Central Nervous System Metastases in HER-2–Overexpressing Metastatic Breast Cancer: A Treatment Challenge

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Key Words. CNS metastases • Metastatic breast cancer • HER-2 overexpression • Treatment modalities • Radiotherapy • Tyrosine kinase inhibitors

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ABSTRACT
With improvements in diagnostic and therapeutic options and a corresponding improvement in survival, central nervous system (CNS) metastasis is becoming a more frequent diagnosis in breast cancer patients. It can be assumed that up to 30% of metastatic breast cancer (MBC) patients may experience CNS metastasis during the course of their disease. Moreover, it has been reported that patients with human epidermal growth factor receptor (HER)-2–overexpressing MBC are at a higher risk for CNS involvement.

Whereas locoregional treatment modalities such as surgery, radiosurgery, and whole-brain radiotherapy still must be considered as the treatment of first choice, the armamentarium of systemic treatment modalities has been expanded by the introduction of small molecules such as the tyrosine kinase inhibitors.

Rather than analyzing the risk factors for the development of CNS metastasis and reviewing the standard diagnostic and therapeutic approaches in patients with CNS involvement, this review focuses specifically on systemic treatment modalities in patients suffering from CNS metastasis from HER-2–overexpressing MBC. The Oncologist 2008;13:000–000

INTRODUCTION
At present, breast cancer is estimated to be the second most frequent cause of brain metastasis [1]. Central nervous system (CNS) metastases are diagnosed in approximately 6%–16% of metastatic breast cancer (MBC) patients, while in autopsy studies the incidence is in the range of 18%–30%.

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Previous investigators have reported a higher incidence of clinically overt CNS metastasis in the range of 25%–34% for patients who received trastuzumab-based regimens for human epidermal growth factor receptor (HER)-2–overexpressing MBC [4–9]. The biological explanation for this high incidence of CNS metastasis may be a greater affinity of HER-2–overexpressing breast cancer metastases for the CNS. Alternatively, it may be argued that trastuzumab-based therapy prolongs survival to such an extent that CNS metastasis, which is known to be a late event in the course of metastatic disease, becomes apparent. In this case, the changing pattern of metastasis would be interpreted as a result of a prolonged duration of disease.

Trastuzumab (Herceptin®; F. Hoffmann-La Roche, Basel, Switzerland) is a humanized monoclonal antibody directed against the HER-2/neu (c-erbB-2) oncoprotein. This protein is encoded by the HER-2/neu gene and is characterized as a transmembrane growth factor receptor belonging to the epidermal growth factor receptor family, and is overexpressed in approximately 25%–30% of all human breast carcinomas [10]. Preclinical and clinical studies have shown the ability of trastuzumab to inhibit tumor growth in breast cancer patients overexpressing HER-2 [11].

Single-agent treatment with trastuzumab yielded a response rate of 35% in the first-line treatment of MBC (clinical benefit rate, 48%), while a response rate of 15% was observed for second-line therapy [12–14]. The addition of trastuzumab to first-line chemotherapy (anthracycline or taxane based) was associated with a longer time to disease progression (median, 7.4 versus 4.6 months; \( p < .001 \)), a higher rate of objective response (50% versus 32%; \( p < .001 \)), and a longer duration of response (median, 9.1 versus 6.1 months; \( p < .001 \)) [10, 11]. Additionally, it was shown that the first-line use of trastuzumab together with chemotherapy resulted in a significantly longer median survival time, 25.4 versus 20.0 months (\( p = .045 \)), after a median follow-up of 25 months [11]. It was concluded that trastuzumab acts synergistically when added to chemotherapy.

Little is known so far about the pharmacology and activity of trastuzumab in the CNS. However, there is some evidence that trastuzumab is unable to penetrate into the cerebrospinal fluid (CSF) [15–17].

This review focuses on risk factors for the development of CNS metastasis, the prognostic factors and the pattern of CNS involvement, and finally on treatment modalities in patients suffering from CNS metastasis of HER-2–overexpressing MBC.

**METHODS**

The MEDLINE database was searched from 1980 through to 2008 using variations on the following search terms: CNS metastases, metastatic breast cancer, HER-2 overexpression, treatment modalities, radiotherapy, tyrosine kinase inhibitors. Moreover, the American Society of Clinical Oncology annual meeting proceedings and the published abstracts of the annual San Antonio Breast Cancer Symposium were searched from 2000 to 2008 for reports of new or ongoing trials. A search was also conducted for published practice guidelines, meta-analyses, and systematic reviews.

Relevant articles and abstracts were selected, and the reference lists from these sources were searched for additional trials.

Articles were selected for inclusion in this review of the evidence if they were fully published reports or published abstracts of clinical trials or meta-analyses of clinical trials. Articles were required to report on any of the following specified outcomes of interest: response rates, progression-free survival, overall survival, quality of life, or adverse effects. Trials published in a language other than English or German were excluded because of limited translation resources.

Most of the data on this topic have the limitation of being retrospective, and many of the trials reported on small patient numbers.

**Epidemiology, Incidence, and Pathology**

**Metastasis to the Brain**

Metastasis to the parenchyma of the brain primarily occurs as hematogenous metastasis, while metastasis via lymphatic vessels plays a less important role. At present, it is assumed that the subsequent steps of metastasis are comparable between brain and other distant organs. For brain metastasis to evolve, it is necessary that tumor cells invade blood vessels, that they survive intravasation, and that they subsequently lodge, extravasate, migrate, and grow in an adequate microenvironment [18]. Factors involved in the process of metastasis to the brain are vascular endothelial growth factors, chemokines, epidermal growth factor receptor (EGFR)-1, and HER-2. However, their exact role in CNS metastasis has yet to be elucidated.

**Incidence of CNS Metastasis**

In MBC, the incidence of CNS metastasis is the range of 14%–16% [19]. Evidence from screening and autopsy series indicates that another 15% of breast cancer patients may have asymptomatic CNS metastasis. Based on these data, one would assume that up to 30% of MBC patients may experience CNS metastasis during the course of their disease [20–22].

Several reports have suggested a higher risk for CNS metastasis in breast cancer patients overexpressing HER-2, while others did not.
Within a median follow-up time of 8 years after primary treatment of breast cancer, the incidence of brain metastasis was shown to be 1.7% in HER-2-negative patients, while it was 8% in patients overexpressing HER-2 [23]. In a population-based study evaluating patients between the years 1998 and 2003, Abdulkarim and coworkers observed an incidence of 10% in HER-negative patients and a higher rate of 24% in HER-2-overexpressing patients [23]. Another retrospective analysis reported an incidence of 2.6% in HER-2-negative patients compared with 7.2% in HER-2-positive patients during a follow-up time of 8.1 years [24]. In contrast, Tham and coworkers reported on 2,685 patients never exposed to trastuzumab, for whom HER-2 overexpression was not associated with a greater risk [19].

In the majority of patients, CNS metastasis develops subsequent to extracranial tumor manifestations, while CNS metastasis is a first site of recurrence in only 20%–39% of patients [19]. In one study, the interval between the first diagnosis of breast cancer and the development of brain metastasis was 34 months, while it was only 16 months after diagnosis of metastatic disease [3].

Increasing Incidence of CNS Metastasis in MBC Patients?
Several analyses support a growing incidence of CNS metastasis in MBC patients. This may be explained by an increased awareness on the side of patients and treating physicians. Moreover, better diagnostic tools are available, including computed tomography (CT) and, specifically, contrast-enhanced magnetic resonance imaging (MRI). Finally, it cannot be ruled out that the improvement in therapeutic options and longer survival times also may contribute to a higher rate of diagnosis of CNS metastasis, which notably occurs during the later course of the disease.

Pathology of Brain Metastases: Concordance of Receptor Status—Estrogen Receptor and HER-2
Clearly, it is of interest to ask if brain metastases differ from extracranial metastases by a genetic predisposition that might allow them to invade the brain and grow in this unique environment. Regarding the overexpression of HER-2, a retrospective study described a 97% concordance of primary breast tumors and subsequent brain metastases [25]. Another study, by Ibrahim et al. [26], reported a concordance of 88% for both the estrogen receptor and the HER-2 status between the primary tumor and the brain metastases.

Risk Factors
Risk Factors for the Development of Brain Metastasis
Several analyses support young age and a negative hormone receptor status as the main risk factors for the development of brain metastasis in breast cancer patients. In a large retrospective investigation of patients diagnosed and treated with breast cancer between the years 1970 and 1999, 2,685 patients were identified who suffered distant recurrence [19]. CNS metastasis occurred in 383 patients (14%). In a univariate analysis, CNS metastasis was significantly associated with younger age, premenopausal status, invasive ductal carcinoma, hormone receptor negativity, p53 mutation, and EGFR overexpression. The multivariate analysis identified only young age, estrogen receptor negativity, and invasive ductal carcinoma histology as independent risk factors.

In the retrospective analysis by Tham et al. [19], HER-2 overexpression was not associated with a higher risk. However, none of the HER-2–overexpressing patients had received a trastuzumab-based regimen at the time. Another study determined the incidence of brain metastases in 301 newly diagnosed HER-2–positive and 363 HER-2–negative patients in the years 1998–2003 [27]. Within a median follow-up of 3.9 years, brain metastases were observed in 9% of HER-2–overexpressing and 1.9% of HER-2–negative patients. Significant risk factors in the univariate analysis were HER-2 overexpression, tumor size >2 cm, lymph node positivity, grade 2 or 3 disease, and hormone receptor negativity. In the multivariate analysis, HER-2 overexpression (hazard ratio [HR], 3.55; p = .006), tumor size >2 cm (HR, 2.76; p = .13), and estrogen receptor status (HR, 0.32; p = .002) were isolated as significant risk factors [27].

CNS Metastasis and HER-2 Overexpression
Several retrospective analyses indicate that HER-2-overexpressing patients are at a greater risk for CNS metastasis (Table 1) [6, 9, 27–30]. A retrospective analysis of 3,871 breast cancer patients with known HER-2 status indicated that the cumulative 10-year risk for brain metastasis was significantly greater in patients with HER-2-overexpressing primary tumors (6.8% versus 3.5%; p < .01) [28].

Recent evidence indicates that HER-2–overexpressing MBC patients receiving trastuzumab have a high risk of developing brain metastasis, as several investigators have reported incidence rates of 25%–34% [4–9]. The interval between the diagnosis of distant metastasis and CNS metastasis was in the range of 14–27.5 months. The median time from the start of trastuzumab therapy to the diagnosis of brain metastasis was 4–24 months [5, 6, 8, 31]. The me-
CNS Metastases in HER-2–Positive MBC

Median survival time after the diagnosis of CNS metastasis was in the range of 5.4–13 months in three trials [4–6]. However, whereas HER-2 overexpression conveys a greater risk for CNS metastases, there are data indicating that the development of brain metastases in late relapses (median time to relapse, 7 years) of HER-2–overexpressing breast cancer patients is a rare event [32, 33]. The high incidence of brain metastasis in HER-2–overexpressing breast cancer is not completely understood. Certainly, HER-2 overexpression reflects a more aggressive type of disease with a greater propensity to induce distant metastasis. Brain metastasis mostly occurs late in the course of treatment, so improvement of survival by trastuzumab may allow brain metastases to become symptomatic to a greater extent than in the pretrastuzumab era when patients with HER-2–overexpressing tumors had a rather short survival duration.

Given that a high proportion of HER-2–overexpressing breast cancer patients will develop symptomatic brain metastases, it is critical to discuss whether or not those patients should be followed with regular MRI scans for asymptomatic brain metastases [34]. It has been claimed that irradiation of asymptomatic brain metastases can prevent them from becoming symptomatic.

**Prognostic Factors and Survival**

**Interval from Primary Breast Cancer to Brain Metastasis**

In a retrospective analysis of 198 patients with solitary or multiple brain metastases, the median interval from the primary diagnosis of breast cancer to brain metastasis was 32.3 months [35]. A low hormone receptor expression level (immune reactivity score, 0–3), a high pathological grade, and age <45 years were associated with a shorter interval. HER-2 status, size of the primary tumor, lymph node status, lymph vessel invasion, and adjuvant pretreatment status had no impact on the interval from primary tumor to brain metastasis. Two independent analyses indicated that the factors associated with a shorter interval to the development of brain metastasis do not influence survival [19, 35].

**Impact of CNS Metastasis on Survival**

CNS metastasis is generally associated with a dismal prognosis in breast cancer. The retrospective analysis by Tham and coworkers was performed in the pretrastuzumab era. In 383 patients, a median survival time of only 5.5 months was documented [19]. At 1 and 2 years after diagnosis, only 25% and 10% of patients were alive, respectively. Comparable data were also reported by Lee et al. [35], who observed a median survival time of 5.6 months and a 1-year survival rate of 23.1% in 198 patients.

Interestingly, a recent report on 50 patients did not find a negative effect of brain metastasis on survival [36]. The authors related this observation to the more aggressive management of brain metastasis or the lack of extracranial tumor progression.

**Prognostic Factors in Patients with Brain Metastasis**

Solitary brain metastases, controlled extracranial disease, and a good performance status are among the most important prognostic factors for patients with brain metastasis. In a retrospective single-institution study by Lee and coworkers [35], patients with a poor performance status (Eastern Cooperative Oncology Group [ECOG] performance status score ≥3) had a shorter survival duration (3.2 months versus 6.5 months) than those with a good performance status (ECOG score ≤2). Also, extracranial metastasis was associated with a shorter survival time (5.3 months versus 9.0 months). Tham and coworkers analyzed 2,685 patients with distant recurrence who never received trastuzumab. They

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### Table 1. Incidence of brain metastasis in HER-2–overexpressing MBC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Incidence (%)</th>
<th>Interval between initial and CNS metastases (mos)</th>
<th>Duration of trastuzumab until CNS metastases (mos)</th>
<th>Median survival after CNS metastases (mos)</th>
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<td>6.1</td>
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<td>–</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>Weitzen et al. [9]</td>
<td>42</td>
<td>29</td>
<td>27.5</td>
<td>12.4</td>
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</tr>
</tbody>
</table>

**Abbreviations:** CNS, central nervous system; HER-2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer.
described HER-2 overexpression as an important negative predictor of survival [19]. Among factors without predictive importance for survival were age, menopausal status, histology, pathological grading, and hormone receptor status [19, 35].

Survival in MBC patients with brain metastasis greatly depends on adequate therapy of the brain metastasis. In untreated patients, survival may be as short as 1–2 months. After whole-brain radiotherapy (WBRT), survival may increase up to 3–6 months. Patients with solitary brain lesions are expected to have a more favorable course of disease, and a median survival time of 14–15 months may be reached [35]. At the same time, adequate treatment of extracranial disease is important. Patients who received systemic hormone therapy or chemotherapy after local therapy of brain metastasis had a longer survival duration (7.8 months versus 3.6 months) than those who did not. Although the study of Lee et al. [35] suggests a benefit of chemotherapy subsequent to local therapy for brain metastasis, it is critical to discuss that conclusions drawn from such a small (n = 55) and retrospective analysis remain disputable. Moreover, the benefit of such an aggressive treatment is limited to patients with a good performance status [35].

**Diagnostic Procedures and Patterns of CNS Metastasis**

While CT is able to detect the majority of CNS metastases, the sensitivity is markedly greater in gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA)–enhanced MRI. Gd-DTPA is a hydrophilic paramagnetic contrast material agent with a molecular weight of 938 Da, which does not cross the intact blood–brain barrier (BBB). Therefore, Gd-DTPA does not accumulate in normal brain tissue or in lesions that do not have an abnormal BBB. However, disruption of the BBB or abnormal vascularity allows accumulation in lesions such as neoplasms.

Early diagnosis of CNS involvement may be essential for the patient because neurological symptoms, once they have developed, often do not completely resolve even in patients responding to treatment. Quality of life is therefore enhanced in patients who are diagnosed timely [22].

A precise determination of the extent of disease is clearly essential for the choice of the appropriate therapeutic approach. A singular lesion must be differentiated from multiple lesions. Moreover, a solitary lesion is defined by the absence of any extracranial manifestations. 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 diagnosis of a singular CNS metastasis could not be maintained in 11% of the subjects [37].

CNS metastases in MBC are mostly located at the border between marrow and cortex. A majority are distributed in the hemispheres (80%), followed by the cerebellum (15%) and brainstem (5%). Solitary lesions were diagnosed in 56% of patients while multiple lesions were diagnosed in 44% of afflicted patients [38].

**Clinical Presentation**

CNS metastasis is a clinically relevant factor in that it may severely impair sensory or motor neural functions. It may not only disable patients, but may also be responsible for pain, and may finally cause life-threatening complications of metastatic disease. Metastases to the brain and/or perifocal edema cause neurological dysfunction obligatorily leading to death within a short time when untreated [3]. Common symptoms consist of headaches (24%–48%), focal neurological dysfunction (20%–40%), and nausea, vomiting, and seizures (10%–20%) [22, 39, 40].

**Treatment: Locoregional**

**Surgery and Stereotactic Radiosurgery**

Surgical resection and/or radiotherapy are among the primary treatment options in brain metastasis. Solitary brain metastases may primarily be an indication for surgical resection. Moreover, surgical strategies are indicated in cases of urgently required decompression. Generally, there is no indication for surgical resection in patients suffering from multiple lesions except in such cases of bleeding or decompression.

Two prospective randomized trials and two retrospective analyses have shown that surgery followed by radiotherapy is superior to WBRT. The median survival time for patients who received additional radiation was 10–16 months, compared with 4–6 months in those who had surgery alone (Table 2) [37, 41–43].

If there is evidence of a limited number (three or fewer lesions) of small (≤3 cm) metastases, stereotactic radiosurgery (SRS) including gamma-knife or cyber-knife radiation needs to be considered. The median overall survival time after surgery or SRS was 14.9 months in a retrospective analysis [35, 45]. These approaches are applicable even in whole brain–irradiated patients who have recurrent brain metastasis. A major limitation of SRS consists of the fact that 37% of the patients who receive SRS develop further brain metastases [37].

**WBRT**

Patients with disseminated brain metastasis are primarily candidates for WBRT. Radiation is commonly applied to a total dose of 30 Gy delivered within 2 weeks [22]. How-
ever, an optimal regimen regarding the dose and number of fractions has still not been defined. Patients who receive higher daily doses within a shorter time respond earlier, but without any survival benefit. On the other hand, cognitive dysfunction is greater in patients irradiated with higher doses within a shorter time. Therefore, patients with a better prognosis, for example, patients with a solitary metastasis who receive radiotherapy subsequent to surgery, should not receive daily doses exceeding 2.5 Gy.

Dexamethasone at a dose of $3 \times 8$ mg orally per day is generally given to protect radiation-induced brain edema. An improvement in neurological symptoms could be achieved in 75%–85% of patients [22]. The median survival time in these patients is expected to be in the range of 5–6 months [35].

Recurrence Disease After Radiotherapy of the Brain

When progression of CNS metastasis occurs after radiotherapy, decisions are taken according to the prior therapy. After previous SRS, patients may be offered further SRS treatment in the case of single small lesions. When disseminated recurrence in the brain is evident, WBRT may be the treatment of choice. If WBRT was performed as initial therapy, SRS may be performed at progression if feasible. Disseminated recurrence after WBRT requires the use of systemic treatment approaches.

TREATMENT: SYSTEMIC

Effect of the BBB on Systemic Therapy

The BBB is created by tightly aligned endothelial cells within the capillary vessels connecting the endothelial cell vessels. These endothelial cells are connected to each other by tight junctions and are surrounded by a basement membrane, which in turn is supported by astrocytes and numerous pericytes. This tight physical barrier separates the circulation from the microenvironment of the brain and shows a selective permeability for substances with a diameter of $<20$ nm [46].

As a result, the intact BBB is crossed only by small lipid-soluble molecules, and chemotherapeutic agents such as anthracyclines, vinca alkaloids, or taxanes are poorly taken up into the brain. Specifically, monoclonal antibodies like trastuzumab are too large (148 kDa) to pass the BBB [47]. However, changes in the permeability of the BBB were observed in experimental animals as well as in clinical studies evaluating patients who received WBRT for several malignant brain tumors [48]. It is critical to discuss that at least the local, intratumoral integrity of the BBB is questionable in patients suffering from brain metastases. Hydrophilic Gd-based contrast agents such as those generally used for MRI (Gd-DTPA; molecular weight, 938 Da) have a molecular weight exceeding the critical mass of 200 Da that allows penetration across the BBB. However, intracerebral metastases often show impressive contrast material enhancement on MRI, supporting the assumption of impaired BBB integrity.

Chemotherapy of Brain Metastasis

Chemotherapy is not the appropriate first-line approach for isolated brain metastases. An indication for chemotherapy is given once locoregional treatment approaches like surgery, SRS, or WBRT are excluded or have failed. It is unclear to what extent the BBB is intact in brain metastasis. Moreover, a high expression of p-glycoprotein effectively prevents the uptake of chemotherapeutic agents by endothelial cells [22].

Once an indication for systemic therapy is given, chemotherapeutic agents are primarily chosen for their activity with regard to extracranial disease. Selected agents like capecitabine, 5-fluorouracil, platinum analogues, temozolomide, methotrexate, topotecan, or bendamustine may, however, be preferred because of their known activity in the brain [22, 49–66].

A seminal study by Rosner et al. [49] reported on 100 patients with symptomatic brain metastases who were...
treated with systemic chemotherapy. Primary chemotherapy of brain metastases yielded response rates of 52% treated with cyclophosphamide, 5-fluorouracil, and prednisone (CFP); 54% receiving CFP plus methotrexate (M) and vincristine (V); 43% treated with MVP; and 17% receiving cyclophosphamide plus doxorubicin. Moreover, 13 of the 35 patients (37%) who subsequently had a relapse of brain metastases were retreated successfully with secondary chemotherapy. The median survival times for responders were 39.5 months and 10.5 months, respectively, in contrast to nonresponders who had a median survival time of 1.5 months [49].

In a retrospective review of patients with MBC, Kurt et al. [67] reported on 20 patients who had received single-agent capecitabine for recurrent or refractory brain metastases after WBRT. Capecitabine resulted in an overall response rate of 45% and a median progression-free survival time of 7.3 months.

In a pilot study by Oberhoff et al. [68], 24 patients with newly diagnosed, bidimensionally measurable brain metastases received topotecan at a dose of 1.5 mg/m² daily for 5 days on a 3-week schedule. Patients with prior radiotherapy were excluded. Most of the patients had received prior adjuvant or palliative chemotherapy. The objective response rate was 38% and the median time of survival was 6.25 months [68].

Boogerd et al. [69] reported on a prospective, nonrandomized study investigating the efficacy of 4-week courses of cyclophosphamide, methotrexate, and 5-fluorouracil in 20 patients or 3-week courses of cyclophosphamide, doxorubicin, and 5-fluorouracil in two patients. Seven patients had previously been treated for brain metastases with the use of surgery and/or radiation therapy. Initial tumor regression occurred after two courses of chemotherapy in 76% of the patients. In patients who were evaluated after six courses, the response rate was 47%. The median overall survival time was 25 weeks (range, 2–83 weeks) [69].

Temozolomide is often considered in recurrent or persistent brain metastases. When used as single-agent chemotherapy, the response rate is in the range of 0%–57.6%, the latter in combination with radiotherapy [54, 59]. Limited experience exists regarding combination chemotherapy including temozolomide and vinorelbine (objective response [OR] rate, 11%), capecitabine (OR rate, 18%), or cisplatin (OR rate, 28.1%) [56, 59, 61]. Moreover, some case reports have demonstrated the efficacy of single-agent bendamustine given for brain metastases in CNS metastases from MBC [51].

Assuming an intact BBB in brain metastases, chemotherapy may serve as a “rescue approach” for recurrent or persistent CNS metastases. Despite some promising clinical data, chemotherapy remains the treatment of second or third choice, subsequent to surgery or radiotherapy strategies (Table 3).

### Endocrine Therapy of Brain Metastasis

Both tamoxifen and megestrol acetate have shown activity in brain metastasis [73–78]. Preclinical studies indicate that fulvestrant does not cross the BBB. Because the effect of aromatase inhibitors on estrogen synthesis is not specifically bound to tumor tissue, their penetration of the BBB may be of secondary importance [79].

### Monoclonal Antibodies

#### Trastuzumab

Little is known so far about the pharmacokinetics and state of activity of trastuzumab in the CNS. Yet, there is some evidence that trastuzumab may be unable to pass the BBB and build up therapeutically relevant concentrations in the CSF [15–17]. Reviewing the literature, some investigators reported that the concentrations of trastuzumab were 300–420-fold lower in CSF than in serum [15–17]. The intact BBB limits CNS penetration to molecules with molecular weights up to 200 Da (trastuzumab molecular weight, 185 kDa) [47]. However, changes in the permeability of the BBB were observed in experimental animals as well as in clinical studies evaluating patients who received WBRT for several malignant brain tumors [48]. Even in patients with brain metastases of HER-2–overexpressing breast cancer, it was shown that the penetration of trastuzumab into the CSF is facilitated during WBRT [17].

Baculi and coworkers reported on a breast cancer patient who presented with meningeal carcinomatosis responding to trastuzumab treatment and for whom impairment of the BBB was therefore suspected [80]. Furthermore, Stemmler et al. [81] and Laufman et al. [82] each reported on a patient with meningeal carcinomatosis from MBC who was treated successfully by intrathecal trastuzumab via an Ommaya reservoir. Nevertheless, this approach is highly experimental and is not indicated outside a clinical trial.

Although there is limited evidence that trastuzumab may be effective under conditions of an impaired BBB or direct intrathecal application, these approaches may be overcome by other drugs that are administered systemically and target HER-2, but are small enough to cross the BBB.

### Tyrosine Kinase Inhibitors

#### Gefitinib and Erlotinib

The EGFR, like ErbB-2, is a member of the ErbB family of receptors (also known as type I receptor tyrosine kinases).
This family of receptors plays a major role in promoting proliferation and the malignant growth of breast cancer cells. The expression of EGFR in breast cancer has been studied extensively and has been associated with a poor prognosis. As a consequence, inhibiting EGFR function may be a fruitful approach in breast cancer therapy. Preclinical studies demonstrated that gefitinib inhibited proliferation of breast cancer cells both in vitro and in vivo. Interestingly, antitumor activity in breast cancer cells has been seen in cells expressing varying degrees of EGFR and also in cells expressing high levels of ErbB-2.

Wu and coworkers [83] reported on a phase II study that investigated the efficacy of gefitinib in the palliative therapy of advanced patients with adenocarcinoma and brain metastases, but exclusively from non-small cell lung cancer. All 40 pretreated patients received 250-mg doses of gefitinib daily. The overall OR rate was 32%, with a disease control rate of 77%. The median progression-free survival and overall survival times were 9.0 months and 15.0 months, respectively [83].

In a phase II multicenter study of patients with taxane- and anthracycline-pretreated MBC, gefitinib was given to 58 patients until disease progression. One patient (1.7%) had an objective partial tumor response, whereas 57 patients (98.3%) were nonresponders. The authors concluded that single-agent gefitinib at a dose of 500 mg daily did not appear to be efficacious in the treatment of heavily pretreated MBC patients. There was no correlation between EGFR expression and response in that study [84].

In summary, data regarding the efficacy of both tyrosine kinase inhibitors (gefitinib and erlotinib) in brain metastases of breast cancer still remained anecdotal.

**Lapatinib**

Lapatinib is a small molecule (<1 kDa) that acts as a dual inhibitor of EGFR-1 and EGFR-2 (HER-2) tyrosine kinases [85–87]. Preclinical studies demonstrated that breast cancer cell lines that were resistant to trastuzumab remained sensitive to lapatinib, thus supporting a different mechanism of action and noncrossresistance of the two agents. Furthermore, it was shown that lapatinib could effectively inhibit brain metastasis in a mouse model [88]. Palmieri et al. [89] reported on a mouse model that investigated the efficacy of lapatinib in preventing the metastatic colonization of EGFR-positive and HER-2–positive breast cancer in the brain. Mice received intracardiac injections of either the control or HER-2–transfected 231-BR cells. Five days later, mice were randomized to vehicle or a 30- or 100-mg/kg lapatinib twice daily oral application. The HER-2–transfected 231-BR cells produced 2.5–3-fold greater large

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Regimen</th>
<th>OR (%)</th>
<th>Median survival (mos)</th>
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<td>CFP, CFPMV, CA, MiVe</td>
<td>61</td>
<td>12 (responders)</td>
</tr>
<tr>
<td>Kaba et al. [72]</td>
<td>115</td>
<td>TPDC-FuHu</td>
<td>66</td>
<td>–</td>
</tr>
<tr>
<td>Oberhoff et al. [68]</td>
<td>16</td>
<td>Topo</td>
<td>38</td>
<td>6.25</td>
</tr>
<tr>
<td>Kouvaris et al. [54]</td>
<td>33</td>
<td>Tem + RT</td>
<td>57.6</td>
<td>12</td>
</tr>
<tr>
<td>Rivera et al. [56]</td>
<td>24</td>
<td>Tem + Cap</td>
<td>18</td>
<td>3 (TTP)</td>
</tr>
<tr>
<td>Omuro et al. [58]</td>
<td>21</td>
<td>Vin + Tem</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Trudeau et al. [59]</td>
<td>19</td>
<td>Tem</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Christodoulo et al. [61]</td>
<td>32</td>
<td>Tem + CDDP</td>
<td>28.1</td>
<td>5.5</td>
</tr>
<tr>
<td>Abrey et al. [64]</td>
<td>41</td>
<td>Tem</td>
<td>5.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Christodoulo et al. [61]</td>
<td>27</td>
<td>Tem</td>
<td>4</td>
<td>4.5</td>
</tr>
<tr>
<td>Kurt et al. [67]</td>
<td>20</td>
<td>Cap</td>
<td>45</td>
<td>7.3 (TTP)</td>
</tr>
</tbody>
</table>

**Table 3. Chemotherapy for brain metastases in solid tumours including MBC: Efficacy and median survival**

Abbreviations: BCNU, carmustine CA, cyclophosphamide and doxorubicin; CAF, cyclophosphamide, doxorubicin, and 5-fluorouracil; Cap, capecitabine; CDDP, cisplatin; CFP, cyclophosphamide, 5-fluorouracil, prednisone; CFPMV, cyclophosphamide, 5-fluorouracil, prednisone, methotrexate, and vincristine; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; Ifo, ifosfamide; MiVe, mitomycin and vinblastine; MVP, methotrexate, vincristine, and prednisone; OR, objective response; RT, radiotherapy; Tem, temozolomide; Topo, topotecan; TPDC-FuHu, thioguanine, procarbazine, dibromodulcitol, CCNU, 5-fluorouracil, and hydroxyurea; TTP, time to progression; Vin, vinorelbine; VP16, etoposide.
brain metastases than the control vector. Moreover, treatment with lapatinib resulted in a significant decline in size of the HER-2–transfected brain metastases [89]. Taken together, there is a basis for the assumption that lapatinib may be effective in MBC patients progressing with brain metastases during treatment with trastuzumab.

The relevance of the preclinical data was supported by the EGF100151 trial reported by Geyer et al. [90]. In this phase III trial, HER-2–overexpressing MBC patients who had progressed after treatment with anthracyclines, taxanes, and trastuzumab were included. Patients were randomized to receive either the combination of lapatinib (1,250 mg orally daily continuously) and capecitabine (2 × 1,000 mg/m² per day orally on days 1–14 every 3 weeks) or capecitabine alone (2 × 1,250 mg/m² per day orally on days 1–14 every 3 weeks). That trial showed the significant superiority of the lapatinib–capecitabine combination with regard to time to progression (8.4 versus 4.4 months), which was predefined as the primary endpoint. In addition, a more recent update indicated that the combination was also effective in reducing CNS metastasis as the first site of recurrence, [fewer cases with CNS involvement at first progression (4% versus 13%; p = .045)] [91].

Based on the preclinical and clinical evidence, the efficacy of single-agent lapatinib was evaluated in the EGF105084 trial. In this phase II trial patients received lapatinib at a dose of 750 mg twice daily [92]. At disease progression, patients could opt for a continuation of treatment with lapatinib plus capecitabine (extension trial). The trial included 241 HER-positive MBC patients who had previously been exposed to trastuzumab and had received prior radiotherapy of the CNS. A ≧50% volumetric reduction of the CNS lesions was observed in 19 of 241 (7%) patients, while a ≧20% reduction was reported in 19% of patients. The median progression-free survival time was 15.1 weeks (95% confidence interval, 12.4–15.7 weeks).

A summary of studies including tyrosine kinase inhibitors for MBC is given in Table 4.

### Table 4. TKIs for metastatic breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>TKI/schedule</th>
<th>OR (%)</th>
<th>TTP (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dennison et al. [94]</td>
<td>33</td>
<td>Gef + Doc, first-line MBC</td>
<td>39.4</td>
<td>10.9</td>
</tr>
<tr>
<td>Ciardello et al. [95]</td>
<td>41</td>
<td>Gef + Doc, first-line MBC</td>
<td>54</td>
<td>–</td>
</tr>
<tr>
<td>Gasparini et al. [96]</td>
<td>15</td>
<td>Gef + Epi, phase I</td>
<td>14.3</td>
<td>–</td>
</tr>
<tr>
<td>Baselga et al. [11]</td>
<td>31</td>
<td>Gef, pretreated MBC</td>
<td>0</td>
<td>38.7% SD &gt;6 mos</td>
</tr>
<tr>
<td>von Minckwitz et al. [84]</td>
<td>58</td>
<td>Gef, pretreated MBC</td>
<td>1.7</td>
<td>12</td>
</tr>
<tr>
<td>Catania et al. [97]</td>
<td>1</td>
<td>Erl responders (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geyer et al. [90]</td>
<td>324</td>
<td>Lap + Cap versus Cap</td>
<td>22 versus 14</td>
<td>8.4 versus 4.4 (p &lt; .05); incidence of brain metastases: 2% versus 6% (p = .045)</td>
</tr>
<tr>
<td>Cameron et al. [91] (update, Geyer et al. [90])</td>
<td>399</td>
<td>Lap + Cap versus Cap</td>
<td>Fewer cases with CNS progression; 4 versus 13; p = .045</td>
<td></td>
</tr>
<tr>
<td>MBC brain metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin et al. [92]</td>
<td>241</td>
<td>Lap</td>
<td>&lt;50% reduction in 7 patients</td>
<td>15.1 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;20% reduction in 19 patients</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Cap, capecitabine; Doc, docetaxel; Epi, epirubicin; Erl, erlotinib; Gef, gefitinib; Lap, lapatinib; MBC, metastatic breast cancer; OR, objective response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTP, time to progression.

ONGOING CLINICAL TRIALS

The results of the EGF100151 study [90] and the EGF105084 extension trial [92] strongly suggest that the combination of lapatinib and capecitabine is clinically relevant and should be investigated in more detail. This need is met by a presently ongoing trial that is being performed in...
HER-positive MBC patients previously exposed to trastuzumab and CNS radiation. In that phase II study, patients are being randomized between lapatinib plus capecitabine and lapatinib plus topotecan, and will be evaluated with regard to overall remission rate as the primary endpoint.

**OUTLOOK**

Given that almost one third of HER-2–overexpressing MBC patients will develop brain metastasis, it appears necessary to consider strategies of early diagnosis. Screening studies need to investigate whether or not routine CNS imaging of HER-2–positive MBC patients may allow a prolongation of survival. In this context, patients may receive regular CT scans or the even more sensitive contrast-enhanced MRI once a diagnosis of extracranial HER-2–positive metastasis has been established. Certainly, early diagnosis can only be helpful if adequate surgical or radiosurgical interventions are defined for treatment of isolated or oligofocal brain metastases.

A further approach may consist of the development of preventive strategies. HER-2–overexpressing breast cancer patients may be offered lapatinib-containing regimens as part of their perioperative treatment. This concept is presently being tested in the ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) Study, in which patients are being randomized to postoperative treatment with either trastuzumab, lapatinib, or a combination of both agents [93].

Also in MBC it may be worthwhile to consider an early use of lapatinib-based regimens within the framework of a preventive strategy. Given the results of the EGF100151 study, it may be assumed that the early use of lapatinib may reduce or at least postpone the occurrence of CNS metastasis [90]. Lapatinib therefore needs to be evaluated in regimens applied for first-line treatment of HER-2–positive MBC.

**AUTHOR CONTRIBUTIONS**

Administrative support: Hans-Joachim Stemmler, Volker Heinemann
Collection/assembly of data: Hans-Joachim Stemmler, Volker Heinemann
Data analysis and interpretation: Hans-Joachim Stemmler, Volker Heinemann
Manuscript writing: Hans-Joachim Stemmler, Volker Heinemann
Final approval of manuscript: Hans-Joachim Stemmler, Volker Heinemann

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