Clinical Perspectives in Brain Metastasis

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Brain metastases (BMs) are responsible for decline in neurological function, reduction in overall quality of life, and mortality from recurrent or untreatable lesions. Advances in diagnostics and imaging have led to increased detection of central nervous system (CNS) metastases in patients with progressive cancers. Improved control of extracranial systemic disease, and the limited ability of current therapeutics to cross the blood–brain barrier (BBB) also contribute to the increase in incidence of brain metastases, as tumor cells seek refuge in the brain. Surgery, chemotherapy, and/or radiation (whole-brain radiation therapy and stereotactic radiation surgery [WBRT/SRS]) are a clinically established treatment paradigm for patients with brain metastases. With the advent of genetic and molecular characterization of tumors and their immune microenvironment, clinical trials seek to include targeted drugs into the therapeutic regimen for eligible patients. Several challenges, like treatment of multiple CNS lesions, superior uptake of chemotherapy into the brain, and trials with multidisciplinary approaches, are now being clinically addressed.

Brain metastases (BMs) are the most common cause of intracranial neoplasms in adults with invasive cancers. Twenty to 45% of cancer patients are diagnosed with BMs in their lifetime (Achrol et al. 2019). Metastatic brain tumors occur at a much higher rate than both adult and pediatric primary brain tumors, and are the major cause of mortality from malignant brain disease (Tabouret et al. 2012; Owonikoko et al. 2014). Intracranial metastasis is associated with worse prognosis (<1 yr), moderate to severe neurodegeneration, and overall reduction in quality of life. At diagnosis, symptomatic patients usually present with headaches, seizures, motor weakness, and dysphasia (Rodin et al. 2016). The incidence and severity of brain metastatic disease varies according to the origin of the primary tumor, and the treatment strategy followed for the patient. Lung, breast, melanoma, colorectal, and renal cancers show most proclivity for the brain, followed more uncommonly by thyroid, gastrointestinal (GI) and prostate cancers (Valiente et al. 2018).

Systemic metastases were usually considered end-stage, and patients were only subjected to palliative therapy. But, because of the advances in control of primary tumors and extracranial metastases, as well as superior methods of early detection, patient survival has increased. This has however led to rising numbers of patients being diagnosed with BMs, with or without concomitant extracranial disease. Tumors originating from different tissues show varying latency to metastasize to the brain. This can be explained

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by the aggressiveness of the tumor type, modes of dissemination, development of resistance to therapy, or molecular affinity for the neuronal niche. Despite considerable advances in elucidating the cellular and molecular events underway in metastasis, few treatments have been realized and as such prognoses remains poor. The current standard of care for BMs includes surgical excision, whole-brain radiation therapy (WBRT), and stereotactic radiation surgery (SRS) combined with steroids (Lin and DeAngelis 2015). Targeted molecular therapies show little or no effect mainly because of their inability to penetrate the elusive blood–brain barrier (BBB). Thus, with limited options available, malignant tumors take refuge in the brain and escape most forms of intervention, contributing to patient mortality. The management of BMs is an urgent unmet clinical need and warrants immediate attention and investigation. This article summarizes and provides perspective on the current understanding of brain malignancies in the context of their clinical biology, diagnosis, and management. We hope that this knowledge is translated into innovative therapeutic interventions that enhance the quality and expectancy of life for affected patients.

DIAGNOSIS OF BRAIN METASTASES

Sixty to 75% of brain metastases (BMs) are symptomatic, whereas a smaller number of patients harbor central nervous system (CNS) metastases without any neurological signs. Imaging is crucial in the detection and diagnosis of BMs. It is used to confirm previously undiagnosed CNS metastases in patients with neurological symptoms, to confirm brain involvement in a person with systemic metastatic disease, and for staging and monitoring of BMs over the course of therapy. Imaging is also essential before surgery to plan safe excision of the tumor from the brain.

BMs can present as solitary or multiple lesions. Most BMs are solitary with 20% of diagnoses having two or less lesions, although 30% of cases have three or more lesions. Lung and melanoma primarily lead to multiple BMs, whereas breast, renal, colon usually present as single lesions. Contrast enhanced magnetic resonance imaging (MRI) is the preferred method of detection, but nonenhanced computed tomography (NECT) scans are often used for initial screening purposes, especially for naive patients who present with new neurological symptoms. For certain cancers like small cell lung cancers (SCLC), contrast enhanced computerized tomography (CECT) is equivalent to detection by MRI, because no survival benefit is offered by magnetic resonance imaging (MRI) versus computerized tomography (CT). On MRIs, metastases appear hypo-intense on T1 and hyperintense on T2. Gadolinium contrast MRIs are important in detection of small multiple lesions, and their use improves diagnostic confidence (Fink and Fink 2013).

Diagnosis of nonparenchymal BMs can be challenging. Pachymeningeal (dural) metastases can be hard to distinguish from meningiomas. For this, information about the previous history of systemic or CNS metastasis in the patient is key. Detection/diagnosis of leptomeningeal metastases is also difficult by CT, and therefore evaluation of the cerebrospinal fluid (CSF) in suspected cases is essential for confirmation (Sawaya 2001).

CANCER TYPE AND PROPENSITY OF BRAIN METASTASIS

Metastasis is a carefully orchestrated process involving breakage of cells from the primary tumor, gain of invasive properties, and interaction with the microenvironmental niche to establish tumors at distant sites. Clinically, different kinds of tumors show varying proclivities in their ability to successfully metastasize within the CNS. The most common primary sites are lung, breast, and melanoma, in that order. These are followed more uncommonly by thyroid, GI, and prostate cancers. Propensity of occurrence of brain metastasis can also be further ranked by clinical subtypes of solid cancers.

Lung Cancer

Lung cancer is the primary tumor in ~40%–50% of patients diagnosed with BMs. 50% of lung

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cancer BMs occur at disease presentation/diagnosis, and sometimes the CNS is the only location of dissemination. This highlights the aggressive nature of the primary tumor, and the short latency period seen for lung-to-brain metastasis. Because of higher incidence, non-small-cell lung cancer (NSCLC) comprises a higher percentage of BMs than small-cell lung cancer (SCLC), but recent studies show that SCLC has a higher biological propensity for CNS spread (Lukas et al. 2017). About 7% of patients with NSCLC present with brain BMs at diagnosis and ~25%–30% develop BMs over the course of their disease (Owen and Souhami 2014). Surgical resection has been shown to improve disease control in patients with solitary resectable lung-to-brain metastasis (LBM). A combined approach of surgery and WBRT has also improved intracranial disease control for such patients (Patchell et al. 1990; Noordijk et al. 1994; Chi and Komaki 2010), although the efficacy of this combined approach has not yet been unequivocally verified in patients with multiple or advanced LBMs. Targeted therapy is recommended for NSCLC patients with genetic mutations, but in cases of mass effect or impending brain herniation, surgery and subsequent systemic therapy are preferred. BMs are seen at diagnosis in 23.8% of ALK-rearranged tumors, and in 24.4% epidermal growth factor receptor (EGFR)-mutated NSCLC (Bulbul et al. 2018). Patients that harbor mutations in such oncogenic drivers may be treated using targeted therapies. ALK gene fusions have been reported in 2%–7% of patients with NSCLC, but might be higher in select groups (Shaw et al. 2009). Crizotinib was used as a first generation ALK inhibitor for systemic treatment, but patients developed CNS metastases within 1 yr of starting therapy (Costa et al. 2015). Crizotinib also has low CNS penetrance and is a substrate for P-glycoprotein efflux transporters (Petrelli et al. 2018), but showed CNS disease control rates (DCR) comparable to systemic DCR (Bulbul et al. 2018). Current trials are investigating methods to increase CNS availability of crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib are second generation ALK tyrosine kinase inhibitors that have shown improved CNS-efficacy and increased intracranial response rates in *ALK*-positive NSCLC patients with BMs (Dempke et al. 2015; Bulbul et al. 2018; Petrelli et al. 2018). These drugs are more effective partly because of their increased CNS availability and BBB penetration.

Ten to 20% of patients with lung adenocarcinoma show EGFR mutations. Erlotinib and afatinib are first and second generation EGFR inhibitors that can be used as standalone treatments (without chemotherapy) for EGFR-mutated NSCLC. These drugs have moderate CNS penetrance and have showed substantial intracranial rate of response (RR) (Jamal-Hanjani and Spicer 2012; Dempke et al. 2015; Bulbul et al. 2018; Kelly et al. 2018). But, secondary EGFR T790M mutations have arisen as a mechanism of resistance to these drugs (Joo et al. 2018). Osimertinib is a United States Food and Drug Administration (USFDA)-approved third generation EGFR-mutant inhibitor effective against EGFR T790M (Leonetti et al. 2018). Osimertinib has BBB permeability greater than older EGFR inhibitors (Ballard et al. 2016; Koba et al. 2017), and was shown to be effective in a phase I trial in leptomeningeal disease in EGFR-mutant NSCLC (Yang et al. 2017).

For SCLC patients with BMs, the median overall survival (OS) is 4.9 mo, and 1.9–2.4 mo for leptomeningeal metastases. SCLC usually manifests as multiple brain lesions, and thus surgery is not a common therapeutic avenue for patients. Therapeutic WBRT is the standard of care for SCLC patients with BMs, who have never undergone prophylactic cranial irradiation (PCI). Stereotactic radiosurgery (SRS) is only performed in cases of recurrent BMs, to avoid exacerbation of cognitive decline by repeated WBRT. Systemic chemotherapy is not routinely used for SCLC patients with newly diagnosed or recurrent BMs. Several studies have investigated the use of systemic nontargeted cytotoxic drugs (e.g., cisplatin, temozolomide, etoposide) along with WBRT, and have shown some CNS RR, but OS still remains dismal (Lukas et al. 2017). There are very few indications of SCLC specific targets (Pezzuto et al. 2019) unlike NSCLC, but immunotherapy trials with antibodies targeting programmed cell

death (nivolumab) and CTLA4 (ipilimumab) are underway.

Breast Cancer

Up to 30% of all breast cancer patients are diagnosed with BMs within their lifetime. Out of these, patients diagnosed with the triple-negative subtype (TNBC) show increased risk of brain metastasis, followed by the Her2+ and hormone-positive (ER^+/PR^+) subtypes (Niwinska et al. 2010; Witzel et al. 2016). Successful control of extracranial breast carcinoma, and emergence of advanced diagnostics has increased the incidence and diagnosis of breast-to-brain metastases (BBMs). Breast cancer cells that escape chemotherapy or surgical extraction can persist in the patient's body and eventually lead to BBMs. Breast cancer is unique in its longer latency to forming BMs (Saunus et al. 2011) and this has been associated with the acquisition of neuronal characteristics (Neman et al. 2013, 2014). A recent clinical study also substantiated that BBMs are able to acquire mutations in clinically targetable genes (*HER2*) and that ~20% of Her2-negative diagnosed breast tumors showed a switch to Her2-positivity in the brain (Priedigkeit et al. 2017). This highlights the need for molecular characterization of highly invasive breast tumors for patients over the course of their disease, to avoid nonrelevant therapeutic interventions.

Currently, there are no breast-cancer specific treatments for BMs in particular, and a multivariate approach with surgery and radiation is used. For a limited number of BMs lesions (1–4), surgical resection followed by SRS or WBRT is performed. SRS is preferred over WBRT to avoid the associated neurocognitive decline, similar to treatment in other cancers with BMs. For multiple metastatic lesion (>4) or where surgery or SRS is not feasible, WBRT is performed, with a shift toward hippocampal sparing WBRT. This approach is reasonable given the low incidence of BBMs occurring in or around (5 mm margin) the hippocampus (Brosnan and Anders 2018). Currently, systemic drugs such as lapatinib are being investigated as radiosensitizers (Koo and Kim 2016). Recent trials also investigated the inclusion of prophylactic memantine (an oral NMDAR antagonist), which may delay the loss of cognitive capabilities after WBRT. Accordingly, newer regimens with combined use of memantine and hippocampal-sparing WBRT are being tested in patients (Brown et al. 2013).

Systemic targeted therapies especially for Her2+ breast cancer (trastuzumab, lapatinib) have limited CNS permeability, and are not protective against BMs. Lapatinib as monotherapy showed very meager CNS response, but showed improved efficacy in BMs patients when combined with capectabine (Bachelot et al. 2013; Petrelli et al. 2017).Targeted therapies like neratinib and tucatinib are now being investigated for CNS response and efficacy (Freedman et al. 2016, 2019; Murthy et al. 2018). PI3K and cyclin-dependent kinase (CDK) inhibitors in the context of hormone-positive breast cancers are in trials for CNS response in patients with BMs (Liu et al. 2016). For triple-negative breast cancer patients, poly(ADP-ribose) polymerase (PARP) and microtubule inhibitors are currently in trial for treatment of CNS metastases (Pegram et al. 2018).

Melanoma

BMs are a significant complication in patients diagnosed with advanced melanoma. About 20% of these patients present with BMs at diagnosis, and ~40%–50% develop BMs during the course of the disease (Vosoughi et al. 2018). Melanoma BMs (MBMs) can present as single or multiple intracranial lesions, with better prognostic index for patients presenting with single BMs at melanoma diagnosis. The median survival for melanoma patients with BMs is 3 mo (without treatment) to ~9 mo (with treatment) (Chukwueke et al. 2016).

Therapy for MBMs has been controversial, and is evolving as more postdiagnostic and -therapeutic data are collected. Surgery is preferred for patients with solitary MBM, and has an overall survival benefit when compared with patients who get radiation alone (Bafaloukos and Gogas 2004). Surgery has an advantage for symptomatic relief, as well as for procurement of tumor tissue for molecular charac-

terization. WBRT has been shown to confer survival benefit to melanoma patients with favorable prognostic profile according to Karnofsky performance score (KPS), age, and number of extracranial metastases. WBRT after surgery or stereotactic radiation (SR) although, does not improve survival, but leads to better intracranial disease control. Because of observed neurocognitive decline after WBRT, hippocampal sparing WBRT, and inclusion of prophylactic memantine (an oral NMDAR antagonist), are in trials for MBM therapy. Stereotactic radiosurgery (SRS) is used to achieve local control in patients with small (<3 cm) and fewer than three brain lesions. SRS use is dependent on a variety of factors including accessibility of lesion, proximity to eloquent brain regions, and suitable candidacy of patient. About 50% of patients with advanced melanoma show BRAF mutations. Inclusion of BRAF-targeted small molecules in metastatic melanoma therapy has shown significant results, and is being tested for intracranial disease (Chukwueke et al. 2016). A retrospective study showed that patients with MBMs who were treated with BRAF inhibitor Vemurafenib showed 71% control of intracranial disease, and 50% of extracranial disease (Dummer et al. 2014). Immunotherapy, especially immune checkpoint inhibitors like CTLA4, PD-1 and PDL-1 antibodies have shown promise in metastatic melanoma. A phase-II trial with ipilimumab in patients with small and asymptomatic MBMs showed that 24% of patients showed partial response or stable disease (Margolin et al. 2012).

BARRIERS TO ENTRY

A highly regulated milieu is the cornerstone for reliable neural signaling within the CNS. The CNS must therefore be shielded from external influence at interfaces where blood and CSF come into close contact with neural elements. Several key zones of restriction have evolved to that end: the BBB, its caudal extension the blood–spinal cord barrier (BSCB) and the blood–cerebrospinal fluid barrier (BCSFB) (Fig. 1) (Abbott et al. 2010). The BBB is a nonfenestrated capillary endothelium ensheathed by a network of pericytes, astrocytic foot processes, and microglia that together constitute the neurovascular unit. This collective has the responsibility of maintaining the CNS as an immunologically and pharmacologically privileged site. Central to this role are the presence of tight junctions (zonulae occludentes), which interconnect endothelial cells and restrict paracellular diffusion between plasma and brain interstitium. In addition, low rates of pinocytosis within the endothelium limit transcellular movement of molecules while a metabolic barrier continually degrades molecules en route to the CNS to achieve their functional exclusion (Serlin et al. 2015).

At the molecular level, selective permissiveness of the BBB and BSCB is the result of junctional complexes linking endothelial cells through a combination of adherens and tight junctions. Adherens junctions rely on cadherin proteins to form an intercellular conduit that couples the cytoplasm of adjacent cells and provides architectural support. Meanwhile, tight junctions consist of transmembrane and cytoplasmic proteins anchored to actin cytoskeleton; they include: occludin, claudins, and junctional adhesion molecules (JAMs). These are in turn associated with a host of regulatory proteins including cingulin, zona-occludens (ZO)-1, ZO-2, and ZO-3, among others (Abbott et al. 2010). Migration across the BBB and BCSFB under physiologic conditions offers incredible insight into the mechanisms by which tumor cells might gain entry into the CNS parenchyma during brain metastasis. For example, mononuclear cells possess the ability to pierce through the cytoplasm of BBB endothelium in a transcellular fashion, which precludes the need for tight junction rearrangement as is the case with paracellular modes of entry (Engelhardt and Wolburg 2004). Could tumor cells acquire the phenotypic metasignature of mononuclear cells to accomplish transcytoplasmic diapedesis?

Pathologic states are equally informative. Studies using the well-established animal model for multiple sclerosis, experimental allergic encephalomyelitis (EAE), have corroborated a role for transendothelial migration of immune cells,

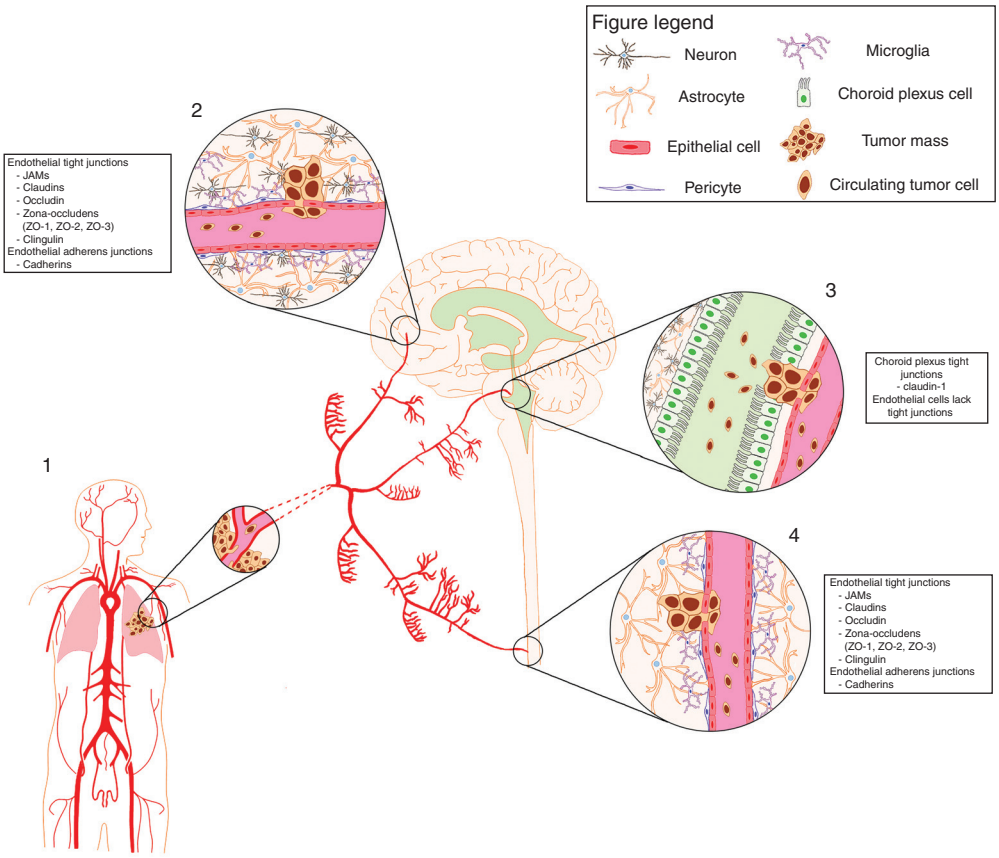

Figure 1. Barriers to entry. The blood–brain barrier, the blood–cerebrospinal fluid barrier, and the blood–spinal cord barrier: (1) A primary tumor originating in the body enters the blood stream in the beginning phases of metastasis. (2–4) Circulating tumors cells in the blood stream arrive at three different locations in the central nervous system (CNS): (2) the blood–brain barrier (BBB), (3) the blood–cerebrospinal fluid barrier (BCSFB), and (4) the blood–spinal cord barrier (BSCB). Each of these barriers comprise of different molecules designed to shield the CNS from external influence. (2) The BBB is composed of tight junctions (zonulae occludens) between endothelial cells, which create a mostly impenetrable barrier. Tight junctions include transmembrane and cytoplasmic proteins consisting of occludin, claudins, and junctional adhesion molecules (JAMs). These are further associated with regulatory proteins including ZO-1, ZO-2, ZO-3, and cingulin. (3) The BCSFB is a structure, which has increased permeability compared with the BBB. BCSFB endothelial cells lack tight junctions and are thus have a leaky choroid plexus tight junction for membrane integrity. (4) The overall framework for the BSCB is similar to the BBB with main difference being in the architecture of the endothelial cells.

suggesting that this process can be modulated by inflammation (Wolburg et al. 2005). In addition, a causal relationship between loss of tight junction protein claudin 3 and increased BBB permeability (Wolburg et al. 2003) has been established in EAE. Altogether, this implies that up-regulation of both transcellular and paracellular migration occurs during CNS invasion with diseased states. Although the skeletal framework is the same for both BBB and BSCB, specific differences exist in the ultrastructure of the endothelial cells (Bartanusz et al. 2011). This might explain their proclivity to certain pathologies, and avenues for CNS metastasis. Extensive research into immune cell transgression across the BBB and BSCB has unearthed a cornucopia of molecular players, but despite years of active investigation, the precise details of

diapedesis across an otherwise impervious barrier remain elusive.

The CSF comes into close contact with blood in two key areas, which formally make up the blood–CSF barrier (BCSFB): (1) where the arachnoid membrane envelopes the subarachnoid space and (2), where choroid plexus (CP) projects into the ventricular system (Johanson et al. 2011). Because CP microvasculature lack tight junctions, they are notorious for being porous to large molecules in contradistinction to brain endothelium. This can be explained by the absence of capillary ensheathment by astrocytic foot processes and the expression of "pore-forming" claudin-1 in choroid plexus, rather than "barrier-forming" claudins 3, 5, and 12 evident in brain. The functional BCSFB is therefore dependent on tight junctions within choroid epithelium, rather than their "leaky" endothelium. The increased permeability of the BCSFB is made evident by measuring the transendothelial resistance (TEER) of the barrier. in vitro TEER measurements of the choroid plexus are ~150 $\Omega.cm^2$, compared with 1500 $\Omega.cm^2$ measured in the BBB in vivo (Redzic 2011).

In addition to its barrier properties, the choroid epithelium is responsible for generating CSF. CP endothelial permeability is not a static feature, but can be modulated. Whereas vascular endothelial growth factor (VEGF) secreted by CP epithelial cells has the capacity to diffuse across their basal surface and into the CP interstitium to enhance vessel porosity (Esser et al. 1998), angiopoietin-1 does the opposite (Nourhaghighi et al. 2003). This interface represents a potential point of vulnerability within CNS defenses because plasma-borne solutes, and by extension, pathogenic cells, have unfettered access to the CP interstitium lying between the choroid plexus endothelium and epithelium. Dexamethasone administered during meningitis is theorized to act by stabilizing MMP-3 in the interstitium and in so doing hinders bacterial dissemination into CSF (Tenenbaum et al. 2008). However, it is unclear what role, if any, the BCSFB plays in the spread of malignancy, particularly those prone to dissemination through CSF.

AVENUES FOR DISSEMINATION

The incidence for BMs has grown over the years, owing to increased patient survivability from evolving therapeutics and widespread availability of magnetic resonance imaging. The brain provides a refuge/sanctuary for tumor cells to escape chemotherapy, immune response, and natural clearance. Formation of successful distant metastases requires hematogenous or lymphatic transport of tumor cells. For the CNS, the most commonly known and studied route is transport via the bloodstream. Seeding can occur both in the meninges as well as parenchyma of the brain. This process requires the tumor cells to cross the BBB, according to studies so far. Several new avenues of CNS dissemination are now under consideration, and will be discussed in this section.

Seeding through the BBB

Because the brain is structurally and functionally isolated from the rest of the body by an intricate BBB, it takes longer for tumor cells to successfully invade the CNS, as compared with other organs. Studies have shown that lung cancer cells require 48 h, whereas breast cancer needs 2–7 d, and melanoma takes up to 14 d to cross the BBB (Wrobel and Toborek 2016). These results are also indicative of the intrinsic properties of these primary tumors. The molecular mechanisms of BBB disruption by brain-trophic tumors are not well known, but are an urgent area of investigation. Interference in normal functioning of endothelial cells contributes to CNS spread. Research in patient-derived xenograft (PDX) models showed that BBB is selectively disrupted in BMs through inhibition of Mfsd2a, a fatty acid transporter expressed by endothelial cells. This was accompanied by BBB leakage and loss of transforming growth factor (TGF)β and basic fibroblast growth factor (bFGF) signaling in the BMs endothelium (Tiwary et al. 2018). Exosomal microRNAs (miR-105) secreted by invasive breast cancer cells were shown to target tight junction mRNAs in brain vascular endothelial cells, thereby influencing their barrier properties (Zhou et al. 2014).

Exosomal miR-181c from metastatic breast cancer cells also promotes dysregulation of the BBB in vitro through abnormal localization of endothelial N-cadherin and actin via down-regulation target gene PDPK1 (Tominaga et al. 2015).

Radiation therapy for intra- and peri-CNS tumors can also disrupt the integrity of the BBB (van Vulpen et al. 2002). Increase in endothelial and glial ICAM-1 was found after radiation-induced disruption of the BSCB in rats (Nordal and Wong 2004). ICAM-1 is essential for binding and extravasation of immune cells through the CNS vasculature (Ma et al. 2013), and could potentially be used as a gateway by tumor cells for access into the CNS.

Seeding through the CSF and BCSFB

Circulating tumor cells (CTCs) in the CSF and leptomeninges are therapeutic roadblocks, and potential "seeds" of metastasis in the brain and spine. A large number of leptomeningeal CNS metastases come from breast and lung tumors (Corbin and Nagpal 2016). Because the CSF is a nutrient-weak microenvironment, tumor cells modify this niche to their benefit. A recent study showed that invasive tumor cells in the CSF secrete complement C3. This binds to receptor C3aR on the choroid plexus cells, thus disrupting the BSCFB, and allowing unfettered access of nutrients and growth factors into the CSF (Boire et al. 2017). Further research should be conducted to analyze if disruption of the BSCFB can facilitate tumor invasion into the brain parenchyma.

Although BBB disruption is a well-research phenomenon in metastatic cancers, the role of choroid plexus (CP) cells in CNS metastasis is relatively unknown. Rare cases of intraventricular metastases have been reported from renal, lung, GI, breast, and bladder cancers (Tanimoto et al. 1991; Nakabayashi et al. 1994; Della Puppa et al. 2010; Shapira et al. 2014). Some of these have been found to be juxtaposed right alongside CP cells that line the lateral ventricles. Neuroblastoma cells were shown to cross an intact choroid plexus barrier in vitro (Vandenhaute et al. 2015). In mouse models, lymphoma cells have been shown to localize to the brain through the choroid plexus and cranial nerves (Hochman et al. 2001). These studies indicate a role for the BCSFB in CNS-metastatic cancers

Pachymeningeal Seeding Postneurosurgical Resection

Solitary metastatic lesions in the dura are rare in extracranial carcinomas, but have been reported in metastatic breast, lung, prostate cancers, and lymphoma (Fink and Fink 2013; Heo et al. 2017). When they do occur, the origin of spread is mainly hematogenous. The role of therapeutic intervention in facilitating CNS metastasis is an emerging area of research. A recent retrospective study showed that patients whose CNS metastases were treated with a combination of surgical resection and subsequent SRS, versus SRS alone, had an increased probability of developing pachymeningeal (dural/outer arachnoid) lesions away from the SRS site (Cagney et al. 2019). This suggests that individual cells that get dispersed during surgical removal can manifest as detectable tumors outside the targeted lesion region.

THERAPEUTIC PERSPECTIVES IN BRAIN METASTASES

Using conventional therapy to treat brain metastases (BMs) has limited to no efficacy. Chemotherapeutic agents' entry and access to CNS lesions are blocked or limited by BBB. In addition, the high sensitivity of brain and its significance limit radiotherapy and radiation dosage and constrain resection margins. Therefore, neurosurgical resection of individual BMs using modern microneurosurgical techniques remains the standard of care. Decision making for brain metastasis care is determined based on the histological type of the tumors, number and location of lesions, and the molecular and genetic characteristics of the tumor. Traditionally, WBRT is the first choice after surgical resection of a single lesion or when there are several asymptomatic lesions; however, WBRT is associated with significant risk of cognitive decline. Additionally, the recurrence of the tumor leads to the failure of radiotherapy. Irradi-

ation of the whole brain is associated with hypoxia-inducible factor-1 and stromal cell-derived factor-1 (SDF-1) production, which alternatively increases macrophage recruitment and angiogenesis at the site of the tumor invasion (Lerman et al. 2010; Wang et al. 2013). Overcoming the biological cause of the radiation resistance can allow more effective delivery of radiotherapy. Studies in murine models have shown that inhibition of Chk1 (a DNA-damage checkpoint protein) and c-Met (a receptor tyrosine kinase with downstream oncogenes) can improve the survival and response to radiation (Cullinane et al. 2007; Bhardwaj et al. 2013). Depending on tumor histology and its origin, standard chemotherapy might be implemented following the healing of the surgical site. Personalization of metastatic cancer treatment using molecular profiling to select therapies that benefit the patients while avoiding irrelevant therapies with potential toxicity is limited by poor penetration of most chemotherapeutic agents across the BBB. Mannitol has been used as a nonspecific permeabilizing agent with limited success (Siegal et al. 2000). Since then, attempts have been made to develop selective permeabilization of the BBB at the site of metastasis using intravenous tumor necrosis factor (Connell et al. 2013) and MRI-focused ultrasound combined with microbubbles (Song et al. 2018). Multiple researchers are working on developing novel targeted delivery strategies; therefore, it is likely to have more options available in the future.

Preoperative diagnosis of BMs and inspecting the microscopic edges of the lesions are challenging. Using confocal microscopy as an alternative to light microscopy has become particularly appealing for accurate detecting the edge of the metastases within the resection cavity and residual tumor (Sanai et al. 2011; Mooney et al. 2014). Recent advances have improved the ability of MRI-guided laser interstitial therapy (LITT) technology to resect lesion tissue accurately and safely with higher protection of the nearby brain tissue. Patients with poor response to traditional radiotherapy have shown good result with LITT (Sharma et al. 2016). LITT can be a good option to improve the quality and quantity of life for patients with BMs in deep locations, which are radiation-resistant. However, further studies are required to investigate its effect on neurological morbidity and progression of CNS diseases.

Each stage of brain metastasis process can be a target for personalized intervention or, at least, better prognosis regarding the molecular properties of the metastases. Metastatic tumor cells evolve after establishing themselves within the brain parenchyma. Genomic studies have shown that the molecular profile of BMs is distinctive from the primary tumor. These alterations are clinically critical in patients with inoperative BMs in which primary tumors remain as the only tissue available for genomic analysis for the selection of the proper therapy (Han and Brastianos 2017; Liao et al. 2018). In coming years, further DNA- and RNA-based high-throughput sequencing comparing primary and BMs genomic profiling will reveal additional information on the metastatic process and, subsequently, the potential individual therapies.

The growth, invasion, and colonization of the brain tumors is dependent on several microenvironment-derived signals and on different factor secreted from microglia/macrophages. Therefore, targeting the microglia/macrophage-derived signals has been considered as a potential therapy to inhibit brain tumor growth. For instance, it has been shown that BMs form gap junctions with reactive astrocytes surrounding them (Chen et al. 2016). Metastatic cells use this interaction to clear out the toxic metabolites generated by various stress conditions such as chemotherapy. Targeting gap junctions using BBB permeable drugs has shown promising result supporting the potential of targeting interactions within the microenvironment.

Currently, several immunotherapy approaches are under study for treating the brain tumor patients. Immunotherapy treatment either stimulates immune system or enhances its activity. The immune system promotes tolerance through down-regulating the immune response via the cell surface receptors referred to as immune checkpoints. These receptors are responsible for inhibiting the immune response against cancer cells. Thus, developing the

inhibitors of these receptors, known as checkpoint inhibitors, have been widely used for the treatment of certain cancers. A monoclonal antibody, called ipilimumab, targeting the immune checkpoint cytotoxic T-lymphocytes-associated protein 4 (CTLA4) has been approved for treating unresectable and metastatic melanoma. The other checkpoint inhibitor, a monoclonal antibody known as nivolumab, targets immunoglobulin G4 (IgG4) and the programmed cell-death protein1 (PD-1), and is approved to be used in patients with unresectable or metastatic melanoma, previously treated with ipilimumab, and patients with BRAF-mutated melanoma earlier treated with BRAF-inhibitor (Tawbi et al. 2018). Additionally, recent clinical trials showed efficacy of nivolumab and ipilimumab combination against asymptomatic melanoma patients with BMs (Long et al. 2018).

CONCLUDING REMARKS

Brain metastasis has become a common cause of mortality in cancer patients. Around 20%–40% of cancer patients develop brain metastases (BMs) with 60%–75% of the brain metastatic patients become symptomatic. Advances in treating the primary cancers have led to patients living longer and, therefore, the patients are more likely to experience brain metastasis complications. Multiple BMs make their prognosis challenging and worsen the long-term rate of survival.

Surgical resection, radiotherapy, and chemotherapy have remained as available treatments with poor outcome. Personalized therapy through targeting specific tumor molecular pathways is predicted to dominate BM management in the future. Considering the complexity of BMs treatments, a multidisciplinary collaboration between neurosurgeons, medical oncologists, and radiation oncologists is required. Researchers and clinicians have to overcome several obstacles and challenges when designing treatment strategies for cancer patients with BMs. The progress made with targeted therapies in recent years makes us hopeful that continued research for drugs with ability to reach and treat BMs will eventually help patients to have improved quality of life and extended survival.

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