Trastuzumab treatment in patients with breast cancer and metastatic CNS disease

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Background: Patients with metastatic central nervous system (mCNS) disease progression from breast cancer have a poor prognosis and often develop associated neurological complications. Human epidermal growth factor receptor 2 (HER2)-positivity status increases the risk of developing mCNS disease. Trastuzumab is an mAb that targets HER2 and is known to extend survival across all stages of HER2-positive breast cancer.

Design: This review considers evidence from preclinical and clinical studies examining the value of continuing trastuzumab treatment in patients who develop mCNS disease. A wealth of data from clinical studies showed that trastuzumab prolonged survival in patients with mCNS disease, compared with no trastuzumab treatment, by effectively controlling their non-CNS disease. Trastuzumab has also been shown to penetrate an impaired blood–brain barrier to a limited degree, such as during radiotherapy, and intrathecal delivery of trastuzumab to the central nervous system (CNS) has shown promise. Research efforts are focussing on improving the delivery of trastuzumab to the CNS.

Conclusion: Evidence indicates that patients with mCNS disease from HER2-positive breast cancer should continue to receive trastuzumab to control HER2-positive metastases outside the CNS and receive established therapies to control the mCNS disease.

Key words: breast cancer, metastatic CNS disease, trastuzumab

introduction

Metastatic central nervous system (mCNS) disease is diagnosed in ~6% to 16% of patients with metastatic breast cancer (MBC) [1, 2]. There is no routine screening for mCNS disease in patients with breast cancer and it may, therefore, be underdiagnosed. Autopsy data indicate that up to 30% of women with breast cancer may have mCNS disease and that ~70% of the mCNS cases are not clinically diagnosed or suspected before death [3, 4]. Patients who develop mCNS disease from breast cancer have a poor prognosis, with an 1-year survival rate of ~20%, and associated neurological complications that often lead to significant morbidity and mortality [5].

Generally, mCNS disease from breast cancer develops after metastases have appeared systemically. Since most systemic anticancer treatments cannot pass through the blood–brain barrier, the central nervous system (CNS) can become a sanctuary site for tumour cells [6]. With the improvements achieved in managing systemic disease, mCNS disease is becoming an important treatment consideration for oncologists.

Standard clinical management of mCNS disease is determined by the location of the metastases within the CNS (e.g. brain or meninges). Brain metastases are generally treated using whole-brain radiotherapy (WBRT), either alone or with surgery, stereotactic radiosurgery and systemic chemotherapy [7]. Prognosis depends on performance status, visceral metastases and systemic therapy after WBRT [8, 9]. In a review of studies published from 1969 to 2000, the median survival of patients who received WBRT to treat breast cancer brain metastases ranged from 1.2 to 18 months. WBRT was significantly more effective in patients with one or a low number of CNS metastases, in patients who received WBRT after surgery and in patients who had an increased Karnofsky performance status score [10].

Meningeal carcinomatosis (MC), also known as leptomeningeal metastases, is not amenable to surgery and current therapies include focal radiotherapy, intrathecal cytotoxic therapy and systemic chemotherapy [11]. In a retrospective study of 67 patients with breast cancer treated consecutively at a single centre, i.e. chemotherapy and intrathecal therapy were shown to improve survival in those patients who developed MC [12].
Cyclophosphamide-based chemotherapy regimens are the most commonly used for mCNS disease and achieve response rates of 17%–61% [13]. Supportive care can include corticosteroids, such as dexamethasone, to manage cerebral oedema and anticonvulsants for patients who present with seizures or develop seizures during therapy [14].

Owing to the poor prognosis for patients who develop mCNS disease, research into prophylactic treatment strategies is a priority. Although prophylactic cranial irradiation has a well-recognised role in the treatment of mCNS disease in leukaemia and small-cell lung cancer, its clinical utility has yet to be determined for breast cancer [15].

An area of current focus in the treatment of mCNS disease is human epidermal growth factor receptor 2 (HER2)-positive breast cancer because retrospective studies have indicated that HER2-positive status may increase the risk of developing mCNS disease [16]. For example, a large retrospective study of 9524 patients with early breast cancer (EBC) recruited to clinical trials in the pre-trastuzumab (Herceptin®, F. Hoffmann-La Roche Ltd, Switzerland) era identified HER2 positivity as a significant predictive factor for mCNS disease development: the 10-year cumulative incidence of mCNS disease was 7% in patients with HER2-positive primary tumours compared with 3.5% in those with HER2-negative primary tumours (P < 0.01) [16]. Also, in the epidemiological registHER (registry of HER2-positive patients) study of 1009 patients with newly diagnosed HER2-positive MBC, 33% of patients had developed mCNS disease at 25-month median follow-up [17]. Of these, 7% had clinically apparent mCNS disease when MBC was initially diagnosed and 26% developed mCNS disease later as a site of disease progression.

Overall, approximately one-fifth of the women with breast cancer have HER2-positive tumours, a status associated with poor clinical prognosis [18]. Trastuzumab, a humanised anti-HER2 mAb, has redefined clinical practice for patients with HER2-positive breast cancer [19, 20]. Large-scale, randomised studies have demonstrated the clinical benefits of trastuzumab, including improvements in survival in both the EBC and MBC settings [21–24].

We present recent preclinical and clinical studies examining how trastuzumab may be enabled to cross the blood–brain barrier and the value of continuing trastuzumab treatment in patients who develop mCNS disease from breast cancer.

### Table 1. Summary of the number of mCNS disease events in the NCCTG N9831, NSABP B-31 and HERA trials [21, 23]

<table>
<thead>
<tr>
<th></th>
<th>With trastuzumab</th>
<th>Without trastuzumab</th>
<th>Hazard ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCCTG N9831 (median follow-up 1.5 years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with mCNS disease as first event (%)</td>
<td>12 (1.5)</td>
<td>4 (0.5)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>NSABP B-31 (median follow-up 2.4 years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with mCNS disease as first event (%)</td>
<td>21 (2.4)</td>
<td>11 (1.3)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>No. of patients with mCNS disease as first or subsequent event (%)</td>
<td>28 (3.2)</td>
<td>35 (4.0)</td>
<td>0.79</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>HERA (median follow-up 2 years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with mCNS disease as first event (%)</td>
<td>26 (1.5)</td>
<td>22 (1.3)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Received 1 year of trastuzumab.

mCNS, metastatic central nervous system; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; HERA, Herceptin Adjuvant; NR, not reported.

### Incidence of mCNS disease after trastuzumab treatment

Several studies have documented a relatively high incidence (24%–48%) of mCNS disease in patients with HER2-positive MBC following treatment with trastuzumab [25–28]. However, evidence indicates that this apparent increase in the prevalence of mCNS disease is a consequence of trastuzumab prolonging survival [29]. As mCNS disease tends to develop later than metastases at other sites, the observed higher incidence of mCNS disease as site of first progression with trastuzumab most likely reflects the control of HER2-positive metastases outside the CNS by trastuzumab [30].

In the HER2-positive EBC setting, major clinical studies indicate that the risk of developing mCNS disease is not increased (or decreased) with adjuvant trastuzumab therapy [21, 23]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group N9831 trials included treatment arms of either 1 year of adjuvant trastuzumab plus concurrent paclitaxel after doxorubicin/cyclophosphamide or chemotherapy alone. In a planned combined analysis of these two trials, disease-free survival [hazard ratio (HR) 0.49; P < 0.0001] and overall survival (OS) (HR 0.63; P = 0.0004) were significantly improved with the addition of trastuzumab at 3-year median follow-up [31]. In each trial, the incidence of isolated mCNS disease as the first recurrence event was higher in the trastuzumab arm than the chemotherapy-alone arm (21 versus 11 patients in B-31; 12 versus 4 patients in N9831) (Table 1) [23]. However, it is important to note that analysis of only the first events can introduce bias since the true rate of mCNS disease would be masked by rapid progression at other sites. In the NSABP B-31 trial, the overall incidence of mCNS disease events (first or subsequent) was actually lower in the trastuzumab arm than the chemotherapy-alone arm (28 versus 35 patients; HR 0.79; P = 0.35) (Table 1).

In the HERceptin Adjuvant trial, 1 year of adjuvant trastuzumab after standard neoadjuvant chemotherapy (with or without radiotherapy) significantly improved disease-free survival (HR 0.64; P < 0.0001) and OS (HR 0.66; P = 0.0115) compared with observation alone at 2-year median follow-up [21]. The occurrence of mCNS disease as the site of first event was similarly low between the two treatment arms: 1.5% in the...
trastuzumab-containing arm; 1.3% in the observation-alone arm (Table 1). Thus, even without correction for potential bias introduced by evaluating the site of first events only, there was little difference in the occurrence of mCNS disease between the treatment arms.

Evidence from retrospective analyses indicates that trastuzumab may, in some circumstances, delay the development of mCNS disease. In a large retrospective study of 280 patients with mCNS disease from HER2-positive breast cancer, those who did not receive trastuzumab had a shorter time to mCNS disease than those given trastuzumab as first-line therapy for metastases (median 2.1 versus 13.1 months; \( P = 0.0008 \)) [32].

**trastuzumab prolongs survival in patients with mCNS disease**

As shown in Table 2, a wealth of data from clinical studies provides evidence that trastuzumab therapy improves survival for patients with HER2-positive mCNS disease, compared with patients who have not received trastuzumab [17, 26, 32–40].

In a retrospective study including 36 patients with HER2-positive breast cancer who developed mCNS disease, median OS was 13 months in patients who received trastuzumab after diagnosis of mCNS disease compared with 4 months in those who did not receive trastuzumab after diagnosis and 3 months in the control group (\( n = 70 \)) with HER2-negative tumours (\( P = 0.0011 \)) [38].

A further retrospective study compared clinical outcomes of 17 patients with HER2-positive MBC, who were continuing trastuzumab following WBRT treatment of mCNS disease, with a historical control group of 36 patients with HER2-positive disease and mCNS metastases not treated with trastuzumab after WBRT [36]. Median OS was 21 months for patients receiving ongoing trastuzumab versus 9 months for those receiving ongoing chemotherapy alone and 3 months with no further treatment (\( P < 0.001 \)) (Figure 1).

Case reports have been published showing the response of mCNS disease to trastuzumab-based regimens [41–43] (Table 3).

**trastuzumab penetration of the blood–brain barrier**

Normally, the blood–brain barrier limits the access of molecules of >200 kDa to the CNS. As an 185-kDa mAb, trastuzumab is not anticipated to penetrate an intact blood–brain barrier with more than minimal infiltration into the cerebrospinal fluid (CSF) [44–46]. However, infiltration may be facilitated when the blood–brain barrier is impaired, as occurs in cases of MC or during radiotherapy for mCNS disease.

Visual evidence that trastuzumab can penetrate the blood–brain barrier has been provided by immuno-posiiton emission tomography (immuno-PET) imaging of HER2-positive tumours with radiolabelled trastuzumab [47]. Patients (\( n = 8 \)) with HER2-positive MBC received trastuzumab radiolabelled with zirconium 89 (Zr 89) followed by an immuno-PET scan on days 1–5. The subsequent images demonstrated that trastuzumab Zr 89 uptake strongly correlated with known tumour lesions in brain, lung, liver and bone; moreover, the study revealed a previously undiagnosed HER2-positive mCNS disease (the number of patients with known CNS disease was not reported) [47].

Investigation of trastuzumab levels in six patients before and after radiotherapy for mCNS disease revealed a median serum : CSF trastuzumab level of 420 : 1 (52 054 versus 124 ng/ml) before radiotherapy [46]. After completion of radiotherapy, this ratio was improved to 76 : 1 (20 158 versus 266 ng/ml) indicating that trastuzumab penetration

<table>
<thead>
<tr>
<th>Study</th>
<th>( n )</th>
<th>Disease</th>
<th>Time period</th>
<th>Median overall survival, months</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichinitser et al. [33]</td>
<td>15</td>
<td>MBC</td>
<td>Time period not reported</td>
<td>60.6</td>
<td>19.8</td>
</tr>
<tr>
<td>Lower et al. [34]</td>
<td>80</td>
<td>MBC</td>
<td>From trastuzumab initiation or MBC diagnosis</td>
<td>49.9</td>
<td>( \sim28.9^a ) ( \sim0.05 )</td>
</tr>
<tr>
<td>Pinder et al. [26]</td>
<td>292</td>
<td>MBC</td>
<td>From MBC diagnosis</td>
<td>33.5</td>
<td>29.4</td>
</tr>
<tr>
<td>Kirsch et al. [35]</td>
<td>47</td>
<td>MBC</td>
<td>From CNS diagnosis</td>
<td>( \sim26 )</td>
<td>( \sim9 ) ( \sim0.001 )</td>
</tr>
<tr>
<td>Bartsch et al. [36]</td>
<td>53</td>
<td>MBC</td>
<td>From CNS diagnosis</td>
<td>21.0</td>
<td>( 9.0^b ) and ( 3.0^c ) ( &lt;0.001 )</td>
</tr>
<tr>
<td>Brußky et al. [17]</td>
<td>332</td>
<td>MBC</td>
<td>From MBC diagnosis</td>
<td>17.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Park et al. [37]</td>
<td>78</td>
<td>MBC</td>
<td>From CNS diagnosis</td>
<td>13.6</td>
<td>5.5</td>
</tr>
<tr>
<td>Nam et al. [38]</td>
<td>56</td>
<td>MBC</td>
<td>From CNS diagnosis</td>
<td>12.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Church et al. [39]</td>
<td>26</td>
<td>MBC</td>
<td>From CNS diagnosis</td>
<td>11.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Dawood et al. [32]</td>
<td>280</td>
<td>Invasive breast cancer</td>
<td>From CNS diagnosis</td>
<td>11.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Verma et al. [40]</td>
<td>52</td>
<td>MBC</td>
<td>From CNS diagnosis</td>
<td>11.2</td>
<td>NR</td>
</tr>
</tbody>
</table>

\(^a\)Mixed population of patients with HER2-negative and -positive tumours.  
\(^b\)Patients received chemotherapy only.  
\(^c\)Patients received no systemic therapy.  
mCNS, metastatic central nervous system; MBC, metastatic breast cancer, NR, not reported; HER2, human epidermal growth factor receptor 2.
of the blood–brain barrier is facilitated by radiotherapy for mCNS disease.

In a case study of a patient with MC who received weekly trastuzumab therapy, trastuzumab levels measured a few hours after treatment were 300-fold lower in the CSF than in the serum despite a possibly impaired blood–brain barrier [45]. Conversely, in a second case study, trastuzumab treatment resulted in partial response (evaluation was done according to RECIST) of the MC [44].

**methods for delivering trastuzumab to the CNS**

The development of strategies to circumvent or alter the blood–brain barrier, allowing delivery of trastuzumab and other agents to the CNS, will further expand treatment options. Preclinical studies have provided evidence on promising methods for delivering trastuzumab to the CNS. Using a mouse model, trastuzumab was delivered locally and noninvasively through the blood–brain barrier by a magnetic resonance imaging-guided focused ultrasound disruption technique (after injection of 20 mg/kg trastuzumab and a microbubble-based ultrasound contrast agent into a tail vein; sonication of the mouse brain was carried out using a focused, piezoelectric transducer) [48].

In unsonicated tissue, the amount of trastuzumab in the brain was below a detectable level in eight of nine mice but after 0.6 or 0.8 MPa of sonication, trastuzumab levels increased to a mean of 1504 and 3257 ng/g of brain tissue, respectively, with no associated toxicity. Another study reported the use of a direct intracerebral microinfusion (ICM) technique to deliver trastuzumab directly to the CNS, in a model in which a human breast cancer cell line (MCF-7) transfected to overexpress HER2 was transplanted into the cerebellum of athymic rats [49]. The median OS of rats given trastuzumab by ICM was approximately twice as long as those given trastuzumab systemically; 52 versus 27 days (P = 0.009). In two of the nine rats given trastuzumab by ICM, there was no evidence of a tumour for >120 days.

Preliminary data from case reports investigating intrathecal delivery of trastuzumab have also been promising [50–54] (Table 4). The reports indicate that intrathecal delivery of trastuzumab is feasible and tolerable for patients with MC from breast cancer.

**evolving strategies for treating HER2-positive breast cancer**

A number of new agents are involved in clinical trials focussing on HER2-positive breast cancer. However, only the small-molecule tyrosine kinase inhibitor lapatinib (Tykerb®/Tyverb®, Glaxosmithkline, UK)—which targets HER1 and HER2—has been evaluated for activity in patients with mCNS disease from HER2-positive breast cancer. Other anti-HER2 mAbs under clinical evaluation are pertuzumab, which targets both HER1 and HER2; ertumaxomab (Rexomun®, Fresenius Biotech), which targets HER2 and CD3; 2B1, which targets the HER2 and FcgRII extracellular domains; MDX-H210, which targets HER2 and FcgRI and the recombinant antibody toxin ScFv(FRP5)-ETA, which binds to HER2. However, none of these antibodies has yet been evaluated in patients with mCNS disease from HER2-positive breast cancer.

The pivotal lapatinib trial (EGF100151), evaluating lapatinib plus capecitabine (Xeloda®, F. Hoffmann-La Roche Ltd, Switzerland) versus capecitabine alone in patients with disease progression following prior trastuzumab-based therapy, was not designed to investigate sites of disease progression. None the less, an exploratory analysis showed a lower incidence of first progression at CNS sites in the lapatinib plus capecitabine
Table 4. Case reports evaluating intrathecal delivery of trastuzumab in MC from breast cancer

<table>
<thead>
<tr>
<th>Case reports</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient with symptomatic MC and stabilised neurological symptoms [50]</td>
<td>● Intrathecal methotrexate</td>
<td>● No benefit</td>
</tr>
<tr>
<td></td>
<td>● Three intrathecal trastuzumab doses over 2 weeks</td>
<td>● Intrathecal trastuzumab well tolerated; neurological stability achieved for 30 days (alternate-day dexamethasone also administered over this period); 6 weeks later, left-hand weakness occurred</td>
</tr>
<tr>
<td></td>
<td>○ 5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ 10 mg+ thiopeta</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ 20 mg + intrathecal methotrexane, systemic trastuzumab and paclitaxel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Fourth intrathecal trastuzumab dose (20 mg) + thiopeta</td>
<td></td>
</tr>
<tr>
<td>Patient with MC and neurological symptoms [53]</td>
<td>● Five intrathecal trastuzumab doses</td>
<td>● Patient died of progressive paralysis and respiratory arrest soon after</td>
</tr>
<tr>
<td></td>
<td>○ Four escalating doses of 5–20 mg over 2 weeks</td>
<td>● All intrathecal trastuzumab doses well tolerated; within 2 weeks from last dose, neurological symptoms improved</td>
</tr>
<tr>
<td></td>
<td>○ One dose 3 weeks later</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Systemic trastuzumab + capecitabine q3w continued</td>
<td></td>
</tr>
<tr>
<td>Patient with MC and neurological symptoms [54]</td>
<td>● Intrathecal methotrexate and trastuzumab (20 mg) repeated at 3–6 day intervals (four doses in total)</td>
<td>● All intrathecal doses were well tolerated</td>
</tr>
<tr>
<td>Patient with MC [52]</td>
<td>● Intrathecal methotrexate and cytarabine + WBRT</td>
<td>● CSF tumour cell count remained low for 11 months from first diagnosis of MC; progression of meningeal and cerebral disease occurred 11 months after first diagnosis of MC</td>
</tr>
<tr>
<td></td>
<td>● Intrathecal trastuzumab qw</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Six injections of 25 mg/body</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Intrathecal trastuzumab qw continued</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Twenty-four injections of 25 mg/body over 6 months</td>
<td></td>
</tr>
<tr>
<td>Patient with MC and elevated CSF protein level and malignant cell count [51]</td>
<td>● High-dose methotrexate</td>
<td>● Rapid progression of lung and liver visceral metastases soon after remission was confirmed and patient died</td>
</tr>
<tr>
<td></td>
<td>● Intrathecal trastuzumab qw</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ 20 mg starting dose increased to 25 mg because of good tolerance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Systemic trastuzumab + paclitaxel also given</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Intrathecal trastuzumab qw continued</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Paclitaxel replaced with doxo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Intrathecal trastuzumab qw and systemic trastuzumab continued</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Dooxo stopped</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Prednisone + thiopeta given</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● All trastuzum stopped</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Letrozole-based therapy initiated</td>
<td></td>
</tr>
</tbody>
</table>

MC, meningeal carcinomatosis; q3w, 3 weekly; CSF, cerebrospinal fluid; WBRT, whole-brain radiotherapy; qw, weekly; doxo, liposomal doxorubicin.

arm (4 versus 13 patients in the capcitabine-alone arm) [55]. However, the numbers were small and only the first progression event was reported, not the overall incidence of mCNS disease, which would be the appropriate measure.

After enrolment for the EGF100151 trial stopped, the Lapatinib Expanded Access Programme and French Authorisation Temporaire d’Utilisation studies were initiated to further investigate lapatinib plus capcitabine for patients with HER2-positive breast cancer following prior taxane, anthracycline and trastuzumab therapy [56]. Exploratory results from 138 patients in these studies who developed brain metastases demonstrated an overall response rate of 18% in the CNS.

Two phase II trials (EGF105084 and NCI-6969) were designed to investigate the potential effect of lapatinib monotherapy in patients with mCNS disease from HER2-positive breast cancer after prior trastuzumab-based therapy [57–59]. However, both trials failed to meet their primary end points and were prematurely terminated. In EGF105084, 241 patients with mCNS disease, who had received prior...
trastuzumab-based treatment and WBRT, were given lapatinib monotherapy [60]. The CNS response rate (by composite criteria including volumetric reduction in tumour volume of 50%) of these patients was low, at 6%. As neurological signs and symptoms frequently accompany CNS metastases, a subgroup analysis of patients with these symptoms (n = 205) was carried out to assess if any changes were predictive of clinical benefit [61]. An improvement in symptoms was shown to be associated with a decrease in volume of CNS metastases: 17% of patients had a volume decrease of 0%–20% and 24% had a volume decrease ≥20%. An extension phase to this trial evaluated the addition of capecitabine to lapatinib in 51 patients with mCNS disease progression on lapatinib alone [58]. CNS responses (by composite criteria including volumetric reduction in tumour volume of 50%) occurred in 20% of these patients. This most likely reflects the efficacy of capecitabine against mCNS disease. The NCI-6969 trial evaluated lapatinib monotherapy for 39 patients who had previously received trastuzumab-based treatment and also had a low CNS response rate (by RECIST) of 3% [59]. It should be noted that since patients in both trials had previously received trastuzumab-based treatment, and there was no information on the treatment-free interval between radiotherapy, trastuzumab and lapatinib, it is not clear if prior treatment may have influenced the observed responses.

In the EGF105084 and NCI-6969 trials, the CNS response rates with lapatinib were modest (<10%) compared with other treatments for mCNS disease (Figure 2) [57–59, 62–69]. For example, in a phase I/II trial, patients (n = 75) with mCNS disease derived from solid tumours, including primary breast cancer, received WBRT plus topotecan (Hycaatin®, Glaxosmithkline, UK) resulting in a CNS response rate of 72% [63]. In two smaller studies evaluating patients with mCNS disease from breast cancer, the CNS response rate was 43% for capecitabine monotherapy [62] and 38% for topotecan monotherapy [64]. It should be noted that lapatinib has potential drug–drug interactions with some standard palliative medications for symptomatic mCNS disease, including corticosteroids and anticonvulsants.

Preclinical data have shown that CNS concentrations of lapatinib are low in healthy animals due to the action of blood–brain barrier efflux transporters [70]. However, high doses of lapatinib can inhibit efflux transporters, which may allow drug accumulation after repeated dosing [70, 71]. It is possible that, like trastuzumab, lapatinib may have some limited delivery into the CNS in patients with HER2-positive MBC [72]. In the NCI-6969 trial, 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography scan data showed substantially fewer responses to lapatinib monotherapy in the brain than in the body (7% versus 57% metabolic partial response at 8 weeks after lapatinib initiation). This indicated that the delivery of lapatinib to the CNS was limited [72]. Currently, there are no clinical data available on the pharmacokinetics of lapatinib within the CNS.

### conclusions

A wealth of data from clinical studies has provided evidence that trastuzumab extends survival in patients with HER2-positive MBC and mCNS disease progression by effectively controlling their non-CNS disease. These data indicate that women who develop mCNS disease should continue to receive trastuzumab to control HER2-positive metastases outside the CNS and receive established therapies to control their mCNS disease. The small-molecule tyrosine kinase inhibitor lapatinib may be a viable treatment option for some patients with HER2-positive mCNS disease though at present supporting data are limited to response rates, not survival data.

It is now known that under certain conditions, such as during radiotherapy for mCNS disease, trastuzumab can cross the blood–brain barrier. Intrathecal trastuzumab treatment is currently being investigated and case reports indicate that this is a promising experimental treatment of patients with symptomatic MC from HER2-positive breast cancer.

The future is clearly not bleak for patients with HER2-positive breast cancer and mCNS disease. Trastuzumab has already been shown to improve survival and research efforts are now focussing on direct delivery of trastuzumab-based therapies to the CNS, modification of blood–brain barrier...
permeability to facilitate systemic drug transfer and development of new targeted therapies.

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references


