcomes in a subset of patients depending on the tumor characteristics, the stage of tumor progression and other unknown factors (46,147) (,).

Another BRAF-mu inhibitor, dabrafenib, showed notable benefits in a phase 1 dose-escalation study in V600E BRAF-melanoma patients with untreated brain metastases (148). Nine out of 26 patients with brain metastases showed intracranial tumor size reduction, and four of them had complete tumor regression (148). Another study performed with a total of 23 patients from a single institution has reported that the response rate in intracranial disease was 78% and that in extracranial disease was 90% in BRAF-mutant melanoma patients with brain metastases (149). According to the study results, both intracranial and extracranial disease appear to respond similarly to dabrafenib. However, importantly, dabrafenib is known to be a substrate of both P-gp and Bcrp, with a brain to plasma ratio in normal mouse brain of 2%. (70). Currently, several clinical studies are ongoing to examine the efficacy of dabrafenib in combination with stereotactic radiosurgery and other therapeutics (www.clinicaltrials.gov). As data from these trials become available, it will be critical to establish if the responses are durable and to examine reasons for relapse. Insufficient drug distribution to areas of brain metastases that have an intact BBB replete with efflux transporters, may be related to disease progression.

Another target in the MAPK pathway that is important in metastatic melanoma is MEK (150). Since MEK is a signaling molecule that is downstream of BRAF (Fig. 6), MEK inhibitors can overcome the resistance developed against BRAF inhibitors (151,152). Trametinib and cobimetinib are FDA approved MEK inhibitors for the treatment of melanoma. Combinations of dabrafenib/trametinib and vemurafenib/cobimetinib have also received FDA approval. Dabrafenib/trametinib combination therapy showed an improvement in progression free survival compared to monotherapy in melanoma patients (151). Cobimetinib/vemurafenib combination also showed a significant improvement in progression free survival in patients with BRAF V600-mutant metastatic melanoma (153). However, both trametinib and cobimetinib are substrates of p-glycoprotein (71,154). There are reports that suggest that MEK inhibitors in combination with BRAF inhibitors or RT may improve survival rates in patients with brain metastases, despite the fact that the brain delivery of both trametinib and cobimetinib can be limited due to active drug efflux in areas of metastases with an intact BBB (155,156). Currently, clinical trials recruiting patients with brain metastases to examine their clinical efficacy in combination with BRAF inhibitor or RT are underway (, ,). Preliminary data from the study in patients with melanoma brain metastases implies that a combination of dabrafenib and trametinib with SRS may show improvements in survival compared to treatment with dabrafenib alone (157). As stated above for dabrafenib, durable responses may be limited by progression of tumor in areas with an intact BBB, and if disease progression occurs, it will be important to investigate why.

Immune modulation using monoclonal antibodies (mAbs) directed towards cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (e.g, ipilimumab) and programmed cell death receptor (PD-1) (e.g., nivolumab) is an emerging strategy to manage tumors, especially in melanoma. Immune checkpoint inhibitors can cause activation and proliferation of T lymphocytes, which can then attack tumor cells. The rationale for using immune checkpoint inhibitors for the treatment of brain tumors is that the activated T cells are able to gain access to the CNS and show responses (158,159). Their efficacy in the treatment of melanoma that has metastasized to the brain is critical to investigate, but there is limited

evidence available to prove it in patients with brain metastases, due to the exclusion of patients with brain metastases in many clinical trials. In an open-label phase 2 clinical trial with melanoma and brain metastases study, ipilimumab proved its potency against small and asymptomatic brain metastases (160). In a different clinical study with asymptomatic brain metastases patients, ipilimumab has shown benefits in patients, who had failed or did not tolerate previous treatments (161). Lately, there are ongoing clinical trials using immune modulation as a single agent or in combination with RT or radiosurgery against brain metastases (, ,).

As we noted in the therapeutic agents for other tumors, many treatments for melanoma have limited access to the brain across the BBB due to efflux transporters. (Table III).

Breast Cancer

The incidence rate of brain metastases from breast cancer is different depending on the subtype. It is about 20% in triple-negative tumors, i.e., those that do not express hormone receptors, including estrogen and progesterone, and HER2, and increases to 25%–50% in HER2 positive tumors (162). Molecularly targeted therapeutics for HER2 positive breast cancer patients have been significantly improved over the last 2 decades, but the efficacy of these agents in patients with breast cancer brain metastases seems to be limited.

The most frequently prescribed therapeutic agent for HER2 positive breast cancer patients is trastuzumab, an anti-HER2 antibody (163). Trastuzumab has shown to be efficacious for systemic HER2 positive breast cancer, however patients receiving trastuzumab tend to have higher incidence of brain metastases (164). The brain penetration of trastuzumab across an intact BBB is very low, as expected for an antibody drug due to its large molecular weight (165). Retrospective research has shown that 50% of patients with CNS metastases responded to the trastuzumab, even though it is difficult to distinguish the systemic efficacy from CNS metastases specific efficacy, due to the limitations in a retrospective study that simply reports the overall objective response rates (166).

Lapatinib is a small molecule dual tyrosine kinase inhibitor of EGFR and HER2, and interestingly, its percentage brain penetration across the BBB is as low as trastuzumab. The ratio between the patient drug concentration in CSF and plasma averaging 0.11% (see Table IV) (167). Preclinical studies in mice have shown that P-gp and Bcrp coordinate with each other to limit the delivery of lapatinib across the BBB (99). Consistent with the heterogeneous integrity of the BBB in breast cancer brain metastases, the distribution of lapatinib is highly variable in breast cancer brain metastases (56,168). The efficacy of lapatinib as a single agent in brain metastases is modest (overall response rate: 21.4%) (169,170), but lapatinib in combination with capecitabine showed increased response rate toward CNS metastases (29.2%) (171).

The triple negative subtype is also prone to develop brain metastases and there are not many treatment options available for this subtype. Few molecularly targeted drugs are currently being tested for their efficacy in patients with triple negative tumors (172). One possible druggable target for this subtype is polyadenosine diphosphate ribose polymerase (PARP). There are several PARP inhibitors already approved and additional compounds are being

tested in clinical trials, including niraparib, rucaparib, olaparib, veliparib (ABT-888), and talazoparib (BMN 673). Of these, niraparib showed good brain penetration in an *in vivo* rat model with brain to plasma ratio of 0.85–0.99 (173). On the other hand, the distribution of rucaparib to the brain is low, due to the effect of the major efflux transporters, P-gp and Bcrp (97). Veliparib showed significantly improved overall median survival in a phase I study when it was used in conjunction with WBRT (174), even though its brain penetration is reported to be low (less than 5%), due to both P-gp and Bcrp (see Table IV) (95).

Vorinostat is the first targeted drug specifically approved to inhibit histone deacetylase (HDAC), a novel target to treat breast cancer, and this compound showed some efficacy in preventing brain metastases in a mouse model with triple negative breast cancer (175). However the brain delivery of Vorinostat seems to be limited by efflux transport (176).

Because of the limited success in treating breast cancer brain metastases with molecularly targeted agents that have limited delivery across the BBB, there has been an emphasis on developing new brain-penetrant therapies. TPI-287 is a new brain permeable taxane that stabilizes microtubules (177) that is under clinical investigation as a treatment of breast cancer brain metastases and primary brain tumor (, ,). There are also several clinical trials evaluating novel compounds for b rain m etastases in cluding 4-dem ethyl-4-cholesteryloxycarbonylpenclome (DM-CHOC-PEN) (), eribulin mesylate (), cabozantinib (), abemaciclib (, ,). Neratinib, a recently approved tyrosine kinase inhibitor, has shown some efficacy against breast cancer brain metastases (178).

Even though there were several successful developments of molecularly targeted agents to treat breast cancer, the incidence of patients with brain metastases has increased and have a poor prognosis (179), mainly due to resistance development and poor brain penetration of therapeutic agents. Several brain penetrant therapeutics have shown to have promising efficacy on brain metastases in preclinical studies.

Renal Cell Carcinoma

The incidence rate of renal cell carcinoma (RCC) in adults is 2–3%, and metastases occur in about 50% of these patients. About 8–10% of metastatic renal cell carcinoma (mRCC) patients are known to develop brain metastases (180). The median overall survival is reported to be less than 13.3 months in the presence of brain metastases when using whole-brain radiotherapy (181). The treatment regimen with molecularly targeted therapeutics has not been established or evaluated for brain metastases, and standard therapy for mRCC has been applied to patients with brain metastases. Several tyro-sine kinase inhibitors are approved by FDA for treatment of mRCC, including sorafenib, sunitinib, and axitinib, and have improved survival (Table IV). Sunitinib has some clinical benefit towards brain metastases as a single agent by stabilizing the disease by more than 3 months, but objective response rate was only 12% among 213 patients enrolled (182,183). Brain distribution of sunitinib is reported to be high (42%) in a preclinical study, even though sunitinib is found to be substrates of both P-gp and BCRP (96). According to a few case reports, a newer generation TKI, pazopanib, seems to have good response rate or increase overall survival as a single agent (184). The efficacy of sorafenib has been studied in advanced metastatic renal cell carcinoma, but most of these studies excluded the patients with diagnosed bran

metastases. Brain penetration of sorafenib is reported to be modest (9.4%) in mice, probably due to the efflux of both P-gp and BCRP. Recently, novel tyrosine kinase inhibitors, including cabozantinib and lenvatinib, received FDA approval for mRCC. However, the brain delivery of these agents across the BBB as well as their efficacy against brain metastases have not been reported. Since brain metastases are distinct from other organ metastases, especially in drug delivery, more clinical studies that examine the efficacy of a treatment specifically against brain metastases should be performed.

CONCLUSION

Several instructive observations can be made from the experience with the use of targeted agents in the context of brain metastases (Box 1). There is an overall correlation of brain penetration and substrate status of efflux transporters at the BBB, especially P-gp and BCRP (see Tables II, III, and IV). Many molecularly targeted agents are substrates of these efflux transporters, and their accessibility to the brain has been shown to be extremely low when the BBB is intact. This could be one reason why the incidence rate of metastases to the brain has been rising, despite of development of numerous molecularly targeted drugs. Tumors that reside in the brain can be protected from exposure to anticancer therapeutics by the BBB, resulting in limited delivery (Fig.7). Therefore, delivery of therapeutic agents to the brain is critical concern in treating metastatic tumors.

There have been many previous reviews on various methods to improve drug delivery to the brain for the treatment of brain tumors by enhancing the brain penetration of drugs that are systemically available. These methods include changing formulations of existing compounds by using nanoparticles (185,186) and using concomitant therapy that inhibits efflux transporters at the BBB to improve brain delivery of substrates (187–189). However, it will be even more critical to assess the efflux transporter liability when developing and designing therapeutics, and consider a brain delivery as a key factor in the early phase of discovery and development, especially for the anticancer therapeutics that are often subject to efflux transporters at the BBB. There are examples of using in silico-guided drug design to make a brain penetrant anticancer drug by reducing efflux liability, including GNE-317 and lorlatinib (133,190,191).

Another important consideration is that the integrity of BBB in and around the tumor in the brain is heterogeneous (11). The BBB around the tumor core can be relatively permeable to therapeutics, since its structure tends to be disrupted. However, the tumor rim and micro-metastases may have an intact BBB, replete with efflux transporter systems, making these regions more likely to be resistant to therapeutics. Previously, several papers have shown that concentration of drugs in tumor is high enough to result in desirable efficacy in the tumor cells, based on the concentration measured in tumors resected from patients, due to disrupted BBB around tumor (Fig 7). However, since the integrity of BBB is heterogeneous depending on the region, and even within a region, the concentration of drug measured in a resected tumor specimen does represent the concentration throughout the entirety of the tumor. Given this, it is feasible that variable efficacy of many agents between patients or even amongst metastatic sites is related to inconsistent delivery. There are some drugs that have been shown to have some efficacy against brain metastases, despite of their limited delivery to the

brain. In case of erlotinib for lung cancer, even though it has low brain penetration due to P-gp and BCRP, its efficacy against brain metastases patients carrying a specific EGFR mutation was demonstrated (response rate of 82.4%, Table II). This can be explained by not only improved delivery of a drug through perturbed BBB around tumor core, but also the selectivity and potency of a drug for a particular tumor. Drug may be able to induce desirable efficacy in the brain, if it has sufficient selectivity and potency against its target so that the concentration of a drug required at the site of action can be achieved. This observation indicates that both potency and delivery need to be considered hand-in-hand when evaluating and deciding upon a course of therapy for brain metastases. The potency of a drug against its target is often represented by an inhibitory concentration or efficacious concentration when measured using *in vitro* experiments. However, that *in vitro* concentration may not be the same as the efficacious concentration needed at the site of action in patients. Therefore, it is important to consider the concentration of a drug needed at the target, because potency can help overcome limited delivery, when potency is high enough. Since a lack of efficacy of systemic anticancer agents in CNS disease can lead to higher incidence rates of brain metastases (85), the BBB penetration, subsequent distribution into the brain metastatic site, and the potency against a particular CNS target, of molecularly-targeted agents need to be considered in the early phases of drug development.

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Box 1

Important factors for successful treatment of brain metastases

I. Knowledge of the biology of metastatic growth in the brain

II. Knowledge of the condition of the blood-brain barrier in brain metastases

- Heterogeneity of the blood-brain barrier within and around the brain metastases

III. The influence of radiation on drug delivery

IV. Free drug concentration at the sites of micro-metastases and the areas behind intact blood-brain barrier

- Pharmacologically active drug concentration at the target

V. Design the drugs to be brain penetrant

- High permeability across the intact blood-brain barrier
- Structural modification to avoid efflux transporters

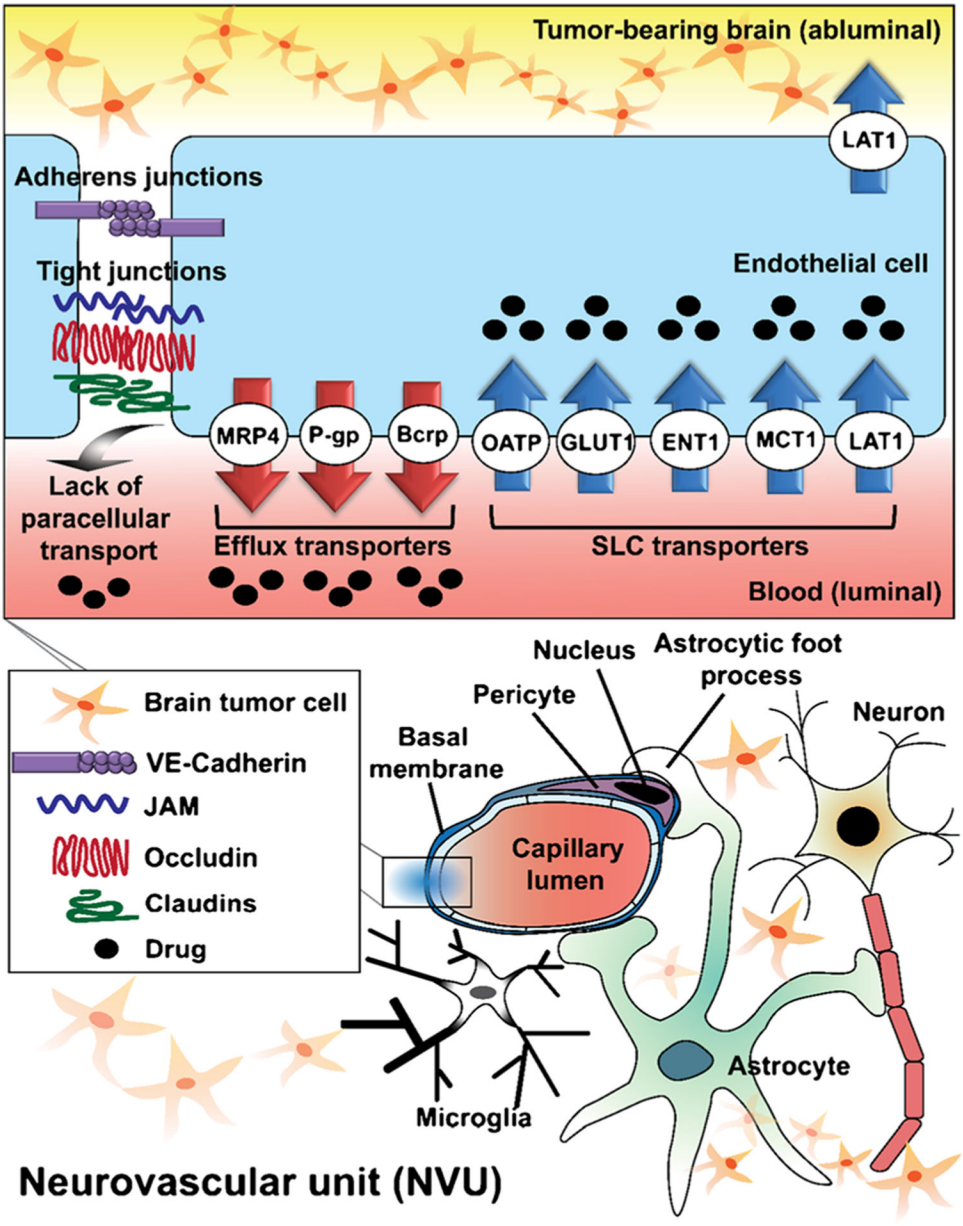

Fig. 1.

The expression and localization of transporters in the brain endothelial cell in the context of the overall composition and structure of the neurovascular unit (NVU). Important drug transporters include: SLC, solute carrier; MRP, multidrug resistance protein; LAT, L-type amino acid transporter; OATP, organic anion transporting polypeptide; MCT, monocarboxylate transporter; ENT, equilibrative nucleoside transporter.

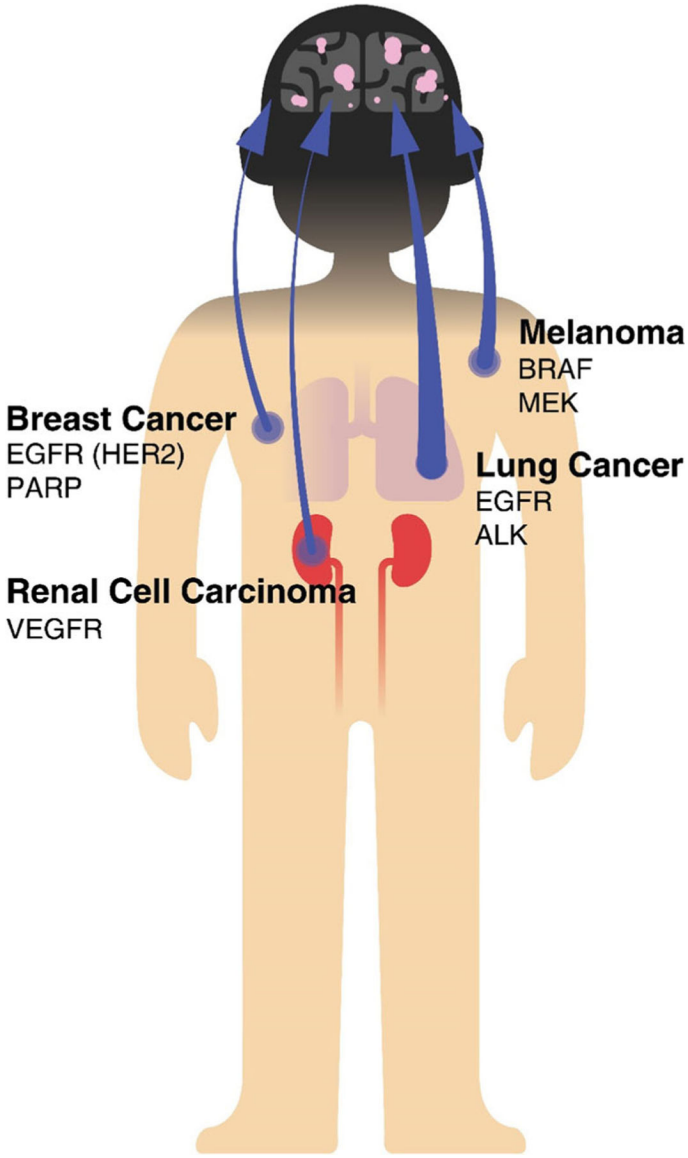

Fig. 2.

Primary tumors that preferentially metastasize to the brain and the occurrence of brain metastases from each of these primary tumors. Examples of key tumor driving oncogenes are represented for each tumor type.

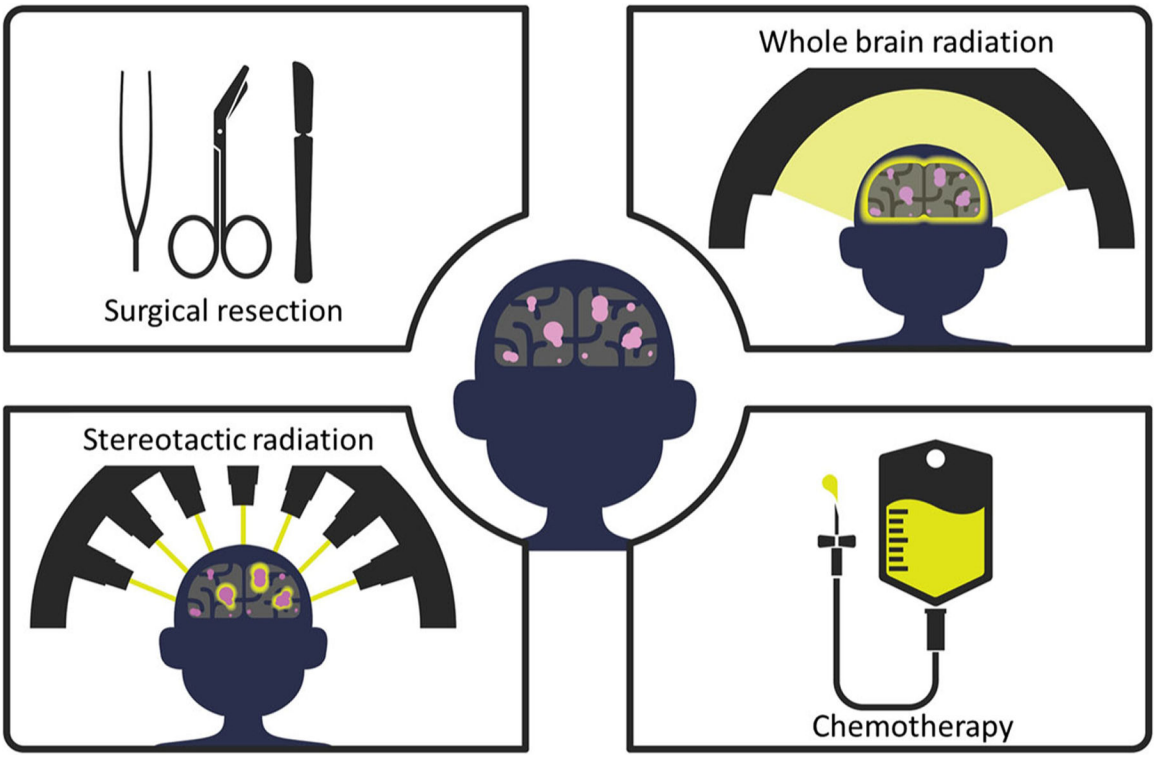

Fig. 3.
Depiction of the most common treatment options for brain metastases.

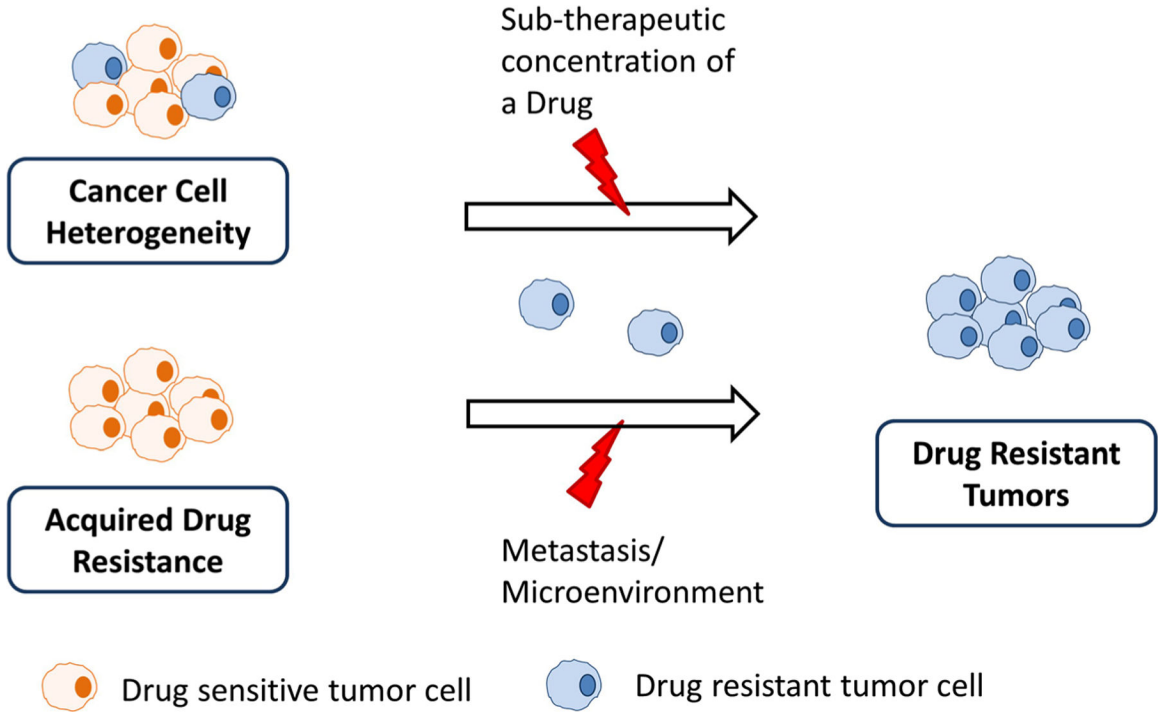

Fig. 4.

Mechanisms of resistance development against drug in brain metastases due to inherent tumor heterogeneity or acquired resistance.

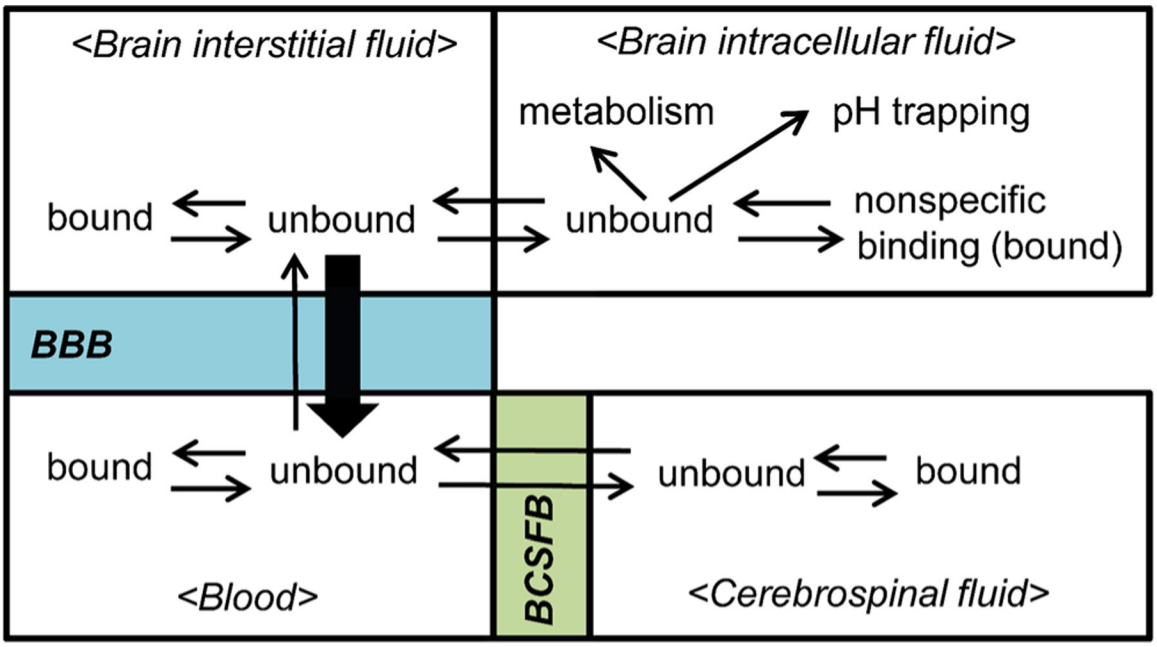

Fig. 5.
Multiple equilibria in different compartments in the brain, blood, and cerebrospinal fluid.

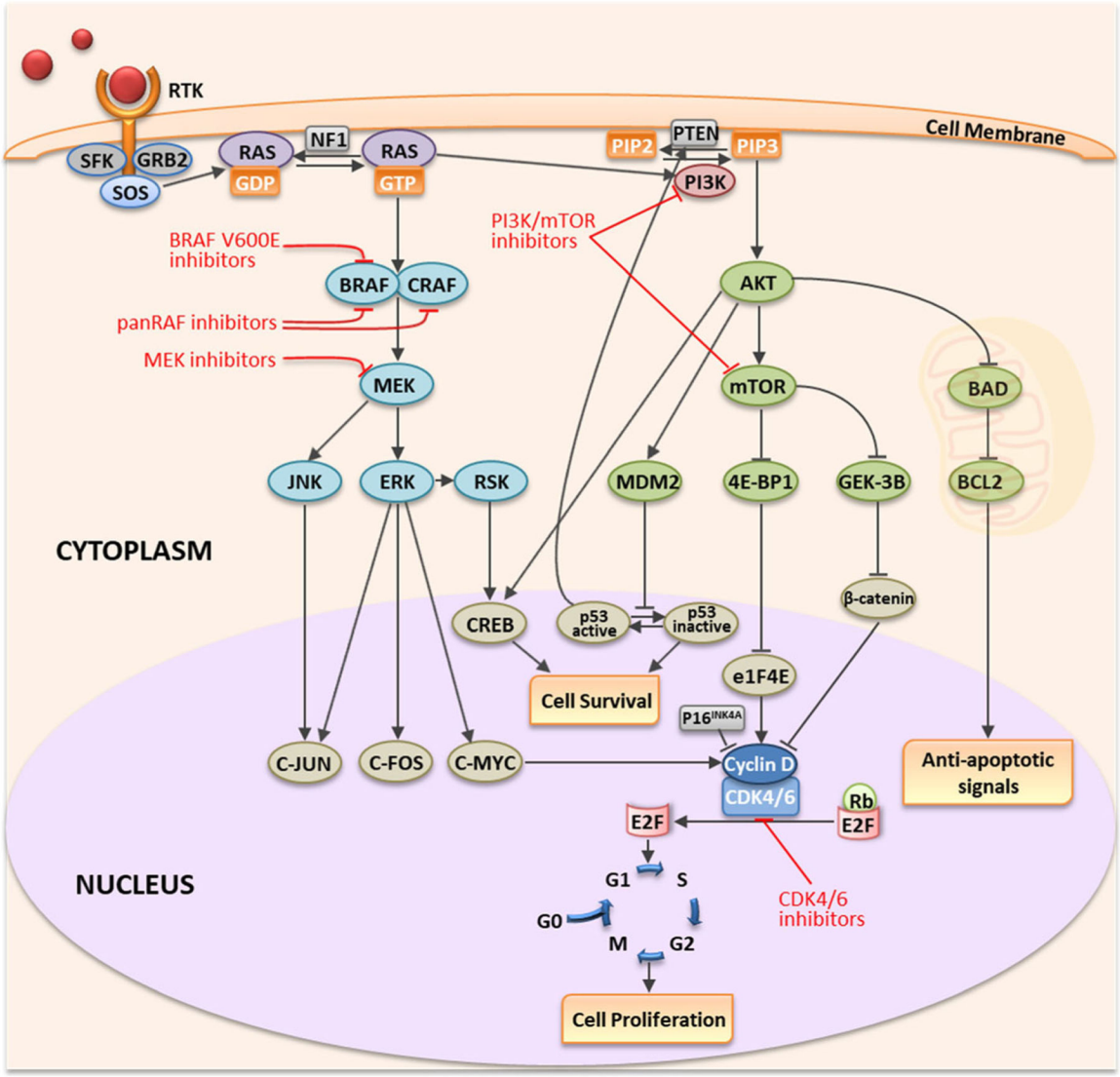

Fig. 6.

Signaling pathways and oncogenic targets of molecularly-targeted therapeutics for melanoma.

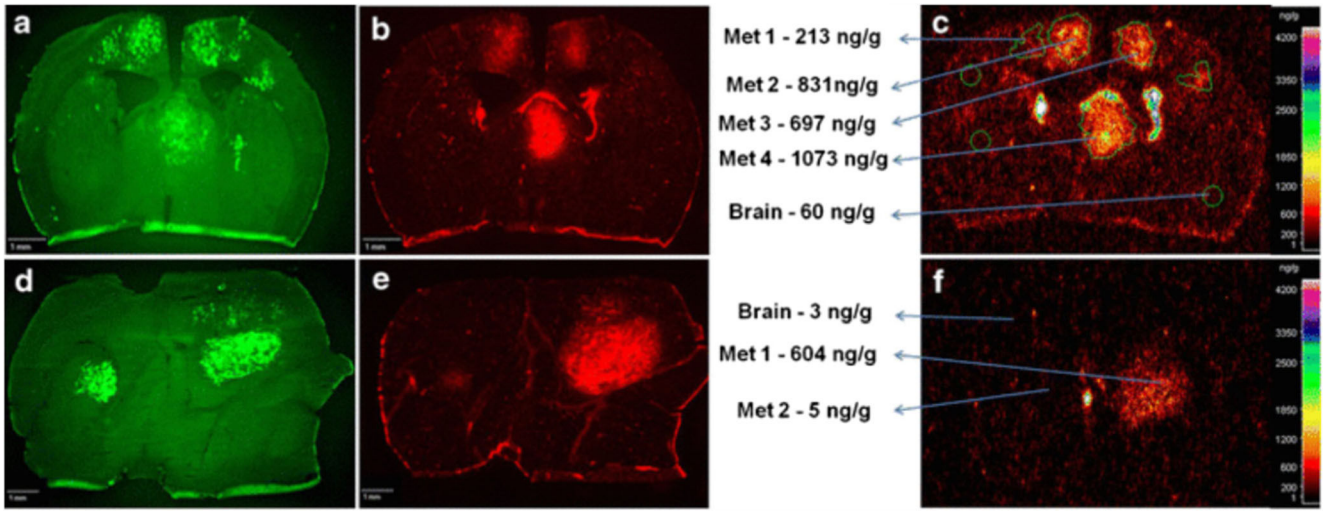

Fig. 7.

Heterogeneity of blood-brain barrier disruption and drug concentration in the experimental model (mice) of breast cancer brain metastases (from reference (56)). ^{14}C-lapatinib was measured in normal brain and different brain metastases by quantitative autoradiography at 2 h (**a-c**) and 12 h (**d-f**) following the oral administration of 100 mg/kg ^{14}C-lapatinib. Signal from metastatic cells labelled with EGFP (**a,d**), Texas Red 3kD dextran (**b,e**), and ^{14}C-lapatinib (**c,f**) indicate the location of tumor cells, the integrity of the BBB, and the concentration of drug, respectively. The concentrations of lapatinib, as well as disruption of BBB, were highly variable within and between the metastatic breast cancer lesions in the brain.

Table I

Incidence Rate of Brain Metastases

Primary site	Incidence Rates	References
Lung (overall)	16.3–19.9%	(17,18)
SCLC *	29.7% (at 5 years)	(17,18)
NSCLC *	12.6% (at 5 years)	(17,18)
Breast	10–15%	(17,18)
HER2 positive	25–50%	(162)
Triple negative	20%	(162)
Melanoma	6.9–7.4%	(17)
Renal	6.5–9.8%	(17)
Colorectal	3.0%	(17)

* can be up to 50–60% depending on study and disease duration (22,23)

Table II

Brain and Transporter Related Features of Molecularly Targeted Therapy for Lung Cancer

Compound	Molecular target	Dose in patients (mg/day)	Brain penetration (% of CSF to plasma levels) in patient*	Brain penetration (% of brain to plasma ratio) in pre-clinical model*	Response rate in BM patients (%)	Transporter effect	Reference
Gefitinib	EGFR-TKI	750–1000	1.07–3.58	27	27%	P-gp substrate	(109,192)
Erlotinib	EGFR-TKI	150	2.77–5.1	13.7	82.4% (EGFR mutation)	P-gp and Bcrp substrate	(93,108,193)
Afatinib	EGFR-TKI	50	0.7	ND	35%	P-gp substrate	(114,194)
Osimertinib	EGFR-TKI	80	NA	180	ND	P-gp and Bcrp substrate	(115)
AZD3759	EGFR-TKI	100–1000	1 1 1	282	83%	ND	(117)
Crizotinib	ALK-TKI	500	0.26	23	18–33%	P-gp substrate but not Bcrp	(100)
Alectinib	ALK-TKI	200	0.3	63–94	52%	Not a P-gp substrate	(127–129)
Ceritinib	ALK-TKI	400	ND	15	34.5–58.8%	P-gp and Bcrp substrate	(132,195,196)
Brigatinib	ALK and EGFR TKI	300	ND	ND	53%	ND	(197)
Lorlatmib (PF-06463922)	ALK-TKI	100	ND	64	ND	Not a P-gp substrate	(133)
Entrectinib	ALK-TKI	ND	ND	43	ND	ND	(134,198)

(ND, not determined; NA, not available)

*Total drug concentrations are reported

Table III

Brain and Transporter Related Features of Molecularly Targeted Therapy for Melanoma

Compound	Molecular target	Dose in patients (mg/day)	Brain penetration (% of CSF to plasma levels) in patient*	Brain penetration (% of brain to plasma ratio) in pre-clinical model*	Response rate in BM patients (%)	Transporter effect	Reference
Vemurafenib	BPAF inhibitor	960 (b.i.d.)	0.98	0.012	NA	P-gp and Bcrp substrate	(144,199)
Dabrafenib	BPAF inhibitor	150×2 (b.i.d.)	ND	4.4	71–78	P-gp and Bcrp substrate	(70,149)
Cobimetinib	MEK inhibitor	60	ND	8	Under investigation ()	P-gp substrate (Not Bcrp)	(154)
Trametinib	MEK inhibitor	2	ND	0.28	NA	P-gp substrate, but not Bcrp	(71)
E620I	MEK inhibitor		ND	270	NA	Minimal effect with P-gp and Bcrp	(200)

(ND, not determined; NA, not available)

*Total drug concentrations are reported

Table IV

Brain and Transporter Related Features of Molecularly Targeted Therapy for Breast Cancer and Renal Cancer Cell

Compound	Molecular target	Dose in patients (mg/day)	Brain penetration (% of CSF to plasma levels) in patient*	Brain penetration (% of brain to plasma ratio) in pre-clinical model*	Response rate in BM patients (%)	Transporter effect	Reference
Lapatinib	EGFR and HER2	1250	0.11	3	6%	P-gp and Bcrp substrate	(99,167,171)
Trastuzumab	HER2	NA	0.24	ND	0.5	NA	(201)
Rucaparib	PARP inhibitor	40	ND		ND	P-gp and Bcrp substrate	(97)
Olaparib	PARP inhibitor	400 × 2 (b.i.d.)	ND	1.1#	ND	P-gp substrate	(202)
Veliparib (ABT-888)	PARP inhibitor	400 × 2 (b.i.d.)	ND	less than 5%	ND	P-gp and Bcrp substrate	(95)
Talazoparib (BMN-673)	PARP inhibitor	1	ND	2	ND	P-gp substrate, but not Bcrp	(203)
Niraparib	PARP inhibitor	300	10–52+	85–99	ND	NA	(173)
Vorinostat	HDAC inhibitor	360	ND	4	ND	P-gp and Bcrp substrate	(176)
Sunitinib	TKI	50	ND	42	12	P-gp and Bcrp substrate	(96,182)
Sorafenib	Multi-kinase inhibitor	400×2 (b.i.d.)	0.02–3.4+	9.4	ND	P-gp and Bcrp substrate	(204)
Axitinib	VEGFR inhibitor	5 mg × 2 (b.i.d.)	ND	Less than 10%	ND	P-gp and Bcrp substrate	(205)

(ND, not determined; NA, not available)

*Total drug concentrations are reported

#Unpublished data

+in non-human primate