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Chronic Diseases and Translational Medicine 3 (2017) 21–32

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Perspective

Management of breast cancer brain metastases: Focus on human epidermal growth factor receptor 2-positive breast cancer

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Received 5 October 2016

Available online 8 March 2017

Abstract

After the introduction of trastuzumab, a monoclonal antibody that binds to human epidermal growth factor receptor 2 (HER2), the overall survival (OS) among patients with HER2-positive breast cancer has been substantially improved. However, among these patients, the incidence of brain metastases (BM) has been increasing and an increased proportion of them have died of intracranial progression, which makes HER2-positive breast cancer brain metastases (BCBM) a critical issue of concern. For local control of limited BM, stereotactic radiosurgery (SRS) and surgical resection are available modalities with different clinical indications. Postoperative or preoperative radiation is usually delivered in conjunction with surgical resection to boost local control. Adjuvant whole-brain radiotherapy (WBRT) should be deferred for limited BM because of its impairment of neurocognitive function while having no benefit for OS. Although WBRT is still the standard treatment for local control of diffuse BM, SRS is a promising treatment for diffuse BM as the technique continues to improve. Although large molecules have difficulty crossing the blood brain barrier, trastuzumab-containing regimens are critical for treating HER2-positive BCBM patients because they significantly prolong OS. Tyrosine kinase inhibitors are more capable of crossing into the brain and they have been shown to be beneficial for treating BM in HER2-positive patients, especially lapatinib combined with capecitabine. The antiangiogenic agent, bevacizumab, can be applied in the HER2-positive BCBM scenario as well. In this review, we also discuss several strategies for delivering drugs into the central nervous system and several microRNAs that have the potential to become biomarkers of BCBM.

Keywords: Breast cancer brain metastases; Human epidermal growth factor receptor 2-positive breast cancer; Local control; Targeted therapy; MicroRNA

Introduction

Breast cancer is the second-leading cause of central nervous system (CNS) metastases among solid malignancies.[1] The incidence of developing brain metastases (BM) has been reported to range from 10% to 16% among advanced breast cancer patients,[2] and autopsy studies indicate that this figure may underestimate the true incidence since another 10% of BM are

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

http://dx.doi.org/10.1016/j.cdtm.2017.01.004

asymptomatic and not diagnosed before death.[3] Patients with human epidermal growth factor receptor 2 (HER2)-positive cancer or triple negative breast cancer (TNBC) have a higher risk of developing BM than patients with luminal-like disease.[4−6] Several studies have shown that HER2-positivity is associated with a biological propensity to metastasize to the brain.[7] After the introduction of trastuzumab, which has significantly improved overall survival (OS) among patients with HER2-positive breast cancer, the incidence of BM among HER2-positive patients (ranging from 30% to 55%[5,8−12]) has been increasing.[10,13−15] Unlike BM in TNBC, which often develops with concurrent extracranial disease progression,[16] BM often occurs in a setting of stable extracranial control among HER2-positive patients.[17]

In the past, even after treatment by whole-brain radiotherapy (WBRT), the median survival of patients with breast cancer brain metastases (BCBM) was poor, ranging from 3 to 6 months.[18] Before the trastuzumab era, the OS was shorter among patients with HER2-positive brain metastases compared with those with HER2-negative disease, which was mainly attributed to the progression of systemic disease.[19] After the introduction of effective anti-HER2 therapy, survival after diagnosis of BM among HER2-positive patients has been significantly improved compared with that among patients with HER2-negative disease, mainly due to the improvement of extracranial disease control.[20,21] Several retrospective studies have reported that the median OS after diagnosis of BM is around 2 years for HER2-positive patients.[20−23] Meanwhile, with the OS significantly prolonged, the proportion of people dying of cerebral progression has been increasing. A retrospective study reported that up to 50% of HER2-positive patients died of cerebral progression,[10] which makes BM among HER2-positive patients a critical issue. To improve management, the American Society of Clinical Oncology (ASCO) published a guideline focusing on this issue in 2014.[24]

In this review, we will discuss treatments for HER2-positive BCBM, including local treatment and targeted therapy. In addition, several cancer biomarkers for BCBM will also be discussed.

Local control

Management of limited BM (1−4 BM)

Surgery

In order to achieve long-lasting control, surgical resection is a standard treatment for patients with a favorable prognosis and a solitary lesion, especially a large lesion (over 3−4 cm). There were several randomized control trials conducted to define the role of surgical resection in solitary BM, and they demonstrated a significant survival benefit for patients receiving surgical resection.[25−28] Surgical resection is also used for immediate mass effect relief in patients with limited BM (2−4 lesions) who have a large lesion causing neurologic symptoms; however, the effect of surgery on survival of these patients with limited BM is still unknown. Since there is a high recurrence rate after surgical resection,[29] postoperative radiation is usually recommended to improve local control, which will be discussed in the postoperative and preoperative radiation therapy section.

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is a radiation therapy technique using intersected beams to deliver a highly conformal and high dose of radiation to a target volume in order to produce an ablative effect with minimal damage to surrounding normal tissues. SRS is usually delivered in a single fraction, but it can also be delivered in multiple fractions [fractionated stereotactic radiotherapy (FSRT)]. For local control of BM, SRS can be used as a therapy alone, a boost after WBRT, or an adjuvant treatment preoperatively or postoperatively.[30]

There are different techniques available for stereotactic radiosurgery including Gamma Knife® (GK) and CyberKnife (CK). GK used to be the standard device for SRS. It is based on an invasive head frame system coupled with cobalt-60 sources and is mainly used for intracranial indications,[31,32] while CK is based on a linear accelerator system without head fixation and can be used for both intra- and extracranial lesions.[33] Because it is frameless and has a wider range of indications, CK has become increasingly popular over the last few decades and has been shown to not be inferior to GK in the accuracy of dose delivery.[34,35] In dosimetry, CK shows a more homogeneous dose distribution across the entire lesion,[36,37] while GK shows an inhomogeneous distribution with a higher dose in the center of the lesion[36,38] that may help to minimize local tumor recurrence.[39] However, a matched-pair analysis demonstrated that the obvious differences in treatment-related parameters between GK and CK had no effect on clinical outcomes after radiosurgery.[40]

Although both SRS and surgery can treat patients with limited BM, there is no prospective randomized trial comparing these two modalities. Actually, they are not competitive modalities in most cases, but are

prescribed for different clinical indications. The choice of modality usually depends on the size of the lesion, the surgical accessibility, symptoms, and the status of the patient. Surgery can alleviate the mass effect of large lesions immediately and has advantages in treating lesions adjacent to critical structures or lesions over 4 cm in size. SRS is an alternative treatment for inoperable patients with limited BM with lesions 4 cm or less. SRS has several advantages over surgery including being noninvasive, able to treat several lesions simultaneously, and it can treat surgically inaccessible lesions, such as lesions in a deep area.[41]

SRS combined with WBRT or SRS alone as primary treatment has been shown to have an excellent rate of local control for patients with limited BM.[42,43] Because of the decline of neurocognitive function and quality of life (QoL) associated with WBRT,[44,45] several trials were conducted to determine whether WBRT could be omitted after SRS for patients with limited BM. Most of them demonstrated that the addition of WBRT to SRS significantly increased local control, but had no beneficial effect on OS.[42,46] Based on these findings, the Choosing Wisely List published by the American Society for Radiation Oncology (ASTRO) in September 2014 recommended that adjuvant WBRT should not be routinely added to SRS for patients with limited BM.[47] However, this recommendation provoked a lot of debate. Several researchers thought that there were not enough patients involved in these randomized trials to demonstrate WBRT's effect on OS, since several trials consistently showed that adjuvant WBRT significantly improved intracranial control and reduced the rate of neurologic causes of death. They argued that more data about adjuvant WBRT should be collected to reevaluate this scenario.[48]

Postoperative and preoperative radiation therapy

Because of the high recurrence rate after surgical resection,[29,46] postoperative radiation is usually recommended as a boost for intracranial control. Adjuvant WBRT is the standard treatment in the postoperative setting.[49] Multiple studies have demonstrated that postoperative WBRT can significantly reduce the risk of local recurrence, distant brain recurrence, and neurologic causes of death, but has no benefit for OS.[29,46] Because of potential toxicity associated with WBRT, clinicians also use postoperative SRS to defer WBRT and to improve intracranial control. Because of the size limitation of SRS, FSRT has been used for large surgical cavities over 3 cm and has a similar control rate as SRS.[50] Several trials demonstrated that SRS/FSRT as a postoperative treatment alone provided acceptable local control,[50–54] and the addition of a 2 mm margin around the resection cavity showed an improved local control compared to the technique with no margin.[55]

A retrospective study demonstrated that compared with WBRT, SRS alone administered to the surgical cavity showed a similar local recurrence rate, a higher rate of leptomeningeal dissemination (LMD), and an inferior distant brain control.[56] Interestingly, a study reported that patients with breast cancer histology were at a higher risk of developing LMD (at 1 year, 24% *vs.* 9%) after postoperative SRS as compared with patients with non-breast cancer histology, but whether the rate of LMD is inherently higher with breast histology or the inclusion of WBRT could decrease this risk of LMD is unknown.[57] A prospective randomized trial (NCT01372774) conducted by the Alliance for Clinical Trials in Oncology (N107C) is ongoing to determine the role of WBRT versus SRS in the postoperative setting.

With a clear target volume definition, preoperative SRS may be a promising treatment to reduce LMD and radiation necrosis (RN) caused by postoperative SRS.[58] Despite limited supporting data, preoperative SRS has been increasingly used in recent years.[30] In a multi-institutional analysis with 180 patients receiving preoperative SRS or postoperative SRS, Patel et al[59] demonstrated a significantly lower rate of symptomatic RN (16.4% *vs.* 4.9%; $P < 0.010$) and LMD (16.6% *vs.* 3.2%; $P < 0.010$) in the preoperative SRS arm, but showed similar rates of local recurrence, distant brain recurrence, and OS between both arms.

Management of diffuse BM

Whole-brain radiation therapy

WBRT has been used for more than 50 years for treatment of BM. Although the development of SRS and concerns about its toxicity have decreased the use of WBRT in patients with limited BM, WBRT remains the standard treatment for patients with multiple BM. The typical dose and fractionation schedule for WBRT is 30 Gray (Gy) in 10 fractions. If patients have a short life expectancy, WBRT could also be delivered in 5 fractions with 20 Gy in total.[41] Compared with the typical schedule (30 Gy in 10 fractions daily), several studies demonstrated that altered dose-fractionation schedules of WBRT do not show any improvement in OS, neurologic function, or symptom control. Meanwhile, additive radiosensitizers failed to show a benefit for OS or brain response but may increase the toxicity to patients.[60]

Aside from a good local control, WBRT is also associated with acute toxicity and long-term side effects. Clinicians are concerned about the decline of neurocognitive function[44] and QoL[45] caused by WBRT, since patients with HER2-positive breast cancer brain metastases have a relatively long survival. In order to ameliorate the decline of neurocognitive function caused by WBRT, several new strategies have been developed, including using intensity-modulated radiotherapy (IMRT) and prescribing medication such as memantine or donepezil. Since the hippocampus is a reservoir of neurological stem cells and plays an important role in memory preservation, IMRT is used to deliver a conformal WBRT to reduce the dose to the bilateral hippocampi, which is called hippocampal-avoidance WBRT (HAWBRT). Gondi et al[61] have demonstrated that compared with historical controls, HAWBRT for BM can significantly mitigate radiation-induced neurocognitive and QoL decline. Memantine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, is a medication used to treat Alzheimer's disease. In a phase III trial, Brown et al[62] demonstrated that a delayed time to cognitive decline and better cognitive function were observed among patients in the WBRT plus memantine arm. In addition, a phase III randomized placebo-controlled clinical trial has demonstrated that a different dementia medication, donepezil, contributes to modest improvements in several cognitive functions, especially among patients with greater pretreatment impairment.[63]

Stereotactic radiosurgery

In order to avoid the toxicity associated with WBRT, SRS has also been used for treating multiple BM. In a prospective observational study, Yamamoto et al[64] demonstrated that SRS alone in patients with 5–10 brain metastases was non-inferior to that in patients with 2–4 brain metastases. In addition, Grandhi et al[65] reported a high rate of local control in patients with ≥10 BM receiving SRS alone, but the median OS was only 4 months. Since a standard GK system can only treat one lesion at a time, treating multiple BM with SRS takes several hours. However, using a single isocenter, several forms of SRS such as intensity-modulated stereotactic radiosurgery,[66] volumetric-modulated arc radiosurgery,[67–69] and tomotherapy can deliver doses to multiple brain metastases simultaneously, which as a consequence decreases the treatment time down to minutes. Several studies have demonstrated that these forms of SRS can produce comparable clinical outcomes with those of conventional SRS for treating multiple intracranial metastases but in a much shorter treatment time,[66–69] which makes SRS a promising treatment for patients with multiple BM.

Targeted therapy for HER2-positive BCBM

Unlike estrogen and progesterone status, expression of HER2 has been reported to be highly concordant between the primary and brain metastatic tumors,[70] which makes targeted therapy possible for treating patients with HER2-positive BCBM. Although the OS of patients with HER2-positive breast cancer has improved substantially in the trastuzumab era,[4–6] the incidence of BM among these patients has been increasing in recent years. One of main reasons for this is that the blood brain barrier (BBB) makes the CNS a perfect sanctuary for tumor cells. The BBB is a barrier that selectively chooses molecules to enter the CNS. It consists of endothelial cells, a basement membrane, and astrocyte foot processes. The permeability of the BBB decreases 100-fold as the molecular weight of the drug increases from 200 Da to 450 Da.[71] As a large molecule (145,531 Da), trastuzumab cannot penetrate the intact BBB, but multiple factors can disrupt the BBB, including metastatic tumors, surgery, and radiotherapy, which then allows limited amounts of large molecular agents to penetrate the CNS. A study has shown a change in the permeability of the BBB induced by WBRT, with a ratio of median trastuzumab level in the serum to cerebrospinal fluid 420:1 and 76:1 before and after WBRT, respectively.[72] Despite the limited permeability of BBB to large molecular agents, it is important for patients with HER2-positive BCBM to improve systemic control, which can significantly prolong OS. Small molecular tyrosine kinase inhibitors (TKIs) have an improved ability to cross the BBB and can block multiple receptors of the erb-b2 receptor tyrosine kinase 2 (ERBB2) family at the same time, and are promising treatments for HER2-positive BCBM. In this section, we are going to discuss targeted therapy for HER2-positive BCBM.

Trastuzumab-containing regimens

Trastuzumab alone

Despite the limited blood-brain permeability, several studies demonstrated that trastuzumab alone for the treatment of HER2-positive breast cancer results in a prolonged time to BM and longer survival time after the diagnosis of BM. For example, Park et al[21] demonstrated that patients receiving

trastuzumab had a significantly longer median time to BM (15 months *vs*. 10 months, $P = 0.035$) and median time to death (14.9 *vs*. 4.0 months, $P = 0.0005$) than patients who were not treated with trastuzumab. Similarly, Rostami et al[73] also demonstrated that the mean survival of patients with HER2-positive BCBM was prolonged when treated with trastuzumab (17.5 *vs*. 11 months).

Trastuzumab, pertuzumab, and taxane

Based on the landmark Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) trial, which has shown both significantly prolonged progression-free survival (PFS) and OS after adding pertuzumab to treatment with trastuzumab and docetaxel,[74] current guidelines recommend dual anti-HER2 blockade with pertuzumab and trastuzumab plus a taxane as the preferred frontline regimen for HER2-positive metastatic disease.[75] Although patients with BM were excluded from this trial, an exploratory analysis of patients who developed BM during the trial was performed. In this analysis, while the rate of BM as the first site of disease progression was similar between the 2 arms, a significantly delayed onset of BM was observed in the pertuzumab arm compared with the control arm. The median OS in the subset of patients who developed BM as the first site of disease progression tended to be longer in the pertuzumab arm (34.4 months) compared with the control arm (26.3 months). The comparison of OS between these 2 arms showed no significance on a log-rank test ($P = 0.1139$), but was significant on a Wilcoxon test ($P = 0.0449$).[76] Furthermore, in a case report, pertuzumab with trastuzumab plus docetaxel was effective in reducing the recurrence of BCBM in a patient who was heavily pretreated.[77] Based on these findings, further trials are warranted to investigate the effect of this regimen among patients with HER2-positive BCBM.

Trastuzumab emtansine

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate of trastuzumab and the anti-microtubule agent emtansine. Based on a phase III trial, which demonstrated that T-DM1 and T-DM1 with pertuzumab were non-inferior in PFS and possibly better tolerated for some patients compared with trastuzumab plus taxane, the NCCN guidelines (version 1.2016) included T-DM1 as one of the first-line options for the treatment of patients with HER2-positive metastatic breast cancer (MBC).[75] Furthermore, although the exploratory analysis of the EMILIA trial demonstrated a similar rate of CNS progression between the T-DM1 and the capecitabine-lapatinib arm, treatment with T-DM1 significantly improved the median OS in patients with CNS metastases (26.8 *vs*. 12.9 months, $P = 0.008$).[78]

Tyrosine kinase inhibitors

Small molecular tyrosine kinase inhibitors (TKIs) are promising anticancer agents for HER2-positive BCBM. TKIs have an improved ability as compared with antibodies to penetrate the BBB and can block multiple receptors of the ERBB2 family at the same time. Lapatinib plus capecitabine has been shown to benefit patients with HER2-positive BCBM. In addition, several other TKIs are involved in ongoing clinical trials to determine their usefulness for patients with HER2-positive BCBM.

Lapatinib

Lapatinib, which was approved by American Food and Drug Administration (FDA) in 2007, is a dual tyrosine kinase inhibitor of human epidermal growth factor receptor 1 (HER1) and HER2. As a small molecular and lipophilic agent, it can in theory penetrate the BBB. However, Taskar et al[79] demonstrated that the lapatinib concentration in the CNS was quite variable among patients with BM, and the average lapatinib concentration in brain lesions was only 10−20% of that in peripheral metastatic lesions. Only in 17% of brain lesions did the lapatinib concentrations approach those in peripheral metastatic lesions. A modest CNS objective response was observed in patients receiving lapatinib as a monotherapy in a multicenter phase II study. Although the rate of CNS objective response was low, an association was observed between volumetric reduction and improvement in PFS and neurologic signs and symptoms.[80] However, when lapatinib was administrated with capecitabine, the response rate in the brain increased to 20% and the rate of patients with a $\geq$20% volumetric reduction increased to 40%. In the LANDSCAPE trial, Bachelot et al[81] demonstrated that among 44 previously untreated patients, an objective CNS response was observed in 29 patients (65.9%). This study also showed that treatment with lapatinib plus capecitabine at the time of diagnosis of BM delayed WBRT. The median time to WBRT was 8.3 months in this study, clinically relevant for a population with a short OS.[81] According to the ASCO practice guideline on management of patients with advanced HER2-positive breast cancer and BM, if patients have asymptomatic, low-volume BM and have not received

radiation therapy, upfront therapy with lapatinib and capecitabine is an option, although radiation therapy in this setting is still the primary option.[24]

Afatinib

Afatinib is an orally available, covalent, and irreversible inhibitor of all ERBB family members.[82] In a phase II study, clinical activity was observed among trastuzumab-refractory patients receiving afatinib. In addition, Hoffknecht et al[83] demonstrated that afatinib appeared to penetrate into the CNS with concentrations high enough to have a clinical effect on non-small cell lung cancer patients with CNS metastases. However, Cortés et al[84] showed that afatinib alone or afatinib plus vinorelbine did not result in better outcomes in patients with HER2-positive BCBM compared with the investigator's choice of treatment.

Neratinib

Neratinib is an orally available, covalent, and irreversible inhibitor of HER1, HER2, and human epidermal growth factor receptor 4 (HER4). As a monotherapy, neratinib has been demonstrated to be an effective agent for either trastuzumab-naïve or heavily pretreated patients with HER2-positive breast cancer. In addition, compared with standard therapy alone, adding neratinib to standard therapy increases the rate of a pathological complete response among patients with HER2-positive, hormone receptor-negative, breast cancer.[85] Neratinib plus capecitabine has shown remarkable systemic activity in patients with metastatic HER2-positive breast cancer in a phase I/II trial.[86] Surprisingly, compared with the trastuzumab-paclitaxel arm, a lower incidence of CNS recurrence and prolonged time to BM were observed in the neratinib-paclitaxel arm in the NEFERT-T trial,[87] which showed neratinib could be a promising agent for treating patients with HER2-positive BCBM. However, recently, a phase II trial demonstrated that neratinib alone resulted in a low CNS objective response rate. Despite the promising effect as monotherapy, the effect of neratinib combined with other agents for patients with HER2-positive BCBM is still unknown.

Trastuzumab vs. lapatinib

There were several studies that compared trastuzumab with lapatinib in patients with HER2-positive BCBM. Yap et al[88] demonstrated that the OS after BM in patients with HER2-positive BCBM treated with lapatinib alone and trastuzumab alone were 21.4 months and 10.5 months, respectively; the best survival benefit (25.9 months) was observed in patients treated with both trastuzumab and lapatinib. Similarly, Kaplan et al[89] also demonstrated that median OS in patients treated with lapatinib plus capecitabine was significantly increased compared with that in patients treated with trastuzumab-based therapy (19.1 *vs*. 12 months; $P = 0.039$). Recently, the CEREBEL trial showed the rates of CNS metastases as first site of relapse were similar in the lapatinib–capecitabine arm and trastuzumab–capecitabine arm (3% *vs*. 5%, $P = 0.360$) but they were both far lower than the expected rates of 12% and 20%, respectively. In addition, the overall rates of CNS progression at any time in both arms (7% *vs*. 6%; $P = 0.8646$) were lower than anticipated as well. Despite the low rates, this trial was inconclusive as to the prophylactic effect of both regimens.[90]

Bevacizumab

Bevacizumab is a monoclonal antibody binding to the ligand of vascular endothelial growth factor (VEGF) and the FDA has approved bevacizumab plus paclitaxel as a first-line therapy in patients with MBC.[91] Several studies have reported that there is a significant positive correlation between VEGF and HER2 expression, suggesting bevacizumab may be useful for treating HER2-positive breast cancer.[92] Despite its large molecular weight, bevacizumab has shown benefits for patients with some primary brain tumors such as glioblastoma multiforme, which gives researchers insight into treating BM.[93] In the past, patients with BM had been excluded from bevacizumab trials since a hepatocellular carcinoma patient with undiagnosed BM suffered a fatal cerebral hemorrhage during a bevacizumab trial in 1997.[94] However, a retrospective exploratory analysis demonstrated that the risk of developing cerebral hemorrhage among patients with CNS metastases was independent of bevacizumab therapy.[95] In a case series of 3 patients with progressive HER2-positive BCBM pretreated by WBRT, the administration of bevacizumab plus anti-HER2 increased the OS of these 3 patients.[96] In a phase II study, bevacizumab followed by etoposide and cisplatin (BEEP regimen), appeared highly effective in BCBM patients (not HER2-positive specific) who were refractory to WBRT. Surprisingly, the clinical efficacy of the BEEP regimen for HER2-positive patients (23 of 35) in this study was higher than that observed in clinical trials in which patients received lapatinib and capecitabine after WBRT.[97] However, the analysis of the AVEREL trial (a phase III trial for HER2-positive MBC)

showed the reduction in the rate of BM was just a trend in the bevacizumab arm, failing to reach statistical significance.[98]

Other strategies to deliver drugs to the CNS

In order to penetrate the BBB, researchers have developed several strategies to deliver drugs with a higher concentration to the brain, such as delivering them mediated with radiation or ultrasound, or with the help of nanotechnology.

Focused ultrasound plus microbubbles

Previous studies have shown that focused ultrasound (FUS) plus microbubbles could temporarily disrupt the tight junctions of the BBB, allowing drugs to penetrate.[99,100] Park et al[101] demonstrated for the first time that the combination of trastuzumab and FUS had an anticancer activity for HER2-positive breast tumor inoculated into rats' brains. During this experiment, after 6 weekly trastuzumab treatments mediated with focused ultrasound, the mean tumor volume was significantly reduced and the survival was significantly prolonged without sequelae. Furthermore, a recent study has also shown a delayed progression of brain metastases from HER2-positive breast cancer in some of the rats receiving treatment with trastuzumab and pertuzumab mediated with FUS.[102] These findings show the therapeutic potential of this noninvasive technique for targeted drug delivery to the brain.

Nanotechnology

Nanoparticles can conjugate with many anticancer agents and have been successfully used as vehicles to deliver therapeutic agents across the BBB.[103] Patil et al[104] demonstrated that compared with mice receiving phosphate buffered saline, a significantly prolonged survival was observed in mice with HER2-positive BCBM that were treated with targeted nanodrugs. In addition, Hamilton et al[105] also showed that nanoparticles coated with a tumor-penetrating peptide (iRGD) may be a promising treatment for prevention of BM. Several clinical trials are ongoing for nanotherapeutic drugs such as MM-302 (NCT02735798) in order to determine their effect on patients with BCBM.

Biomarker for BCBM

Although much progress has been made in recent years, BCBM still seems incurable. A cancer biomarker would represent a significant step towards preventing, delaying, and eliminating brain metastases. microRNAs (miRNAs) are a complex network of noncoding RNA molecules that have been demonstrated to play an important role in regulating tumor metastases.[106] Since a miRNA test is a stable, noninvasive, and highly sensitive approach to reflect tumors inside the body, miRNAs are promising prognostic and diagnostic markers for BM.[107] In this section, we will discuss some miRNAs associated with BCBM (Table 1).

Table 1
Several miRNAs associated with brain metastases from breast cancer.

miRNA	Mechanism of action	Expression in brain metastases
miR-7[108]	Modulate *KLF4* gene expression	Down-regulated
miR-146a[109]	Up-regulate B-catenin and down-regulate hnRNPC	Down-regulated
miR-509[109]	Modulate the RhoC-TNF-α network	Down-regulated
miR-19a[110]	Down-regulate tissue factor expression by binding 3′-UTR of the tissue factor transcript[111]	Down-regulated
miR-29c[110]	Induce apoptosis by reducing MCL-1[112]	Down-regulated
miR-1258[113]	Inhibit the expression and activity of heparanase in BCBM cells	Down-regulated
miR-122[109]	Suppress glucose uptake by niche cells	Up-regulated
miR-200[114]	Prevent TGF beta-induced EMT by regulating E-cadherin transcriptional repressors *ZEB1* and *ZEB2*[115]	Up-regulated
miR-210[50,110]	Promote cancer proliferation by targeting PTP1b and HIF-1α[116]	Up-regulated

miRNAs: microRNAs; *KLF4*: Kruppel-like factor 4; hnRNPC: heterogeneous nuclear ribonucleoproteins C1/C2; RhoC: ras homolog gene family, member C; TNF-α: tumor necrosis factor-α; 3′-UTR: 3′-untranslated region; MCL-1: myeloid cell leukemia-1; BCBM: breast cancer brain metastases; TGF: transforming growth factor; EMT: epithelial to mesenchymal transition; *ZEB1*: zinc finger E-box binding homeobox 1; *ZEB2*: zinc finger E-box binding homeobox 2; PTP1b: protein tyrosine phosphatase-1b; HIF-1α: hypoxia-inducible factor-1α.

There are several miRNAs that are involved in the mechanism of BM from patients with breast cancer and have the potential to serve as signatures to predict it. miRNAs such as miR-181 and miR-122 are able to facilitate brain metastasis of breast cancer.[117,118] For example, Fong et al[118] demonstrated that miR-122 was able to suppress glucose uptake in distant organs, including the brain and lungs, through downregulating the glycolytic enzyme pyruvate kinase, and thus increasing the incidence of metastasis. In contrast, several miRNAs including miR-7, miR-146a, and miR-509 can inhibit BM of breast cancer.[108,109,119] For example, Okuda et al[108] demonstrated that kruppel-like factor 4 (*KLF4*) and miR-7 were dysregulated in brain metastatic tumors. MiR-146a is absent from brain metastatic tumors and can suppress the migratory and invasive potential of breast cancer cells by upregulating β-catenin and down-regulating heterogeneous nuclear ribonucleoproteins C1/C2 (hnRNPC).[109]

Conclusions

After the introduction of effective anti-HER2 treatment, patients with HER2-positive BCBM have experienced a significantly prolonged survival mainly because of better extracranial control. However, the incidence of BM among HER2-positive breast cancer patients has been increasing and an increased proportion of patients with HER2-positive breast cancer have died of intracranial progression in recent years, which makes BM from HER2-positive breast cancer an important issue of concern. For local treatment, QoL and local control should both be taken into account. Adjuvant WBRT should be delayed in treating limited BM because of its impairment of neurocognitive function while having no benefit for OS. With advances in technology, SRS has been shown to not only be an increasingly better treatment for limited BM, but also a promising treatment for diffuse brain metastases. Despite the limited penetrability of large molecular agents, it is critical for patients with HER2-positive BCBM to receive targeted treatment, which can significantly prolong OS. With improved BBB penetrability, TKIs have been shown to be beneficial for patients with HER2-positive BCBM, especially lapatinib combined with capecitabine. While several new drugs have been recently approved and demonstrated better extracranial control, new strategies and more drugs with better BBB permeability need to be developed and confirmed in future studies for better intracranial control. Furthermore, several miRNAs have been found to be involved in the mechanism of BM developing from breast cancer, showing clinical potential as preventive, diagnostic, and prognostic biomarkers for BCBM.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (No. 81672634).

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Edited by Pei-Fang Wei