Therapeutic approaches for HER2-positive brain metastases: Circumventing the blood–brain barrier

Ankit I. Mehta[a,d], **Adam M. Brufsky**[b,e], and **John H. Sampson**[c,*]

Ankit I. Mehta: ankit.mehta@duke.edu; Adam M. Brufsky: brufskyam@upmc.edu; John H. Sampson: john.sampson@duke.edu

[a]Preston Robert Tisch Brain Tumor Center, Division of Neurosurgery, Department of Surgery, Duke University Medical Center, Box #3807, Durham, NC 27710, USA

[b]Division of Hematology/Oncology, University of Pittsburgh Medical Center, Cancer Center at Magee-Womens Hospital, 300 Halket Street, Pittsburgh, PA 15213, USA

[c]Division of Neurosurgery, Department of Surgery, Duke University Medical Center, 220 Sands Building, Research Drive, Durham, NC 27710, USA

Abstract

We aim to summarize data from studies of trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer (MBC) and brain metastasis and to describe novel methods being developed to circumvent the blood–brain barrier (BBB). A literature search was conducted to obtain data on the clinical efficacy of trastuzumab and lapatinib in patients with HER2-positive MBC and brain metastasis, as well as the transport of therapeutic molecules across the BBB. Trastuzumab-based therapy is the standard of care for patients with HER2-positive MBC. Post hoc and retrospective analyses show that trastuzumab significantly prolongs overall survival when given after the diagnosis of central nervous system (CNS) metastasis; this is probably attributable to its control of extracranial disease, although trastuzumab may have a direct effect on CNS disease in patients with local or general perturbation of the BBB. In patients without a compromised BBB, trastuzumab is thought to have limited access to the brain, because of its relatively large molecular size. Several approaches are being developed to enhance the delivery of therapeutic agents to the brain. These include physical or pharmacologic disruption of the BBB, direct intracerebral drug delivery, drug manipulation, and coupling drugs to transport vectors. Available data suggest that trastuzumab extends survival in patients with HER2-positive MBC and brain metastasis. Novel methods for delivery of therapeutic agents into the brain could be used in the future to enhance access to the CNS by trastuzumab, thereby improving its efficacy in this setting.

*Corresponding author. Tel.: +1 919 684 9041; fax: +1 919 684 9045.
[d]Tel.: +1 919 684 7840; fax: +1 919 684 7937.
[e]Tel.: +1 412 641 4530; fax: +1 412 641 2296.

Keywords

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Introduction

The number of patients found to have central nervous system (CNS) metastasis is increasing,[1] with an estimated incidence of up to 170,000 cases per year in the United States alone.[2,3] This increase is due to several factors that include earlier and more accurate detection of CNS disease[4] and the increasing availability of improved treatments for systemic disease.[1]

Brain metastasis is documented in 10–16% of patients with metastatic breast cancer (MBC) during the course of their disease.[5,6] However, a study of data from autopsies suggests that up to 30% of patients with MBC have CNS involvement.[7] Furthermore, since brain metastases generally occur late in the course of MBC, a result of the improving overall survival (OS) rate in these patients is that the incidence of brain metastasis will likely increase.[8] Breast cancer brain metastasis is associated with a poor prognosis with 1- and 2-year survival rates of 20% and 2%, respectively.[9–11]

The overexpression of human epidermal growth factor receptor 2 (HER2) on the surface of breast cancer cells is known to be a risk factor for brain metastasis.[12–15] The HER2-directed monoclonal antibody (mAb) trastuzumab (Herceptin®, Genentech, Inc.; South San Francisco, CA) in combination with chemotherapy is the standard of care for patients with HER2-positive MBC. However no HER2-directed agent, including trastuzumab, is approved for the treatment of brain metastasis. Like many chemotherapeutic and other large biologic agents, the ability of trastuzumab to cross the blood–brain barrier (BBB) when administered as an intravenous infusion is limited. This review discusses the clinical utility of trastuzumab and describes how novel approaches to enhancing drug delivery to the CNS could be applied to trastuzumab for the treatment of HER2-positive breast cancer brain metastasis.

Current standard of care for CNS metastases

Treatment strategies for CNS metastases aim to improve locoregional CNS disease control. Those treatments currently in use include various combinations of surgery, stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT), and chemotherapy. Strategies designed to control symptoms, such as corticosteroids to reduce peritumoral edema and anticonvulsants to prevent recurrent seizures, are combined with these therapeutic approaches.

Surgery and radiosurgery can be effective treatment options for patients with limited CNS disease burden.[16–19] Randomized prospective studies have demonstrated that for a solitary CNS metastasis, an improved median survival rate of 10 months is achieved after surgical resection and WBRT compared with 4–6 months following WBRT alone.[20,21] However,

with only a minority of CNS brain metastases demonstrating solitary disease,[6,22] surgery is not an option for a majority of patients. Notably, the results from two recent studies have demonstrated that SRS alone may provide a comparable survival advantage compared with SRS in combination with WBRT in patients with limited CNS disease.[23,24] Conflicting reports do exist in terms of the neurocognitive effects of WBRT, and its risks and benefits are currently the subject of much debate and study.

Prophylactic WBRT is routinely used in small cell lung cancer as it clearly reduces the incidence of brain metastases and improves survival with a relatively low frequency of neurotoxicity.[25,26] The limited data currently available, however, suggest that prophylactic WBRT may not be appropriate for advanced breast cancer because the risks of this therapy may outweigh the benefits.[27] Neuroimaging can be used to detect occult brain metastases in patients with HER2-positive breast cancer.[5,28,29] Limited data suggest that while overall survival remains the same whether WBRT is given to patients with symptomatic or nonsymptomatic brain metastases identified with neuroimaging techniques,[5,29] the rate of death due to progression within the brain is threefold lower when WBRT is administered to patients with asymptomatic brain metastases.[29] Given the potential improvement in cognitive function that may be gained by controlling the growth of these metastases, further investigation of the impact of routine screening for occult brain metastases on patient care is warranted.

Because CNS metastasis is a stipulated exclusion criterion in most clinical trials of systemic chemotherapy in patients with breast cancer, there are limited clinical data reporting the efficacy of systemic therapy for breast cancer brain metastases; data that are available have, for the most part, been disappointing.[15]

Evidence for HER2 expression in CNS metastases

There is a substantial body of clinical trial data demonstrating that patients with HER2-positive MBC are two to four times more likely to develop brain metastases than patients with HER2-negative disease[13,30] and that HER2-positive status is a significant risk factor for CNS relapse.[14,31–33]

Studies performed before the use of adjuvant trastuzumab therapy became commonplace offer valuable insight into the association between breast cancer brain metastasis and HER2 status. In a large retrospective study of 9524 women with early-stage breast cancer (EBC) who were enrolled in 10 clinical trials between 1978 and 1999, the 10-year cumulative incidences of CNS as first relapse site were 2.7% and 1.0% in patients with HER2-positive and HER2- negative tumors, respectively ($P < 0.01$).[33] Similarly, the cumulative incidences of CNS metastases as either a first or subsequent event were greater in patients with HER2-positive compared with HER2-negative disease (6.8% vs 3.5%; $P < 0.01$). These data are in accordance with the findings of an earlier study in 319 patients that showed a significantly increased risk of lung, liver, and brain metastases in patients with HER2-positive compared with HER2- negative disease ($P = 0.0002$).[34]

The etiology of the higher incidence of brain metastasis in HER2-positive breast cancer has not yet been clearly defined and is most likely multifactorial. Contributing factors include

the more aggressive nature of HER2-positive compared with HER2-negative disease[34,35] and the ability of HER2 to increase brain colonization via downstream targets, such as the protumorigenic and prometastatic enzyme heparanase.[36]

Although the major, prospective clinical trials of adjuvant trastuzumab did not reveal an increased risk of brain metastasis,[37,38] retrospective analyses have reported an apparent increase in CNS disease in patients with HER2-positive disease who received trastuzumab compared with historical controls.[39–41] In a recent population- based registry study in 1458 patients with EBC, CNS as first recurrence was documented for 0.6% of patients with HER2-negative disease and for 4% and 1.2% of patients with HER2-positive disease who had and had not received adjuvant trastuzumab, respectively.[32] Time to CNS as first recurrence, however, was significantly prolonged in patients with HER2-positive disease who received adjuvant trastuzumab (20.3 months) compared with patients with HER2-negative disease (19.8 months) and those with HER2-positive disease who did not receive trastuzumab (10.3 months) ($P = 0.018$).

Another study in 598 patients with invasive breast cancer and CNS metastases showed that time to CNS recurrence was significantly prolonged after trastuzumab (13.1 vs 2.1 months in trastuzumab-naive disease ($P = 0.0008$) and 8.9 months in HER2- negative disease (Fig. 1)).[42] Together, these data indicate that trastuzumab does not itself increase the risk of brain metastasis but that the CNS may represent a potential sanctuary site in patients with HER2-positive disease who are treated with trastuzumab; in effect, the prolonged survival afforded by trastuzumab allows the so-called unmasking of CNS recurrence that would otherwise remain clinically silent before death.

The blood–brain barrier

Structure and function

The BBB is composed of capillary endothelial cells with tight intercellular junctions, pericytes, a basement membrane, and astrocyte foot processes (Fig. 2). The BBB regulates bidirectional control over the passage of a large diversity of regulatory proteins, nutrients, and electrolytes, as well as potential neurotoxins, into the brain.[43] The passage of molecules across the BBB is regulated by complex transport systems that can prevent many drugs from entering the CNS, including a number of chemotherapeutic and molecular-targeted agents. In addition, efflux pumps, such as P-glycoprotein (PgP), impede some chemotherapeutic agents from penetrating the brain by actively removing them.[44]

Tumor cell penetration of the BBB

The metastatic process into the CNS requires that the tumor cell traverse the BBB.[45] It is thought that tumor cells shed from the primary tumor enter the circulation and become trapped in brain capillary beds at vascular branch points. Subsequent changes in the local environment, including the secretion of factors by brain vascular endothelial cells, astrocytes, and tumor cells, then promote tumor cell proliferation and invasion into the CNS.

The integrity of the BBB can be compromised either as a result of neuropathology or because of a precipitating event.[43] Perturbation of the BBB leads to an increase in

permeability and an edematous response. When metastatic tumors grow beyond 1 mm to 2 mm within the brain parenchyma, the BBB becomes structurally and functionally compromised, as evidenced by homogeneous contrast enhancement on magnetic resonance imaging (MRI). In an experimental brain metastasis model, lesions 0.2 mm^2 were associated with perturbation of the BBB.[46] Moreover, CNS metastases from lung adenocarcinomas and melanomas can induce a significant reduction in PgP expression.[44] Recently published evidence also suggests that the integrity of the BBB may be influenced by the phenotype of the metastatic tumor cell. In a small study in 29 patients with breast cancer brain metastases, BBB disruption was observed more frequently with triple-negative (i.e., estrogen receptor–negative, progesterone receptor–negative, HER2-negative) tumors than with HER2-positive tumors.[47]

Antibody penetration of the BBB

Since their introduction, therapeutic mAbs have become widely used in all fields of medicine, including oncology. However, the usefulness of systemic chemotherapies and targeted agents for the treatment of neurologic disease has been called into question as many of these agents are thought to be too large (i.e., molecular mass >450 kDa) or hydrophilic to routinely cross the BBB at relevant levels.[15,48] This is supported by a study reporting cerebrospinal fluid (CSF) concentrations of trastuzumab 420-fold lower than in serum in patients treated with trastuzumab prior to radiotherapy. [49] In addition, preclinical studies assessing tissue distribution of zirconium 89–labeled trastuzumab (^{89}Zr-trastuzumab) in animals bearing HER2-positive tumor xenografts showed minimal penetration into the brain.[50] Penetration of the tumor by mAbs and other agents may also be hindered by increased intratumoral interstitial pressure, which can both limit the uptake of the agent into the tumor and lead to nonuniform distribution of the agent within it,[51] or by the binding of mAbs to tumor antigens near the blood vessel egress site, thereby blocking access of therapeutic mAbs to tumor antigens deeper within the tumor—the so-called binding site barrier.[52,53]

Recently, however, a study using positron electron tomography imaging demonstrated CNS penetration by ^{89}Zr-trastuzumab in patients with MBC with an 18-fold higher uptake in brain tumors than in normal brain tissue (Fig. 3).[54] This increased penetration is likely because of a BBB that is compromised because of MBC (i.e., local or general perturbation). It is interesting to note that tumor- induced perturbation of the BBB would, in effect, aid targeted delivery of trastuzumab, as sites of BBB leakiness would be correlated with the presence of a tumor, at least at a first level of approximation. The increased penetration could also be explained by the effect of antigen-rich sites within the tumors (e.g., necrotic areas), which may serve as so-called antigen sinks for trastuzumab. [55] Another potential mechanism for transporting trastuzumab across the BBB is the Fc receptor for immunoglobulin G (FcRn), which is highly expressed on vessels in the brain.[56]

Radiotherapy may also affect the integrity of the BBB. Changes in BBB permeability have been reported after WBRT in preclinical and clinical evaluations.[57] The influence of WBRT on mAb uptake in the brain was examined in a pilot study in patients with HER2-positive breast cancer brain metastases. This study demonstrated increased trastuzumab uptake after

WBRT; the median serum CSF trastuzumab concentration ratios were 420:1 and 76:1 pre- and post-WBRT (Fig. 4).[49] Notably, a low pre-WBRT ratio was observed in two patients with concomitant meningeal carcinomatosis (ratio, 49:1). However, a case study in a patient with meningeal carcinomatosis reported serum trastuzumab levels 300-fold *greater* than CSF levels.[58]

Taken together, these data suggest that trastuzumab access to the brain may be markedly increased in patients with cancer because of the perturbations in the BBB caused by the cancer itself or by cancer therapy (e.g., WBRT).

Trastuzumab in the management of HER2-positive MBC

Mechanism of action

Trastuzumab is a humanized mAb directed against HER2, which is overexpressed on the surface of 20% to 25% of breast tumors.[59–61] The mechanism of the effect of trastuzumab on tumor cell growth and survival is not fully understood,[62] but it is thought to incorporate the inhibition of intracellular proliferative signal transduction, [63–65] the inhibition of HER2 extracellular domain shedding,[66] the activation of antibody-dependent cellular cytotoxicity,[67] and the inhibition of tumor-induced angiogenesis.[68,69] It is likely that the balance of the different effector functions of trastuzumab differs depending on the tumor phenotypes and microenvironments. For example, whether antibody-dependent cellular cytotoxicity occurs in the intact brain is unknown.

Clinical trials of trastuzumab in patients with MBC and CNS metastases

Trastuzumab-based therapy is firmly established as the standard of care for patients with HER2-positive breast cancer, owing to demonstrated survival benefits in large, randomized clinical trials in both EBC and MBC with survival end points.[37,38,70–72] Evidence obtained from clinical studies also suggests that trastuzumab- based therapy can significantly prolong survival in patients with HER2-positive brain metastases. Median OS in patients with HER2-positive breast cancer who received trastuzumab- based therapy following the diagnosis of brain metastasis ranged from 9.0 to approximately 26 months compared with median OS ranging from 2.0 months to approximately 9 months in patients who did not receive trastuzumab (Table 1).[42,73–82] However it must be noted that the available data derive from post hoc and/or retrospective analyses (see Table 1).

Multiple clinical studies have also reported prolonged OS in patients with HER2-positive disease (4.0–22.4 months) compared with those who had HER2-negative disease (3.4–9.4 months), which is largely attributable to the favorable outcomes observed in patients with HER2-positive breast cancer treated with trastuzumab after diagnosis of brain metastases.[42,76,77,79] Two of these studies reported median OS durations of 4.0 and 5.5 months in patients with HER2-positive breast cancer that was not treated with trastuzumab.[79,80]

In patients with invasive breast cancer who went on to develop brain metastases ($n = 598$), time to development of brain metastasis and survival were extended in patients with HER2-positive disease treated with trastuzumab compared with patients with trastuzumab-naive

HER2-positive disease and those who had HER2-negative disease.[42] Median time to CNS recurrence was 8.9 months in patients with HER2-negative disease and 13.1 and 2.1 months in patients with HER2-positive disease who had and had not received trastuzumab, respectively. The difference in median time to CNS recurrence between patients with trastuzumab-treated and trastuzumab-naive HER2-positive disease was statistically significant ($P = 0.0008$; see Fig. 1).

Further evidence of a benefit with trastuzumab after the development of CNS metastases emerged from a retrospective study in 78 patients with HER2-positive breast cancer brain metastases.[80] This study showed prolonged median survival in patients who had received trastuzumab after diagnosis of brain metastases compared with patients who received trastuzumab before brain metastasis diagnosis and patients who were trastuzumab-naive (13.6 vs 4.0 and 5.5 months, respectively; $P < 0.001$). Notably, median time to brain metastasis was more than doubled in patients who received trastuzumab before diagnosis (19 months) compared with patients in the other two groups (7.0 and 8.0 months in the other two groups, respectively).

Breast cancer leptomeningeal metastasis (LM) is comparatively rare, but it is associated with a particularly poor prognosis.[75] Promising activity has been observed in case reports with trastuzumab-based therapy in patients with LM. The combination of trastuzumab and capecitabine was effective in a case of MBC and lepto-meningeal/bone metastasis. Combination trastuzumab and capecitabine given as sixth-line treatment resulted in a clinically notable reduction of LM and tumor markers.[83] Further case reports also documented the efficacy of intrathecal (IT) trastuzumab in LM, when used either as a high-dose (20 mg weekly) single-agent[84] or in combination with chemotherapy, such as thiotepa[85] or methotrexate.[86]

Taken together, the results from these studies provide a substantial body of evidence to support the continued use of trastuzumab therapy in patients with HER2-positive breast cancer and CNS metastases. It is likely that at least some of the benefit afforded by trastuzumab in this setting is attributable to systemic disease control, but radiologically documented regression or prolonged stabilization of CNS metastases achieved in patients treated with trastuzumab-based therapy highlights the potential for a direct effect on CNS disease.[87,88] Trastuzumab is likely gaining access to the CNS in these patients via a compromised BBB.

Lapatinib in the management of HER2-positive MBC

Lapatinib is another HER2-targeted agent used in the treatment of breast cancer. Lapatinib differs from trastuzumab in that it is a small molecule reversible tyrosine kinase inhibitor that is designed to target both HER1 (epidermal growth factor receptor) and HER2. Because it is a small molecule (molecular weight <1 kDa), it could, theoretically, cross the BBB and access metastases in the CNS. A preclinical study by Smith and colleagues showed that ^{14}C-lapatinib is able to penetrate breast cancer brain metastases in immunocompromised mice.[89] In healthy animals, however, the ability of lapatinib to cross the BBB may be limited. A later preclinical study found that concentrations of lapatinib in the brains of these animals

were low, which may have been the result of the effect of efflux transporters in the BBB, such as PgP.[90]

In the clinical setting, there is little evidence to show that single- agent lapatinib is an effective treatment for patients with HER2-positive breast cancer brain metastases. In a multicenter phase II study (NCI-6969), 39 patients with HER2-positive breast cancer and metastases to the brain received single-agent lapatinib. [91] Because the primary end point of this study (four patients with a CNS response) was not achieved, a volumetric analysis of CNS lesions was carried out. Of the 34 patients assessed, three had a volumetric reduction of 30% and seven had reductions of 10–30%. The clinical significance of these results is, however, unknown.

In a larger study (EGF105084) of single-agent lapatinib in 237 patients with progressive CNS metastases after radiotherapy, CNS objective response (i.e., complete response or 50% reduction in the volumetric sum of all measurable CNS lesions) was the primary end point. The CNS response rate was 6% (15/237; all partial responses). [92] At disease progression, 50 patients received further treatment with lapatinib plus capecitabine. Ten of these patients (20%) had an objective CNS response (all partial responses). While these data are encouraging and suggest that lapatinib plus capecitabine may be active in this setting, the omission of a control arm makes the size of the effect difficult to interpret.

A control arm was included in the pivotal phase III trial of lapatinib, which evaluated the efficacy of lapatinib plus capecitabine compared with capecitabine alone.[93] An exploratory analysis of CNS involvement at first disease progression determined that the addition of lapatinib to capecitabine decreased the risk of CNS metastasis. In the combination treatment group, only four patients (2%) had developed CNS involvement at first progression compared with 13 patients (6%) in the single-agent capecitabine group. However, it is important to consider that the number of patients who participated in this analysis was small and that the statistical methodology employed to calculate the difference between the two treatment arms was not described.

Metro and colleagues conducted a retrospective analysis of data for patients who received lapatinib plus capecitabine for treatment of their brain metastases.[94] They selected patients who had previously received treatment with a taxane, an anthracycline, and trastuzumab, but who were also naive for lapatinib and capecitabine. Of the 22 patients available for response, seven had a partial response (32%) and six had stable disease (27.3%). The duration of response was 6 months, and the median progression-free survival was 5.6 months. Median OS was 27.9 months in the lapatinib-plus-capecitabine group ($n = 22$) compared with 16.7 months in patients who received trastuzumab-based treatment ($n = 23$) beyond brain progression ($P = 0.01$).

More recently, the LANDSCAPE phase II study was conducted to evaluate the use of lapatinib and capecitabine combination therapy to avoid or delay WBRT as first-line treatment for patients with HER2-positive breast cancer brain metastases.[95] In this study, an objective response was defined as a 50% volumetric reduction of CNS lesions. After a median follow-up of 10 months (range, 2.9–16.5 months), the objective response in the CNS

in 43 evaluable patients was an impressive 67% (95% confidence interval, 51–81). A recent prospective phase II study comparing lapatinib plus capecitabine with lapatinib plus topotecan in this patient population found a 38% (95% confidence interval, 14–68) CNS objective response rate (i.e., 50% volumetric reduction of CNS lesions) in the lapatinib-plus-capecitabine arm. No responses were seen in the lapatinib-plus-topotecan arm.[96]

The clinical utility of lapatinib continues to be studied in this setting. Currently, lapatinib is being evaluated in combination with temozolomide in a phase I study[97] and in the CEREBREL study,[98] which uses ^{11}C lapatinib to assess the penetration of this agent into the brains of patients with and without brain metastases.

Enhancing drug delivery to brain tumors

Intraventricular (IVent) administration of mAb therapy represents an opportunity for circumventing the BBB and delivering drugs targeted to leptomeningeal disease. A pilot study of IVent or IT rituximab in six patients with relapsed CNS B-cell lymphoma identified IVent rituximab as a promising strategy.[99] Meningeal tumor cells were completely cleared from the CSF of three patients following treatment, and complete remission of leptomeningeal involvement was reported in a fourth patient. A subsequent phase I study in 10 patients showed that IVent rituximab achieved ventricular concentrations that were similar to peak levels of rituximab in serum obtained following administration via intravenous injection. Furthermore, IVent rituximab demonstrated promising activity: meningeal responses in six patients, intraocular responses in two patients, and resolution of brain parenchymal lymphoma in one patient.[100]

Intracerebral drug delivery via impregnated polymer discs or bolus injection can be used to deliver high concentrations of drugs directly into brain tumors, but its reliance on physical diffusion limits its utility for delivery of mAbs. Alternatively, convection-enhanced delivery has the potential to distribute even large molecules consistently throughout the brain.[55,101–105] However, all of these techniques are invasive and have associated administration risks. Noninvasive strategies to penetrate the BBB remain a focus of research in brain disease.

Drug manipulation techniques, such as lipid encapsulation to exploit transcellular lipopholic pathways (Fig. 5), have been explored, but their use is limited for large molecules such as mAbs. The observed activity of therapeutic mAbs in association with disrupted BBB caused by WBRT or meningeal carcinomatosis has provided a sound rationale for the evaluation of strategies for deliberate perturbation of the BBB to augment mAb penetration in the CNS. Pharmacologic approaches to disrupting the BBB include the use of vasoactive and hyperosmotic agents (Fig. 5a). For example, the use of the phosphodiesterase inhibitor vardenafil resulted in a twofold increase in trastuzumab uptake in brain metastases in mouse models.[106]

Drugs can be coupled to transport vectors to assist in drug penetration; proteins such as cationized albumin and mAbs to the transferrin receptor undergo receptor-mediated transcytosis (Fig. 5b) and absorptive-mediated transport (Fig. 5c), respectively, through the

BBB. These strategies have been investigated as methods of improving penetration of the CNS by mAbs.

Physical approaches to BBB disruption have also been explored. One of the simplest techniques is to schedule radiotherapy and chemotherapy to increase uptake of cytotoxic and targeted agents. Another method that has been evaluated is the use of ultrasound radiation (Fig. 5d). In a study in mice, Kinoshita et al.[107] used MRI-guided focused ultrasound to disrupt the BBB and deliver trastuzumab directly to the CNS. Notably, there was a direct correlation between the amount of trastuzumab delivered and the extent to which the BBB opened. As a result, the amount of trastuzumab delivered to the target tissue could be estimated indirectly.

Conclusions

CNS metastasis affects up to 30% of patients with MBC and is associated with a poor prognosis and substantial morbidity. Current treatment strategies utilize surgery, SRS, WBRT, and chemotherapy in various combinations. Several risk factors have been identified for the development of breast cancer brain metastases, including HER2-positive tumor status. The standard of care for patients with HER2-positive breast cancer is treatment with the HER2-targeted mAb trastuzumab, which is used in combination with chemotherapy. There is a substantial body of clinical evidence that trastuzumab may extend survival in patients with breast cancer brain metastases; these data support the continuation of trastuzumab therapy in patients with breast cancer brain metastases. There are concerns about the usefulness of systemic trastuzumab in patients with breast cancer brain metastases, based on its theoretic inability to cross the BBB. There is evidence, however, that prior WBRT, or even the tumor itself, may compromise the integrity of the BBB, thereby allowing antibody penetration. Current and future research areas for improving the management of HER2-positive CNS metastases include direct delivery of trastuzumab through IVent or IT administration and optimized BBB disruption to achieve enhanced penetration of trastuzumab into the CNS.

Acknowledgments

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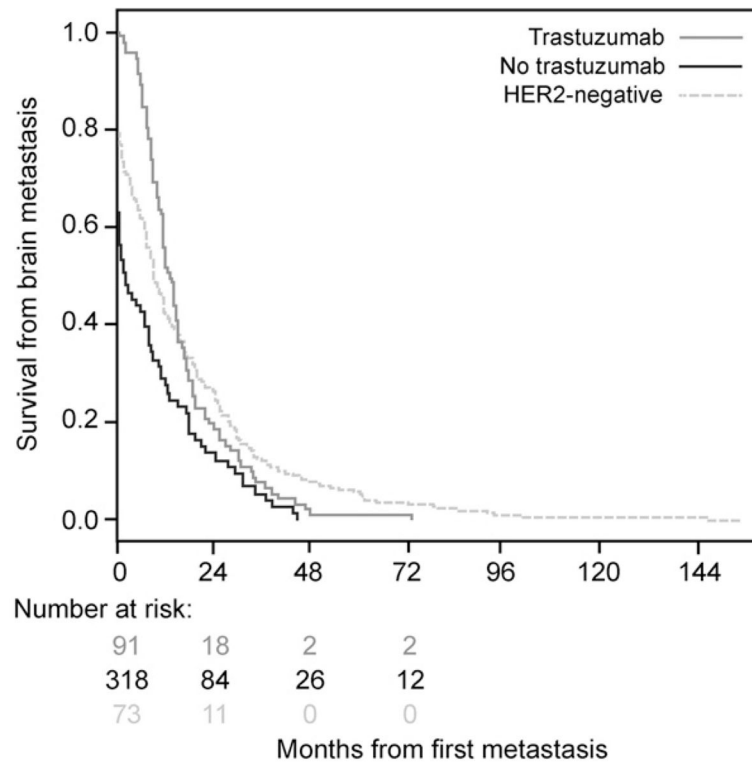
Fig. 1.
Time to central nervous system recurrence in patients with HER2-negative, or HER2-positive metastatic breast cancer who had and had not received treatment with trastuzumab. HER2 indicates human epidermal growth factor receptor 2. Reproduced with permission from Dawood et al.[42]
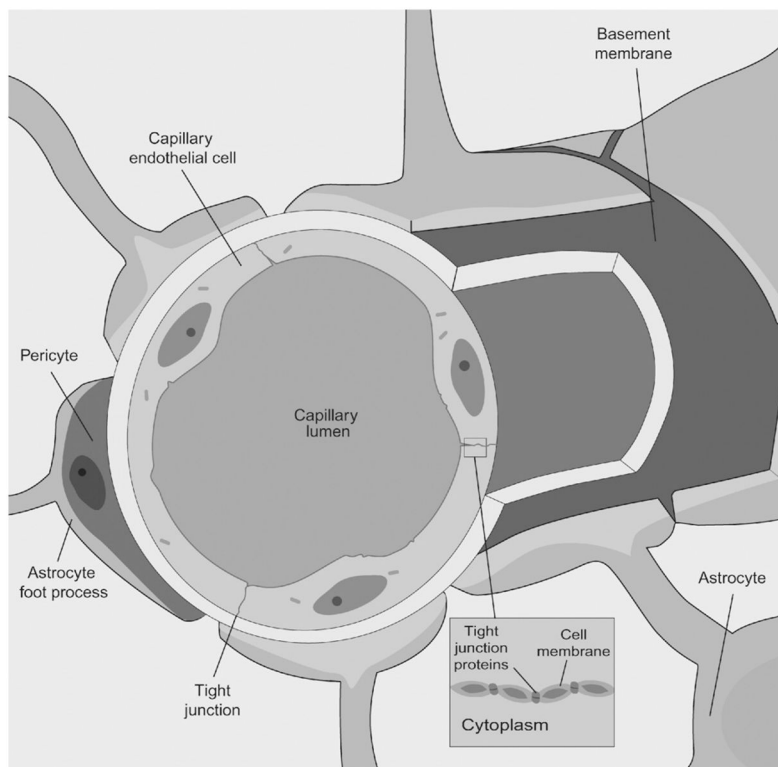
Fig. 2.
Structure of the blood–brain barrier (BBB). The cerebral capillaries are composed of endothelial cells that are sealed by tight junctions. The capillaries are in close contact with pericytes and are ensheathed by astrocyte foot processes and the basal lamina.[43] The passage of molecules across the BBB is tightly regulated; some hydrophilic molecules enter the brain via specific transporters and carrier-mediated endocytosis, and a limited number cross the barrier via diffusion through tight junctions.[44]
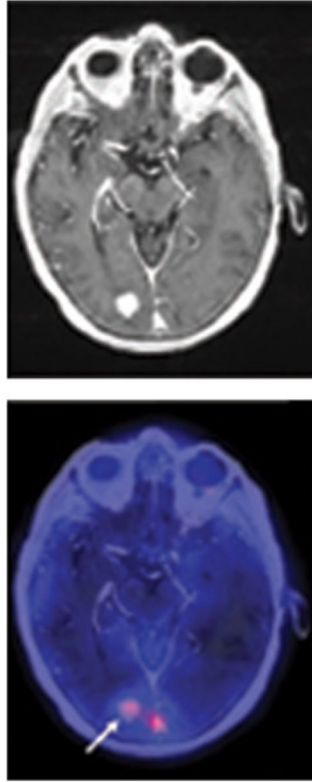
Fig. 3.
PET image showing penetration of the brain in a patient with HER2-positive metastatic breast cancer. Arrow indicates a HER2-positive brain lesion. HER2 indicates human epidermal growth factor receptor 2; PET, positron emission tomography; [89]Zr-trastuzumab, zirconium 89–labeled trastuzumab. Reproduced with permission from Dijkers et al.[54]
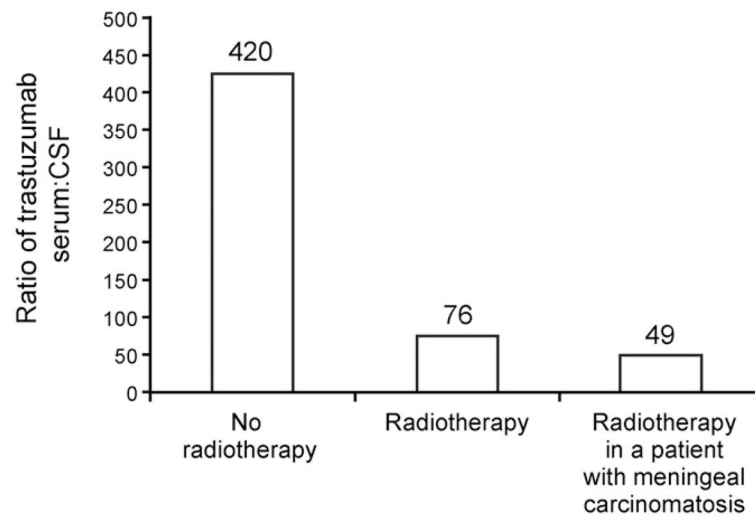
Fig. 4.
Concentrations of functional, reactive trastuzumab in serum and cerebrospinal fluid (CSF) of patients with metastatic breast cancer in relation to clinical parameters. Reproduced with permission from Stemmler.[49]
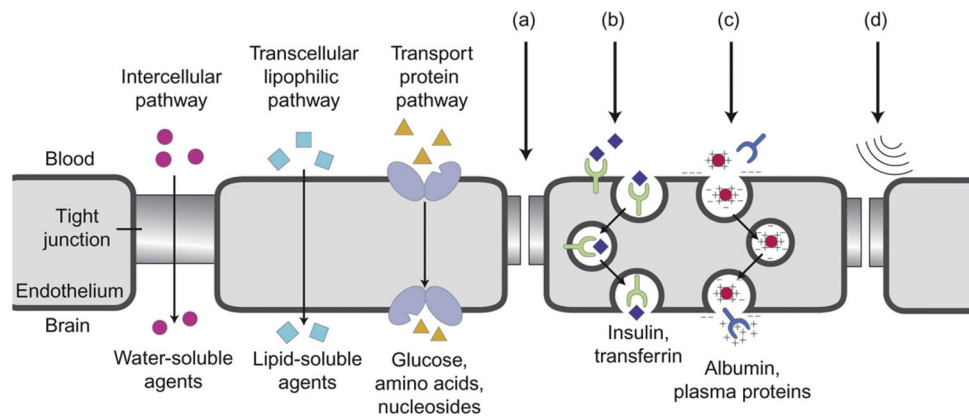
Fig. 5.
Approaches to enhance drug delivery across the blood–brain barrier (a) bradykinin analogs, (b) receptor-mediated endocytosis, (c) absorptive transcytosis, (d) ultrasound. Adapted with permission from Eichler et al.[45].

Table 1

Median survival from diagnosis of brain metastasis in patients who did/did not continue to receive trastuzumab-based treatment.[a].

Study/design	N	Median overall survival, months		P value
		Received trastuzumab after diagnosis of brain metastasis	No trastuzumab following diagnosis of brain metastasis	
Bartsch et al[73]/retrospective analysis	53	21 (range: 3–38)	9 (range: 1–14)	<0.001
Bartsch et al[74]/retrospective analysis	37	13 (95% CI, 8.9–17.2)	9 (95% CI, 0.0–20.7)	Not reported
Brufsky et al[75]/post hoc analysis of a large registry	377	17.5	3.7	<0.001
Church et al[76]/retrospective analysis	26	11.9	3.0	0.05
Dawood et al[42]/retrospective analysis	280	11.6	6.1	0.03
Kirsch et al[77]/retrospective analysis	47	~26	~9	<0.0001
Le Scodan et al[78]/retrospective analysis	52	19.5	5.6	<0.004
Nam et al[79]/retrospective analysis	56	12.8	4.0	0.0011
Park et al[80]/retrospective analysis	78	13.6 (95% CI, 9.0–18.2)	5.5 (95% CI, 0.0–13.6)	<0.001
Park et al[81]/retrospective analysis	77	14.9 (95% CI, 11.6–18.2)	4.0 (95% CI, 2.1–5.9)	0.0005
Witzel et al[82]/restrospective analysis	29	9.0 (95% CI, 7–11)	2.0 (95% CI, 0.7–3)	0.006

Abbreviations: CI, confidence interval.

[a]English language articles were identified for inclusion by searching PubMed [search terms: trastuzumab AND metastatic breast cancer AND (brain metastases OR central nervous system metastases] for articles published within the last 10 years [01012002 to 01012012] that reported overall survival in patients who had received trastuzumab after diagnosis of brain metastases and those who had not.