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Breast cancer brain metastases: a review of the literature and a current multidisciplinary management guideline

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Abstract Breast cancer represents the second most frequent etiology of brain metastasis (BM). It is estimated that 10–30 % of patients with breast cancer are diagnosed with BM. Breast cancer BM are increasing due to the aging population, detection of subclinical disease, and better control of systemic disease. BM is a major cause of morbidity and mortality affecting neurocognition, speech, coordination, behavior, and quality of life. The therapy of BM remains controversial regarding use and timing of surgical resection, application of whole-brain radiotherapy, stereotactic radiosurgery and systemic drugs in patients with particular tumor subtypes. Despite numerous trials, the range of interpretation of these has resulted in differing treatment perspectives. This paper is a review of the state of the art and a multidisciplinary guideline on strategies to improve the therapeutic index in this situation.

Introduction

Breast cancer represents the second most common etiology of brain metastases (BM) and it is estimated that 10–30 % of patients with breast cancer are diagnosed with BM [1].

The incidence of BM has been increasing, thought to be due to the aging population, increased detection of subclinical disease and better control of systemic disease.

Central nervous system (CNS) metastases are a major cause of morbidity and mortality, affecting survival, neurocognition, speech, coordination, behavior, and quality of life. CNS metastases include brain, spinal cord, leptomeninges and eyes metastases. We believe that a correct description of the incidence, prognosis, diagnosis and

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therapeutic approach of leptomeningeal metastasis requires another whole article, therefore not be treated in this paper.

The BM process is complex, requiring invasion from the primary tumor into surrounding tissue, extravasation into the circulatory system and colonization and growth at a distant site [1, 2]. Tumor cells may have or may acquire the ability to preferentially colonize specific organ sites. Moreover, the brain may represent a preferential site of metastasis as many of the currently available therapies are unable to cross the blood–brain barrier (BBB), even if this barrier is disrupted by tumor invasion.

It is now recognized that breast cancer is composed of several subtypes. A further increase in incidence of BM is seen in patients with estrogen receptor (ER) negative as well as HER2 positive breast cancers. With the advent of better systemic therapies, BM is emerging as an increasing clinical problem. In a retrospective series of metastatic breast carcinoma (MBC) patients who died, among the treated with trastuzumab, 52 % seemed to succumb from CNS progression, in the face of stable or responsive non-CNS disease [3].

Relapse in the CNS represents a barrier to cure patients with breast cancer. However, not all patients with BM have an equally poor prognosis. Conventional treatment has been whole-brain radiotherapy (WBRT), which can improve symptoms but potentially results in neurocognitive deficits. In addition, responses are often not durable. Historically, the lack of durability was not a problem for most patients because BM occurred late in the course of illness, and progression in non-CNS sites was the dominant source of morbidity and mortality. Thus, the development of novel approaches to the treatment of CNS metastases has not previously been considered of high priority. Nevertheless, as systemic therapies improve, there is concern that the incidence of BM will increase, and that control of CNS disease will become a more vital component of overall disease control and quality of life.

Topics covered in this review include:

- Incidence by tumor subtype.
- Mechanistic insights into the pathogenesis and recent advances in defining the molecular underpinnings of brain tropism.
- Diagnosis and prevention.
- Prognosis.
- Local treatments.
- Systemic anticancer treatments by tumor subtypes.
- Supportive care.
- Summary and multidisciplinary management guidelines

Incidence

The risk of developing BM varied according to stage at initial diagnosis. Only 2.5 % of patients who initially presented with localized disease ultimately developed CNS disease, whereas 7.6 % of patients diagnosed with regional disease, and 13.4 % of patients presenting with stage IV disease were eventually found to have CNS involvement [4–7]. BM may be the first manifestation of cancer (5–10 %), may present synchronously with both systemic and intracranial cancer (5–10 %) or, more commonly, present metachronously and with known systemic cancer (>80 % of all patients). Single BM is seen in 20–30 % of all patients and a similar percentage of patients have two or three BM, so-called oligometastatic BM. A third or more of patients have four or more BM, so-called polymetastatic BM [5].

Several analyses support young age and a negative ER as the main risk factors for the development of BM in breast cancer patients. [7–9]. In a large study involving 3,726 patients with early-stage breast cancer, who were followed for 15 years, patients with HER2-enriched breast cancer had the highest incidence of BM (14.7 %) compared with 2.2, 4.7, 10.9 and 7.2 % for patients diagnosed with luminal-A, luminal-B, triple-negative basal-like and triple-negative non basal breast cancer, respectively [10]. Duchnowska et al. studied the correlation between quantitative HER2 protein expression ratio by central laboratory fluorescence in situ hybridization (FISH) and risk for BM in 142 consecutive patients who have administered trastuzumab-based therapy for HER2 MBC. Their data revealed a strong relationship between quantitative HER2 protein expression level and the risk for brain relapse [11].

Because most CNS metastases are diagnosed in response to clinical symptoms rather than by routine staging, the total incidence of BM may be underestimated. Studies investigating MBC patients reported alarming rates of BM among patients treated with trastuzumab-based regimens, in the range of 14.8–48 % [3, 11–14]. The CEREBEL study, a trial designed to answer the question of wheter lapatinib plus capecitabine (LC) were superior to trastuzumab plus capecitabine (TC) in prevention of MB in MBC patients after trastuzumab failure, showed asymptomatic BM in 120 of 605 (19.8 %) patients screened [15].

Early detection of asymptomatic BM has not yet shown an improvement in overall survival (OS) but produces a three-fold decrease in cerebral deaths following administration of WBRT [16]. Although this is a very controversial issue, it is arguably that performing a cranial MRI study in asymptomatic HER2-positive MBC patients in progression to trastuzumab could be justified because the information obtained by cranial MRI can change the type of local or systemic treatment with the intention of avoiding neurological complications.

Mechanistic insights into the pathogenesis and recent advances in defining the molecular underpinnings of brain tropism

The wealth of information that can be gained by cross-subtype comparison at the clinical and basic science levels reflects the heterogeneity of breast carcinomas to BM progression. The large numbers of genes differentially expressed between the five molecular subtypes of breast cancer confirm that the underline biology of the subtypes is different [16]. The ability to predict metastatic potential could be of great clinical importance, Some authors analyzed multiple primary tumors and metastasis pairs and determined that >90 % of gene expression signatures were found to be similarly expressed between matched pairs of tumors and metastases. Therefore, primary tumors may be a good predictor of metastatic propensity. BM occurred most frequently in non-luminal samples, liver relapse was associated with HER2-enriched tumors, and lung relapse occurred often within the claudin-low and basal-like subtypes [17, 18]. A gene expression analysis of laser-captured epithelial cells carried out from resected human BM of breast cancer compared with unlinked primary breast tumors found several differentially expressed genes, including phosphatase, glycosylphosphatidylinositol-anchoring proteins, and those regulating extracellular matrix and cell adhesion. Cyclooxygenase (COX) 2, epidermal growth factor receptor (EGFR) ligand HBEGF and ST6GALNACS, a sialyltransferase, have been identified that specifically mediates BM development [19, 20]. An accurate classification of BM proteins by mapping organ-specific BM gene expression signatures found 37 proteins differentially expressed between primary breast tumors with BM and primary breast tumors without BM. Among them GRP94, FN14, and inhibin were the best combination to discriminate between brain and non-BM (ROC AUC 0.85, 95 % CI 0.73–0.96 for the combination of the three proteins) [21]. These markers substantially improve the prediction of BM compared with HER2 alone (ROC AUC 0.76, 95 % CI 0.60–0.93). Finding a genetic signature that shows an increased risk of BM would be useful for more intense monitoring plan to early diagnoses or in the design of BM preventive therapies.

The brain is a site which places different demands on the invading tumor cells, which are compelled to establish glial interactions to colonize it [22]. Moreover, a essential step of metastasis formation is at the vascular branch points, where the persistent close contact between metastatic cells to microvessels induces a perivascular growth by vessel cooption [23]. Within this framework, activated astrocytes surround and infiltrate BM. Being the most active host cell population, they immediately localize individual invading metastatic cells and continually associates with growing metastatic lesions [24]. Functional characterization of genes/proteins differentially expressed in the BM need to be investigated with a focus on determining which gene or set of genes may be critical for establishing growth in the brain. This will provide the identification of novel molecular targets for prevention and treatment.

Diagnosis and prevention

While a cranial CT-scan is able to detect the majority of CNS metastases, sensitivity and specificity is markedly greater in gadolinium enhanced magnetic resonance imaging (MRI) [25].

A precise determination of the extent of disease is clearly essential for choice the appropriate therapeutic approach. A single BM must be differentiated from multiples BM. Moreover, a solitary lesion is defined by the absence of any extracranial tumor and single BM means that can there are other metastases or primary tumor outside CNS.

In such cases, primary CNS tumors and CNS infection must be differentiated from a solitary metastasis. Ruling out these diagnoses often requires a biopsy. In a randomized study, the initial diagnosis of a single BM could not be maintained in 11 % of the subjects [26]. BM are initiated mainly at the border between the gray and white matter. The majority are distributed in the cerebral hemispheres (80 %), followed by the cerebellum (15 %) and brain stem (5 %).

BM may be either symptomatic or asymptomatic. Early diagnosis of CNS involvement may be crucial for the patient because neurological symptoms, once developed, do not often resolve completely, even in patients responding to treatment. Therefore, quality of life could be maintained for longer in patients who are diagnosed timely [27].

Patients are diagnosed when BM, containing millions of tumor cells, are sufficiently large to be observed with imaging. The elimination of occult micrometastases serves as the rationale behind giving WBRT. However, prophylactic WBRT is not free of long-term side effects. Also whether all micrometastasis progressively grow, or alternatively, some enter periods of tumor dormancy, remains a relevant issue. Certain cancers, such as those of the breast, recur years after the primary diagnosis in some patients, suggesting that the tumor cells may lie dormant in a distant location for long periods of time [28]. Prophylactic WBRT therefore is not indicated outside clinical trials.

Given that a high proportion of HER2-overexpressing breast cancer patients will develop symptomatic BM, it is critical to discuss whether or not those patients should be followed with regular MRI scans for detected asymptomatic BM. In our opinion, if a therapeutic approach depends

on a precise determination of the extent of disease and asymptomatic BM is present in 20–30 % of patients [15], MRI scan could be justified [29, 30]. And for this reason, we believe that in case of relapse HER2postive breast cancer, MRI is indicated as extension study.

The CEREBEL study was designed to demonstrate that the combination of LC was able to reduce the incidence of BM compared to TC in patients with HER2-positive MBC [31]. After pre-specified interim analysis including 475 patients, the incidence of BM as first relapse was 3 % for LC vs 4 % for TC (OR 95 % CI 0.75 (0.25, 2.20). The median progression free survival (PFS) was 6.6 and 8.0 months in LC and TC arms (HR 1.3; 95 % CI 1.0, 1.7) and median OS was 22.4 and 27.3 months (HR 1.58; 95 % CI 1.07, 2.32). For these results the study was closed early.

Prognosis

Historically, the OS of patients with breast cancer metastatic to brain has been poor, ranging from 3 to 6 months [32]. Less than 20 % of patients survived >1 year. The appropriate management of patients with BM from breast cancer requires an assessment of independent prognostic factors in order to maximize survival and neurologic function whilst avoiding unnecessary treatments. These important variables include: performance status, commonly Karnofsky performance status score (KPS), number of BM, tumor histology, pathological grading, hormone receptor status, systemic tumor activity (controlled vs uncontrolled) and age less than 65 years. Of these, the KPS score has consistently been shown to be the major determinant of survival in most studies.

On the other hand survival in MBC patients with BM greatly depends on adequate therapy of both BM and extracranial disease. In untreated patients, survival may be as short as 1–2 months. After WBRT, survival may increase up to 3–6 months. Patients with solitary BM have a more favorable course of disease, and a median survival time of 14–25 months may be reached. Patients who received systemic hormone therapy or chemotherapy after local therapy of BM had longer survival duration (7.8 months) than those who did not (3.6 months) [33].

The Radiation Therapy Oncology Group (RTOG) established 3 prognostic categories using recursive partitioning analysis (RPA) of their database [34] (see Table 1). Although the distinction of single vs multiple BM did not retain significance in the original RPA model, it may hold additional prognostic value within classes 1 and 2. OS for patients with a single BM is 13.5 months for RPA class 1 and 6 months for RPA class 2 [35].

For this reason Sperduto et al. [36], using the updated RTOG data base, recently suggested a new prognostic

Table 1 Median survival duration according to RPA class for patient treated with WBRT

RPA class	Clinical characteristics	All tumors BM MS in m [32]	Breast BM MS in m [31]
1	KPS ≥70 and age <65 and controlled primary tumor and no extra cranial metastases	7.1	15
2	KPS ≥70 and age ≥65 or uncontrolled primary tumor or extra cranial metastases	4.2	11
3	KPS <70	2.3	3

MS median survival, *m* months, *KPS* Karnofsky performance status, *BM* brain metastases, *WBRT* whole-brain radiotherapy

scoring system, named Graded Prognostic Assessment (GPA) index. The GPA partitioned patients with BM into four categories ranging in median OS from 2.6 to 11 months (see Table 2). This score has been validated in subsequent studies [37]. Most recently, the GPA has been applied to patients with specific tumor subtypes to develop a diagnosis-specific GPA, which is superior for predicting prognosis [38].

Several groups have published retrospective studies describing improved survival from time of BM diagnosis in patients with HER2-positive, compared with HER2-negative breast cancers. Among patients treated at the Massachusetts General Hospital from 1998 to 2003, the median survival was also significantly longer in HER2-positive patients (22.4 vs 9.4 months; $p = 0.0002$) [39]. In the experience of Niwinska et al. [33] OS was different depending on biological subtypes. Triple negative breast cancer patients had the worst (4 months) and luminal had the best (14 months). In the study of MD Anderson Cancer Center, patients with triple negative tumors showed poor survival [40].

Local treatment

Three local treatments are basically used for BM, namely surgical resection (SR) stereotactic radiotherapy (SRT) and whole brain WBRT. In spite of the long time that all these techniques have been widely available, several questions concerning optimal management remain unanswered in the literature.

The efficacy of SR of BM was demonstrated by Patchell et al. [41]. They randomly assigned 48 patients with a single BM, only three of whom had breast cancer, to either SR followed by WBRT or needle biopsy and WBRT. Brain recurrence (BR) was less frequent in the surgical group than in the radiation alone group (20 vs 52 %; $p < 0.02$). The

Table 2 Graded Prognostic Assessment (GPA) index: (A) GPA score B, (B) Median survival for GPA index brain metastases from breast cancer patients according to GPA index

	Score			
(A)				
	0	0.5	1	
Age	>60	50–59	<50	
KPS	<70	70–80	90–100	
N. CNS metastases	>3	2–3	1	
Extracranial metas.	Present	–	None	
(B)				
GPA	0–1	1.5–2	2.5–3	3.5–4
OS in months All tumors [36]	3.1	5.4	9.6	16.7
OS in months Breast cancer [38]	3.4	7.7	15.1	25.3

CNS central nervous system, *KPS* Karnofsky performance status, *OS* overall survival

median OS was significantly longer in the surgical group than in the radiation group (40 vs 15 weeks; $p < 0.01$), and patients treated with surgery remained functionally independent longer (median of 38 vs 8 weeks; $p < 0.005$).

Several retrospective studies have compared SR + WBRT with SRT + WBRT. All of them reported no significant differences on OS or longer time to BR except for one, that showed an improvement for SR, although probably there may have been a selection bias, since SRT patients were poor candidates for surgery [42]. In addition, patients may undergo SR of a lesion before WBRT, or WBRT may be used in combination with SRT [43].

In the last years, however, some changes of the state of the art in the radiation treatment for BM have been identified. Results of randomized trials showed that BR was high if adjuvant WBRT was not delivered after local treatment [27]. However, controversy has appeared concerning the use of WBRT after SR or SRT of brain oligometastasis. Several randomized trials have been unable to demonstrate an OS improvement [43–45]. The recent EORTC trial has shown that BR was significantly more frequent in the observational arm (78 %) than in the WBRT arm (48 %) [45]. Although, neurocognitive outcomes [46] and quality of life [47] were worse in the early WBRT group. Therefore, some authors suggest that WBRT after SR or SRS could be avoided in some cases, especially in patients with subtypes of MBC who live longer than the the more aggressive triple negative subtypes [48].

The majority of patients with BM are given conventional WBRT, a total dose of 30 Gy in 10 fractions and daily fractions of 3–4 Gy [49]. Nevertheless, acute encephalopathy has been reduced using lower fractions (≤3 Gy).

Re-irradiation has also been explored by several authors. Specifically, RPA class 1 and 2 patients should be considered for repeat radiotherapy [50].

In conclusion, management of a single BM should be started with local treatment unless a really low KPS is present. In some of these patients WBRT may be delayed. If more than four BM are found, WBRT is the standard treatment (See Fig. 1).

Systemic anticancer treatment by tumor subtypes

Treatment of BM from luminal breast cancer (LBC)

Brain metastasis in this subtype of breast cancer appears in lower rates and latest over the course of the disease compared to HER2 positive and triple negative subtypes [51].

No global consensus exists regarding the ideal treatment strategy for BM in LBC but systemic treatment appears to enhance OS. In a retrospective study of over 135 patients with BM from LBC, 88.8 % of them received local therapy (WBRT, RS or SRT), 56.7 % chemotherapy (mostly with taxanes) and 30.6 % hormonal therapy (mostly with aromatase inhibitors). Systemic treatment (chemotherapy ± hormonal therapy ± target therapy) prolonged median OS (14.3 vs 7.1 months, $p = 0.03$) [52]. These data have been recently confirmed in a prospective study including 420 patients: OS with systemic treatment after WBRT increased 9 months in LBC [33].

Evaluation of ER is an important predictive factor for BM response to therapy. BM from breast cancer frequently show changes in hormonal receptors compared to matched primary tumors. Loss of hormonal receptor positivity in BM is more frequent than its gain [53]. Most randomized trials in MBC with endocrine therapy exclude any degree of brain or leptomeningeal spread but response of BM to endocrine therapy has been reported in a few patients. Tamoxifen and megestrol acetate are active against BM [54, 55]. Notably tamoxifen and its metabolites have been

Newly diagnosed brain metastases

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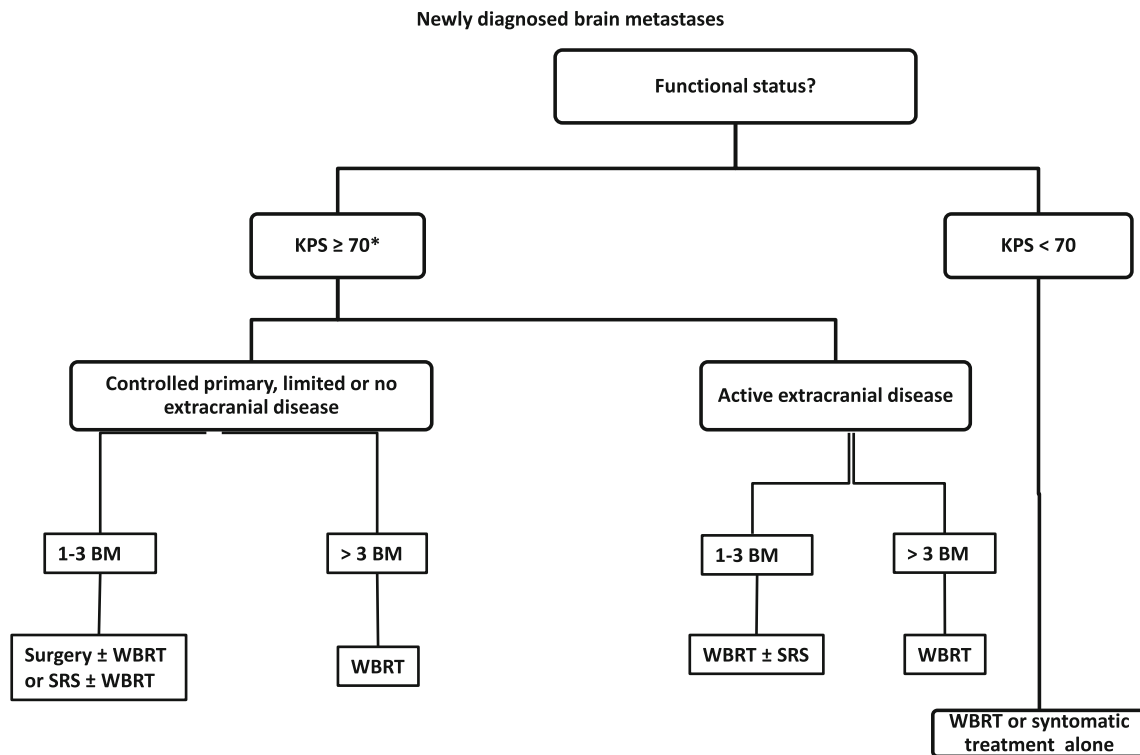
Fig. 1 Algorithm for the initial treatment of brain metastases. *Asterisk* In all cases consider systemic treatment by tumor subtype. *KPS* Karnofsky performance status, *SRS* stereotactic radiosurgery, *WBRT* whole-brain radiotherapy, ±WBRT omission of up-front WBRT is an alternative in patients who are closely observed for progression after surgery or SRS and have an active systemic treatment

reported to achieve high concentrations in the CNS; up to 46-fold higher in BM and brain tissue than in serum [56]. Although there are no data regarding concentration of aromatase inhibitors in brain tissue, responses with letrozole and anastrozole have been reported [57, 58].

In conclusion: BM in LBC must be treated with local therapy plus systemic treatment. This systemic treatment will depend on ER in BM, KPS, extracranial disease, previous systemic treatments and patient's preference.

Treatment of BM from triple negative breast cancer

Actually systemic treatment in triple negative tumors is limited to chemotherapy. So far, there is not an especially approved drug against BM, neither there is a specific designed trial including patients with BM from triple negative breast cancer. We believe it is essential to develop this type of studies with chemotherapy alone or in combination with new target therapies as monoclonal antibodies or tyrosine kinasa inhibitors against EGFR, MET, VGEF, PI3K, or others. Response rate (RR) of BM to chemotherapy, in patients who have not been heavily pretreated, have generally been similar to those of primary tumors. It was thought that the integrity of the BBB limited delivery of large and hydrophilic drugs to the site of BM. In addition, P-glycoprotein is highly expressed by the brain capillary endothelium and actively mediates the efflux of anthracyclines, taxanes, and vinca alkaloids. However, if a BM presents contrast enhancement on CT and MRI, its means that the BBB is partially disrupted and hydrophilic drugs could pass [59]. The degree to which a given agent is believed to penetrate the BBB is usually based on pharmacokinetics animal and/or human studies comparing plasma with cerebrospinal fluid drug concentrations after i.v. or oral administration. This method may underestimate the concentration of drug delivered to the tumor [60].

Clinical data supporting effectiveness of chemotherapy for BM are limited primarily to several phase II studies, often carried out in heavily pretreated patient populations and not specific for triple negative breast tumors (see Table 3). It is important to recognize that adequate randomized phase III trials with most of the currently available agents have not yet been conducted.

Objective RR in the range of 17–55 % have been reported in patients with new BM treated with classical chemotherapy combinations against MBC [61, 62]. These regimens may be considered, either before or after WBRT, in patients with newly BM who have not previously received these chemotherapy combinations.

Table 3 Chemotherapeutic regimens with activity in brain metastases from breast cancer

Chemotherapy	New or recurrent	N	RR (%)	OS (m)	Study (year)	References
CTX + 5FU + PDN	New	52	52	NR	Rosner et al. (1986)	[61]
CMF + VCR + PDN	New	35	54	NR	Rosner et al. (1986)	[61]
AC	New	6	17	NR	Rosner et al. (1986)	[61]
CMF or CAF	New	22	55	6	Boogerd (1992)	[62]
CDDP + VP-16	New	56	38	8	Franciosi (1999)	[63]
CBDCA + CCNU	Both	26	34	NR	Colleoni (1997)	[64]
Topotecan	New	24	37	6.2	Oberhoff (2001)	[65]
	New	19	19	NR	Lorusso (2006)	[66]
TMZ	Recurrent	19	0	NR	Trudeau (2006)	[67]
TMZ + VNR	Recurrent	21	11	NR	Omuro (2006)	[68]
TMZ + CDDP	Recurrent	15	40	5.5	Christodolou (2005)	[69]
TMZ + Cape.	Both	24	18	NR	Rivera (2006)	[70]
Capecitabine	Recurrent	20	45	NR	Kurt (2007)	[71]
HD MTX	NR	9	33	6	Lassman (2006)	[72]

CTX cyclophosphamide, *5FU* 5-fluorouracil, *PDN* prednisone, *CMF* cyclophosphamide, methotrexate and 5-fluorouracil, *CA* cyclophosphamide and doxorubicin, *CAF* cyclophosphamide, doxorubicin, and 5-fluorouracil, *CDDP* cisplatin, *CBDCA* carboplatin, *CCNU* lomustine, *OS* overall survival, *NR* not reported, *RR* response rate, *TMZ* temozolomide, *VNR* vinorelbine, *VP-16* etoposide, *HD MTX* high-dose methotrexate

The combination of cisplatin and etoposide has shown activity in two phase II studies [63]. Carboplatin may achieve slightly higher CNS concentrations than cisplatin and is an active agent in MBC. Although the combination of carboplatin and lomustine showed a RR of 34 % [64].

Oberhoff et al. [65] reported a 37 % objective RR in 24 women treated with topotecan (1.5 mg/m^2 daily for 5 days every 3 weeks) for new BM, but Lorusso et al. [66] reported a 0 % RR in another trial.

Temozolomide (TMZ) has a favorable BBB penetration, but unfortunately has not shown activity in breast cancer BM as a single agent [67] or in combination with vinorelbine [68]. Modest RR have been reported for TMZ combined with cisplatin or capecitabine in small phase II studies, likely reflecting the activity of cisplatin or capecitabine rather than TMZ [69, 70].

There are several case reports suggesting that capecitabine has activity in new and recurrent BM from breast cancer [71]. Larger studies are requested to establish its potential role either as a single agent or in combination with other treatment modalities.

Methotrexate is active in breast cancer and has good BBB penetration at high doses. [72]; however, concern for toxic leukoencephalopathy, particularly when administered after WBRT, limits its use for many patients.

Gefitinib has not demonstrated efficacy in BM from breast cancer in a phase II multicenter study [73].

Recent data suggest that bevacizumab, a monoclonal antibody that binds human vascular endothelial growth factor (VEGF) and inhibits angiogenesis, is safe and effective for progressive BM from breast cancer [74].

Sunitinib and sorafenib, specific VEGF receptor tyrosine kinase inhibitors, are probably able to penetrate the BBB. Sorafenib has been shown to significantly reduce the occurrence of BM [75] and there are trials currently under development to analyze its efficacy as a treatment for BM.

In conclusion classical chemotherapy combinations as CMF or FAC, Carboplatin or capecitabine should be considered, either before or after WBRT, in patients with newly BM who have not previously received these chemotherapy combinations.

Systemic treatment in HER2 positive brain metastases

Consensus guidelines on systemic treatment after BM in HER2 positive breast cancer patients are lacking. Several retrospective studies have demonstrated improved survival with trastuzumab in HER2-positive MBC patients with CNS metastasis [8, 76, 77]. Interestingly, lapatinib has shown a promising activity against BM in clinical studies [77–79]. Taken all these findings together, we can argue that there is a role for systemic treatments in improving the outcome of HER2 positive breast cancer with BM.

It has been reported that almost one-third of MBC patients that receive trastuzumab eventually will develop BM [8, 11]. Moreover, 50 % of these BM were diagnosed in patients with controlled disease outside the CNS. One of the possible explanations for the increased incidence of BM in this population may be that trastuzumab is a large molecule and it is not able to cross the BBB. Nevertheless, there are some data that support that this agent can penetrate the BBB when it is not intact either by radiotherapy or

by the cancer itself [80]. The efficacy data of continuing trastuzumab-based regimens in the management of BM is controversial. Some reports have demonstrated a significant survival benefit with this drug after local treatment [8, 33, 76, 77] (see Table 4). In general, it is assumed that the impact on OS is mainly due to control of systemic disease rather than CNS.

Lapatinib is a small molecule with potential ability to cross the BBB. In preclinical models, lapatinib showed activity in inhibiting BM and reducing the number of large HER2-transfected brain metastases [81]. In a phase III clinical study, LC combination therapy was more effective than capecitabine alone in reducing BM as the first site of recurrence. BM relapses as first progression were 6 % in capecitabine alone vs 2 % in the combination therapy; $p = 0.045$ [82]. In line with these observations, Metro et al. showed that patients treated with sequential combination of trastuzumab and LC had significantly longer survival compared with patients treated with trastuzumab-based treatments alone (27.9 vs 16.7 months; $p = 0.01$) with a 31.8 % of responses. [83]. In another single center retrospective study over 80 patients, Bartsch et al. [77] reported that the use of trastuzumab and lapatinib, either sequentially or concomitantly, with or without chemotherapy, was associated with a 72 % reduction in risk of death compared with trastuzumab alone ($p = 0.012$), and

lapatinib therapy was shown to be an independent positive predictor for better OS (HR 0.279; $p = 0.012$).

Two phase II trials have studied the role of lapatinib in monotherapy for established BM in HER-2 positive breast cancer previously treated with trastuzumab and WBRT. Both reported a volumetric reduction of BM [78, 84]. Other two phase II trials have evaluated LC combination, The study LEAP [84] demonstrated a 21 % of responses with LC, in 35 % of patients LC was administered before WBRT. One randomized phase II study compare LC vs lapatinib plus topotenan. The study was closed early because of unacceptable toxicity in the topotecan arm but reported a RR of 38 % in LC arm [85]. The LANDSCAPE study used LC before WBRT in 48 patients and reported a RR of 67 % in BM [79].

Trastuzumab or lapatinib administered concurrently with WBRT also been studied and have reported a RR of approximately 70 % [86, 87]

In conclusion, antiHER2 treatments, both trastuzumab and lapatinib, after BM diagnosis confer a survival benefit. Data of multiples studies suggest that lapatinib could be an active drug for management of BM in HER2-positive breast cancer, however, well designed prospective clinical trials with uniform criteria are urgently needed in order to define the specific role of these targeted agents in the management of HER2 positive breast cancer BM.

Table 4 Efficacy of antiHER2 therapies after BM diagnoses

	N	Study	Treatment	RR (%)	OS (m)	TTP (m)	p value
Park [76]	29	Retrosp.	With TTZ	NR	13.6	NR	<0.001
	39		Without		5.5		
Brufsky [8]	258	Observational, prosp.	With TTZ	NR	17.5	NR	<0.001
	119		Without		3.8		
Bartsch [77]	15	Retrosp.	TTZ + LPT	NR	Not reached	NR	<0.001
	28		TTZ		13		
	9		CT		9		
	28		No systemic treat		3		
Metro [83]	22	Retrosp.	TTZ + LPT + CPT	31.8	27.9	5.1	0.01
	23		TTZ	NR	16.7		
Sutherland [84]	34	Phase IV	LPT	21	9	5.1	
Lin [78]	240	Phase II	LPT	6	6.4	NR	
	50	Post WBRT	LPT + CPT	20	NR	3.6	
Bachelot [79]	44	Phase II Pre WBRT	LPT + CPT	67	17		
Lin [85]	22	Phase II Rando	LPT + CPT	38	NR	NR	
		Post WBRT	LPT + TT	0			

TTZ trastuzumab, *BM* brain metastases, *CT* chemotherapy, *RR* response rate, *LPT* lapatinib, *CPT* capecitabine, *NR* not reported, *TT* topotecan, *WBRT* whole-brain radiotherapy

Supportive care

Supportive or symptomatic therapy is mainly based on the administration of steroids and anticonvulsants.

Vasogenic edema is commonly seen with BM, it contributes to intracranial mass effect and often can be ameliorated with administration of oral steroids. Dexamethasone (DXM) is most often used for several reasons, including the fact that it is the most potent steroid, has the best CNS penetration, the least mineralocorticoid side effects, the least protein-bound steroid and has a long biologic half-life (24–36 h) [88]. DXM dose–response data have never been established and, therefore, an empiric dose of 4–16 mg/day is used. Based on the biologic half-life, once or twice per day is sufficient, although often DXM is administered four times per day without a clear rationale. The lowest dose of DXM that controls symptoms should be utilized. Asymptomatic patients with BM do not require DXM and may therefore be spared potential steroid-related toxicity. Prolonged use of DXM (defined as longer than 3 weeks) is associated with the emergence of steroid-related side effects (e.g., proximal myopathy, weight gain, skin fragility) that may seriously compromise patient quality of life. How rapidly can the steroid be withdrawn is, again, an issue not evidence-based but rather empiric and determined by patient symptoms.

The use of antiepileptic drugs (AEDs) in patients with BMs should be reserved for patients with seizures and for seizure prophylaxis immediately following surgical resection. Based on the recommendations of American Academy of Neurology guidelines and the European guidelines, AED prophylaxis in patients with primary and metastatic brain tumors should be abandoned [89, 90]. If AEDs are indicated, emerging data recommend the use of nonenzyme-inducing AEDs to minimize drug interactions that may confound the treatment of patients with cancer.

Summary and multidisciplinary management guidelines

Based upon the bibliographic research and the expertise of the authors the following conclusions are made:

1. Early diagnosis of CNS involvement may be crucial: When a patient experiences a systemic relapse of a HER2 positive tumor a cranial MRI could be indicated in order to detect CNS involvement.
2. Patient's performance status determination and neurological symptoms evaluation are essential for an appropriate management of BM.
3. Age is an important prognostic factor and should be included in the decision-making algorithm.

4. A precise determination of disease extension outside and inside the CNS is essential in therapy choice decision-making, so cranial MRI and body CT-scan are indicated for a correct management of BM.
5. If a solitary BM is suspected, a histology confirmation by stereotactic biopsy or BM resection should be recommended.
6. Local (SR, SRT and/o WBRT) and systemic treatment decision should be taken by a multidisciplinary team.
7. Unless KPS <70, 1–3 BM treatment should be initiated with a local treatment (SR o SRT) and WBRT may be delayed.
8. If more than three BM are found, WBRT should be the standard treatment in HER2 negative tumours. LC treatment is an alternative in HER2-positive cases.
9. Knowledge of previous systemic treatments and assessment of ER and HER2 expression or amplification are essential for a precise determination of systemic treatment options.
10. BM from luminal breast cancer must be treated with systemic treatment after local therapy. This treatment will depend on ER, KPS, extracranial disease, previous systemic treatments and the patient's preference.
11. Both trastuzumab and lapatinib confer survival benefit in BM from HER2- positive cancer. Lapatinib plus capecitabine have demonstrated volumetric reduction in phase II trials and could delay WBRT.
12. The best treatment approach should include patient's participation in a clinical trial.

Conflict of interest None.

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