Systemic treatment of brain metastases in HER2-positive breast cancer: current status and future directions

Hamdy A Azim1 & Hatem A Azim Jr*
1Department of Clinical Oncology, Cairo University Hospital, Cairo, Egypt
*Author for correspondence: Breast Cancer Translational Research Laboratory – J.C. Heuson, Institut Jules Bordet, Boulevard de Waterloo, 125, 1000 Brussels, Belgium • Tel.: +32 2 541 3356 • Fax: +32 2 541 3339
hatem.azim@bordet.be

In recent years, brain metastases have emerged as a main challenge affecting the morbidity and mortality of patients with HER2-positive metastatic breast cancer. In the era following trastuzumab, approximately 30% of these patients develop brain metastases. Trastuzumab does not cross the blood–brain barrier, hence its role is limited to controlling extra-CNS metastases. Lapatinib emerged as a potential candidate; however, its use as a single agent was associated with modest responses. Combination with capecitabine was associated with good results, particularly in patients with newly diagnosed brain metastases. In this article, we discuss the role of trastuzumab and lapatinib in patients with HER2-positive breast cancer with brain metastases. We also highlight the complex structure of the blood–brain barrier and elucidate different potential strategies that could be useful in improving drug delivery.

Breast cancer (BC) is the second most common source of brain metastases (BM), being only preceded by lung cancer [1]. The incidence of BM among patients with advanced BC is approximately 10–15% [2,3] and reaches up to 30% in autopsy studies [4]. Although treatment by whole-brain radiotherapy (WBRT) is associated with tumor regression and clinical improvement in the majority of patients, these responses are classically short-lived, ranging from 3 to 6 months [5]. Historically, this was not a major challenge as progression in other visceral sites was the dominant source of mortality and thus, the development of novel strategies to manage BM was not considered of high priority. However, the introduction of novel chemotherapeutics and targeted agents has substantially prolonged survival of patients with metastatic disease, despite the fact that they have limited efficacy in dealing with BM. Therefore, there is a real concern that the incidence of BM will be more frequently encountered – given the improvement in survival – particularly in HER2-positive patients. Hence, BM could considerably impact survival at a time when many of these patients have extra-CNS disease control. In this article, we describe the different available systemic treatment strategies in managing BM in patients with HER2-positive BC. We also elaborate on potential approaches that we believe hold some promise in improving outcomes of such patients in the years to come.

BM & its relation to HER2 expression
Several groups, including ours, have shown a higher predisposition of BM in patients with HER2-positive BC [6–9]. However, in our opinion, the most convincing evidence comes from a large study involving 3726 patients with early-stage BC, who were followed for 15 years, in which patients with HER2-enriched BC 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 BC, respectively [8]. This has also been observed in preclinical models. HER2 overexpression was found to increase the metastatic outgrowth of BC cells in the brain, suggesting that HER2-positive BC cells have a great affinity to colonize in the brain compared with HER2-negative cells [10]. However, the reason behind such predisposition is not very clear. Some have suggested a potential role for certain chemokines, such as CXCR4, which is upregulated in HER2-positive tumors and was shown to facilitate the invasion of cancer cells into the brain by increasing the permeability of brain endothelial cells [11]. However, other studies have also linked CXCR4 expression with metastasis to other sites and not necessarily to the brain [12,13]. Hence, the potential role of chemokines in BM remains speculative and requires further validation.

Keywords
blood–brain barrier • brain metastases • HER2-positive breast cancer • lapatinib • trastuzumab

For reprint orders, please contact: Hatem A Azim Jr, Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Boulevard de Waterloo, 125, 1000 Brussels, Belgium.

In recent years, brain metastases have emerged as a main challenge affecting the morbidity and mortality of patients with HER2-positive metastatic breast cancer. In the era following trastuzumab, approximately 30% of these patients develop brain metastases. Trastuzumab does not cross the blood–brain barrier, hence its role is limited to controlling extra-CNS metastases. Lapatinib emerged as a potential candidate; however, its use as a single agent was associated with modest responses. Combination with capecitabine was associated with good results, particularly in patients with newly diagnosed brain metastases. In this article, we discuss the role of trastuzumab and lapatinib in patients with HER2-positive breast cancer with brain metastases. We also highlight the complex structure of the blood–brain barrier and elucidate different potential strategies that could be useful in improving drug delivery.

Breast cancer (BC) is the second most common source of brain metastases (BM), being only preceded by lung cancer [1]. The incidence of BM among patients with advanced BC is approximately 10–15% [2,3] and reaches up to 30% in autopsy studies [4]. Although treatment by whole-brain radiotherapy (WBRT) is associated with tumor regression and clinical improvement in the majority of patients, these responses are classically short-lived, ranging from 3 to 6 months [5]. Historically, this was not a major challenge as progression in other visceral sites was the dominant source of mortality and thus, the development of novel strategies to manage BM was not considered of high priority. However, the introduction of novel chemotherapeutics and targeted agents has substantially prolonged survival of patients with metastatic disease, despite the fact that they have limited efficacy in dealing with BM. Therefore, there is a real concern that the incidence of BM will be more frequently encountered – given the improvement in survival – particularly in HER2-positive patients. Hence, BM could considerably impact survival at a time when many of these patients have extra-CNS disease control. In this article, we describe the different available systemic treatment strategies in managing BM in patients with HER2-positive BC. We also elaborate on potential approaches that we believe hold some promise in improving outcomes of such patients in the years to come.

BM & its relation to HER2 expression
Several groups, including ours, have shown a higher predisposition of BM in patients with HER2-positive BC [6–9]. However, in our opinion, the most convincing evidence comes from a large study involving 3726 patients with early-stage BC, who were followed for 15 years, in which patients with HER2-enriched BC 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 BC, respectively [8]. This has also been observed in preclinical models. HER2 overexpression was found to increase the metastatic outgrowth of BC cells in the brain, suggesting that HER2-positive BC cells have a great affinity to colonize in the brain compared with HER2-negative cells [10]. However, the reason behind such predisposition is not very clear. Some have suggested a potential role for certain chemokines, such as CXCR4, which is upregulated in HER2-positive tumors and was shown to facilitate the invasion of cancer cells into the brain by increasing the permeability of brain endothelial cells [11]. However, other studies have also linked CXCR4 expression with metastasis to other sites and not necessarily to the brain [12,13]. Hence, the potential role of chemokines in BM remains speculative and requires further validation.

Keywords
blood–brain barrier • brain metastases • HER2-positive breast cancer • lapatinib • trastuzumab

For reprint orders, please contact: Hatem A Azim Jr, Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Boulevard de Waterloo, 125, 1000 Brussels, Belgium.
Trastuzumab & the risk of BM

With the establishment of trastuzumab as a standard therapy for managing patients in metastatic BC [14], the problem of BM has become more clinically evident. Given that trastuzumab resulted in an improvement in survival and BM typically develops later in the disease course [15], there has been an apparent increase in the incidence of BM with approximately 30% of patients treated with trastuzumab developing BM [16–18]. The combination of a tumor type that has a high potential for CNS spread and a treatment that improves clinical outcomes, but with limited CNS penetration – owing to its large molecular weight (~145 kDa) – has resulted in observing this apparent increase in BM [19].

A literature-based meta-analysis of six large Phase III clinical trials has recently addressed this question in the adjuvant setting [20]. The results showed that CNS metastases were significantly increased in the trastuzumab-containing treatment arms compared with the nontrastuzumab-containing arms (odds ratio: 1.57; 95% CI: 1.08–2.3; p = 0.018). Furthermore, trastuzumab treatment was associated with a higher incidence of the brain being the first site of relapse. In the HERA, NCCTG N9831 and NSABP B-31 trials, the incidence was marginally higher in the trastuzumab arm (26% [2%] vs 22 [1%], 12 [1.5%] vs 4 [0.5%] and 21 [2.4%] vs 11 [1.7%] patients, respectively) [21,22]. Data from a large population-based study involving 1458 patients further confirmed that the brain is more frequently the first site of relapse in patients treated with trastuzumab, whether in the adjuvant or metastatic setting [6].

Is there a role for trastuzumab in managing HER2-positive breast cancer with BM?

Given its limited ability to cross the blood–brain barrier (BBB), it is plausible to suppose that trastuzumab has a limited role in patients with established BM. However, this does not appear to be entirely true. To gain more insight, Dawood et al. have recently reported the outcome of 223 patients with BC and BM who received WBRT [23]. Patients were grouped into three groups; estrogen receptor-positive/HER2-negative (30.2%), HER2-positive (45.5%) and triple-negative (24.3%) BC. All three groups were treated with routine systemic therapy following WBRT, including trastuzumab in all patients with HER2-positive disease. Median survival was found to be significantly longer in the HER2-positive group compared with the two other groups (9 vs 5 vs 5 months, respectively; p = 0.006). In the multivariate model, the HER2-positive group had a significant (37%) reduction in the risk of death compared with the other groups. The same results were recently reported by other groups as well [24,25]. This highlights that trastuzumab improves the prognosis of these patients.

To understand the role of trastuzumab within patients with HER2-positive BM, Brufsky et al. have recently published the results of the first and only prospective study addressing the role of trastuzumab in these patients [16]. This observational study included 1023 newly diagnosed metastatic BC patients, of whom 377 (37%) developed CNS metastasis at a median time of approximately 1 year after developing metastatic disease. Following the development of CNS metastasis, 71, 69 and 68% received radiotherapy, chemotherapy and trastuzumab, respectively. In a multivariate model, the latter two were significantly associated with overall survival (hazard ratio: 0.64; 95% CI: 0.48–0.85; p = 0.002 for chemotherapy and hazard ratio: 0.33; 95% CI: 0.25–0.46; p < 0.001 for trastuzumab). Surgery and radiotherapy were not significantly associated with survival in this study. This confirms the results of several older retrospective studies that addressed the same question [26–33]. The later ones, however, suffered some limitations being retrospective and small in size. In addition, inconsistency was observed in the way overall survival was calculated. Some of these studies dated survival from the date of metastasis development [26,33] while others used the date of BM development [27–32]. We believe the latter method better reflects the potential role of trastuzumab in these patients (Table 1). However, it should be noted that the later method could be a subject of lead-time bias, as imaging screening for asymptomatic BM is widely adopted nowadays, despite the lack of evidence to support an impact on patient outcome.

Understanding the magnitude of benefit of lapatinib in BM

Lapatinib was approved in the metastatic setting following the results of a pivotal trial showing an improvement in response rate and progression-free survival to its combination with capecitabine compared with capecitabine alone [34,35]. In this study, the CNS, as the site of first progression, was reported in 13 women treated
with capecitabine and four patients treated with the combination (p = 0.045). Despite the low number of events, such observation was met with considerable interest. This was running in line with preclinical experiments that showed that lapatinib inhibits colonization of brain-seeking HER2-positive BC cell lines and decreases the amount of phosphorylated HER2 in established BM [36]. In addition, acknowledging that lapatinib – unlike trastuzumab – is a small molecule (~1 kDa) with a higher potential to cross the BBB, further suggested that lapatinib is the drug that would overcome the limitations of trastuzumab in this setting.

To unveil the role of lapatinib in BM, Lin and colleagues reported the results of two Phase II studies in which lapatinib at 1500 mg/day was given to patients with progressive BM following trastuzumab and WBRT [37,38]. The first study included 39 patients while the second included 242 patients. Both studies had a similar design and eligibility criteria, with CNS response being the primary end point. However, they differed in the way that response was assessed. In the first study, CNS response was assessed using the response evaluation criteria in solid tumors (RECIST) with partial response defined as ≥30% decrease in size using MRI. In the second study, they used a cutoff of 50% in volumetric reduction of brain lesions on MRI to define partial response. However, in both studies, lapatinib showed modest efficacy with objective responses reported in 2 and 6% of patients, respectively, using the formerly mentioned criteria. Minor responses were reported in a further 18 and 21% of patients, respectively. Interestingly, responding patients (including minor responses) had an improved time-to-progression compared to nonresponding patients. This highlighted that lapatinib could have some activity, yet the results remain below expectations and certainly do not encourage its administration as a single agent against BM.

Combining lapatinib with chemotherapeutics that have the potential for crossing the BBB and with known activity in BC appears to be a more attractive approach as it could potentially augment the activity of lapatinib against BM. To the best of our knowledge, apart from capecitabine, only topotecan was tested in combination with lapatinib in this setting, with no responses and severe toxicity that resulted in study closure [39]. In fact, capecitabine emerged as a good candidate to combine with lapatinib given its established role in metastatic BC, as well as its potential activity against BM [40,41]. The studies that have explored the combination of lapatinib and capecitabine in this setting are summarized in Table 2 [38,39,42–45]. The studies are generally small in size, ranging from 13 to 138 patients. In nearly all studies, 85–100% of patients received prior trastuzumab and WBRT. CNS response ranged from 20 to 30%, which appears to be an improvement over responses observed with lapatinib alone.

Only one study addressed the role of the capecitabine and lapatinib combination prior to WBRT [45]. In this study, 45 patients with newly diagnosed BM were enrolled, of which 36 (80%) patients had two or more BM and 42 (93%) patients received prior trastuzumab. This study showed an impressive (67%) CNS response rate, defined as 50% volumetric reduction of CNS lesions. Median time to progression was 5.5 months (95% CI: 3.9–5.9) and median time to whole-brain irradiation was 8.3 months (95% CI: 5.1–11.7). Several points could be drawn from the results obtained in this study: first, it demonstrates, clearly, the synergy and additive effect of lapatinib and capecitabine in BM. The higher response rate compared with the other studies could be justified by the fact that these patients are less refractory, being newly diagnosed with BM on initiation of therapy. Also, it opens the door for adopting effective systemic strategies that could potentially delay cardiac toxicity.
the need for WBRT. Combining lapatinib or its combination with capecitabine with WBRT could also be an appealing approach. However, careful safety consideration regarding dosing during WBRT should be made. In this regard, a recent Phase I study combined lapatinib at different doses with WBRT [46]. Lapatinib, at a dose of 1250 mg/day, was the maximum tolerated dose and a total of 24 patients received the drug at this dose in combination with WBRT. Approximately 21% of patients experienced a dose-limiting toxicity (n = 5) including two patients who developed a pulmonary embolism. The combination was associated with 83% CNS response at least 8 weeks following WBRT. However, the combination did not meet the predefined criteria for feasibility for safety reasons.

**Novel strategies**

**Targeting the BBB**

The main challenge in managing BM remains in the limited ability of most of – if not all – the investigated agents to cross the BBB. Figure 1 illustrates a simplified diagram of the BBB. Being an almost impermeable structure, it limits the free diffusion of polar solutes allowing only particles with a diameter less than 20 nm to cross to the brain [47]. In addition, it expresses a wide variety of active efflux transporters that further restrict drug access to the brain. This includes p-glycoprotein (P-gp), BC resistance protein, multidrug resistance-associated proteins and organic anion transporter 3 [48]. Furthermore, the endothelial cells within the BBB are equipped with a limited array of transport systems that supply the brain with nutrients, but also eliminate byproducts of brain metabolism [47]. Taken together, these characteristics provide an effective protective shield against not only the high-molecular weight agents, but also small molecules.

On the other hand, the observed contrast enhancement of metastases on computed tomography and MRI would suggest that the BBB is at least partially disrupted in metastasis. It has been shown that, as a result of a macroscopic brain tumor (>4 mm), the tight junctions between the endothelial cells become stretched out with evident formation of gaps, which leads to increased vascular permeability [49]. This altered structure of the BBB is termed the blood–brain tumor barrier (BTB), which also includes the microvessels supplying brain tumors [49]. To gain more insight into the permeability of the BTB in relation to the BBB, Lockman et al. found that the uptake of paclitaxel and doxorubicin in BM was significantly greater than normal brain tissue, but it was less than 15% of that of other metastases [50]. The drug concentrations within the BM showed significant heterogeneity and only reached cytotoxic levels in a small subset (~10%). More interestingly, neither drug could significantly decrease BM in HER2-positive BC, suggesting that the BBB/BTB is less disrupted in this subtype [50]. This could possibly be related to the relatively high expression of P-gp at the BBB in patients with HER2-positive metastatic BC, compared with those

### Table 2. Studies combining lapatinib and capecitabine in patients with HER2-positive metastatic breast cancer with brain metastases.

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Prior RTH (%)</th>
<th>Definition of CNS response</th>
<th>CNS response (%)</th>
<th>Brain TTP (median in months)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boccardo et al. (2008)</td>
<td>138</td>
<td>NS</td>
<td>RECIST</td>
<td>18</td>
<td>NR</td>
<td>[42]</td>
</tr>
<tr>
<td>Lin et al. (2009)</td>
<td>50</td>
<td>100</td>
<td>≥50% volumetric reduction</td>
<td>20</td>
<td>3.65</td>
<td>[38]</td>
</tr>
<tr>
<td>Sutherland et al. (2010)</td>
<td>34</td>
<td>94</td>
<td>RECIST</td>
<td>21</td>
<td>5.5</td>
<td>[43]</td>
</tr>
<tr>
<td>Metro et al. (2011)</td>
<td>22</td>
<td>86.7†</td>
<td>WHO criteria</td>
<td>31.8</td>
<td>5.6</td>
<td>[44]</td>
</tr>
<tr>
<td>Lin et al. (2011)</td>
<td>13</td>
<td>100</td>
<td>≥50% volumetric reduction</td>
<td>38</td>
<td>NR</td>
<td>[39]</td>
</tr>
<tr>
<td>Bachelot et al. (2011)</td>
<td>45</td>
<td>0</td>
<td>≥50% volumetric reduction</td>
<td>67</td>
<td>5.5</td>
<td>[45]</td>
</tr>
</tbody>
</table>

†A subgroup analysis of centers enrolled in Boccardo et al. [42].

Radiotherapy and/or stereotactic radiosurgery and/or surgery.

NR: Not reported; NS: Not specified; RECIST: Response evaluation criteria in solid tumors; RTH: Radiotherapy; TTP: Time-to-progression.
with other BC subtypes [51]. Thus, while BTB is more permissive than the BBB, it remains a significant impediment to standard chemotherapy, particularly in HER2-positive BC.

Having elucidated the principle physiological aspects of the BBB and the BTB, we will highlight three potential strategies that would possibly overcome the resistance observed at the BBB and the BTB levels in the following section.

**Increasing the BTB permeability**

The difference in vascularity between the BBB and the BTB may provide a therapeutic window where certain drugs can selectively increase the permeability in brain tumor capillaries, without causing a significant change in normal brain capillaries permeability, thereby enhancing drug delivery to brain tumors while sparing the normal brain parenchyma.

**cGMP** is an important intracellular secondary messenger that has been implicated in the regulation of vascular permeability and is selectively degraded by phosphodiesterases enzyme (PDE) [52,53]. Thus, inhibition of PDE activity, would subsequently lead to intracellular cGMP accumulation, which may result in increased capillary permeability, including microvessels in brain tumors. Sildenafil (Viagra®) and vardenafil (Levitra®) are selective inhibitors of type 5 PDE (PDE5) [54] and are approved for erectile dysfunction in men. In a brain tumor-bearing animal model, vardenafil and sildenafil selectively increased BTB permeability and enhanced antitumor efficacy of doxorubicin [55]. In this study, rats treated with doxorubicin in combination with vardenafil survived significantly longer than rats treated with doxorubicin alone [55]. While this study was conducted in glioblastoma-bearing mice, it also provides proof of concept that could be explored in BM models. To address the latter point, the same group examined the effect of PDE5 inhibitors in nude mice on the delivery of trastuzumab to intracranially implanted human HER2-positive BC [56]. This was preceded by an in vivo study to check the permeability of trastuzumab through the BTB. Interestingly, the administration of vardenafil doubled the uptake of trastuzumab (p < 0.01) and their coadministration significantly improved survival compared with administration of each drug alone (p < 0.01).

On the other hand, Ding et al. have reported that vardenafil can also block the drug efflux function of P-gp and increase the intracellular accumulation of paclitaxel [57]. Collectively, these preclinical models highlight the potential of developing strategies incorporating PDE5 inhibitors.

**Maximizing drug influx**

P-gp (encoding the gene **ABCB1**) is the most important mediator of multidrug resistance and is responsible for chemotherapeutic drug resistance to a wide variety of agents active in BC, including vinca-alkaloids, anthracyclines, taxanes and lapatinib [58]. Developing drugs that target P-gp, or efflux pump inhibitors in general, have been extensively explored. The discussion of this topic is beyond the scope of this article, but the results were generally disappointing [59–61].

P-gp is involved in the efflux of lapatinib at the BBB, yet the latter has been implicated in inhibiting the function of several transporters by binding to their ATP-binding sites [62]. In experimental models, lapatinib reversed P-gp, and strongly enhanced the effect of paclitaxel and liposomal doxorubicin on the inhibition of growth of the **ABCBI**-overexpressing cancer cells [62]. These findings may suggest that the use of lapatinib in combination with chemotherapy is a more rational approach compared with its monotherapy use, as demonstrated earlier with capecitabine [38]. De Azambuja and colleagues recently reported the results of a Phase I study involving 17 patients...
who were treated with lapatinib in combination with temozolomide [63]. The latter is known to cross the BBB and is effective against primary brain tumors [64], with few small reports showing potential activity when given to treat BM, particularly with WBRT [65–67]. The study showed that both drugs can be combined at a dose of 1500 mg/day for lapatinib and 200 mg/day day 1–5 for temozolamide with acceptable toxicity. However, the study suffered slow accrual and responses were seldom reported. Nearly all patients were pretreated with anthracyclines, taxanes, trastuzumab and WBRT. In addition, 50% were also pretreated with lapatinib. The median time to progression was 2.7 months and median survival was 10.9 months. Another interesting combination could be with pegylated liposomal doxorubicin (Caelyx®) given its higher penetration of the BBB, which is 10–30-fold higher than doxorubicin [68]. Currently, this combination is being explored in the Phase II setting [101].

**Manipulate the drug formulation**

Another attractive approach is to utilize the specific transporters that are localized within the brain capillary endothelium that mediate endogenous substrate transport from the circulation into the brain. Among these transporters, LRP-1 has been reported to possess the ability to mediate effective transport of ligands across endothelial cells of the BBB (Figure 2) [69]. This receptor is involved in BBB transcytosis of several proteins and peptides. Importantly, LRP-1 is highly expressed at the BBB [70] and is also upregulated in brain tumors [71]. Angiopep-2 is a 19-amino acid peptide that was developed to bind to LRP-1 receptors at the BBB, with enhanced transcytosis capacity. Hence, angiopep could be used as a peptide-based delivery technology that provides a platform for transporting drugs into the brain [72]. In other words, it could ferry the chemotherapeutic drugs via the LRP.

**Figure 2. A simplified schematic layout of the molecular composition of the blood–brain barrier.** (A & B) The cerebrovascular endothelium, in addition to restricting passive diffusion for polar solutes, also expresses a wide variety of active efflux transporters, which further restrict drug access to the brain. Transporters that are localized on the apical (luminal) side of the brain capillary endothelium restrict brain uptake of drugs, while transporters at the abluminal side enhance the extrusion of drugs from the brain. (C) The blood–brain barrier endothelial cells are characteristically equipped with a limited array of transport systems that supplies the brain with nutrients and eliminates byproducts of brain metabolism. Among these transporters, LRP-1 has been reported to possess the ability to mediate effective transport of endogenous larger molecules. Ligands on the luminal side of the endothelium, are endocytosed and transported across the cell for release into the brain parenchyma at the abluminal side.

BCRP: Breast cancer resistance protein; Oatp: Organic anion ‑transporting polypeptide; MRP: Multidrug resistance‑associated protein; P‑gp: P‑glycoprotein.
three molecules of paclitaxel linked to angiopep-2. Preclinical studies in BC BM demonstrated that the brain’s uptake of ANG1005 is up to 54-times that of paclitaxel [73]. Recently, a Phase I trial was presented testing ANG1005 in 48 patients with heavily pretreated BM [74]. Overall disease control, including responses plus stable disease, was achieved in 71% of patients. Median time to progression was 18 weeks in responders (standard deviation). The drug was well tolerated and no CNS toxicity was observed, with thrombocytopenia being the dose-limiting toxicity. It is not possible to draw conclusions on the role of this drug in HER2-positive BM from this study as it was a Phase I study and enrolled different types of solid tumors. However, the biological rationale and preliminary safety and efficacy data warrant further evaluation in the Phase II setting, focusing on a more homogenous patient population.

**Future perspective**

Currently, several strategies exist for managing patients with BM secondary to HER2-positive BC; however, the results remain unsatisfactory. WBRT remains the standard of care, yet we aim to identify strategies that would prolong CNS response beyond that achieved by radiation. We believe that patients who are sensitive to trastuzumab should still be offered the drug even with developing BM, despite its poor crossing to the brain. Recently, Chargari and colleagues have combined trastuzumab with WBRT in 31 patients with very good tolerance, and an interesting 74.2% response rate with complete responses in 19% [75]. Median time-to-progression and survival was 10 and 18 months, respectively. The validation of these results in a randomized trial would elucidate the magnitude of benefit of such an approach compared with WBRT alone. In patients who have already received WBRT, combining trastuzumab to lapatinib and capecitabine could be an interesting strategy that is worth exploring. Currently, we have evidence that the combination of trastuzumab and lapatinib improves survival compared with lapatinib alone even in patients with trastuzumab refractory disease [76]. However, we have no data on adding capecitabine to the combination. Such a combination could be effective against BM as well as maintaining an adequate extra-CNS control. Yet, careful consideration should be made regarding the doses of lapatinib and capecitabine used in the triplet combination, and should be investigated in a Phase I/II setting. Another strategy for trastuzumab-sensitive patients is giving the drug in the combination with PDE5 inhibitors. Such combination was associated with better drug delivery in the preclinical setting but we are not aware of any ongoing clinical trials with this strategy.

In patients refractory to WBRT and trastuzumab, offering lapatinib in combination with capecitabine is the current standard of care; however, responses remain short-lived. In this setting, one would argue that combining lapatinib and capecitabine with upfront WBRT could be an interesting approach, although recent safety consideration emerged when lapatinib was combined with WBRT at a dose of 1250 mg. Investigating the transporters at the BBB emerges as a very interesting approach that is worth exploring, perhaps in combination with lapatinib.

**Financial & competing interests disclosure**

HA Azim is on the speaking bureau and advisory board of Roche and GlaxoSmithKline. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.
References

45. Bachelor TD, Romieu G, Campone M et al. LANDSCAPE: an FNCLCC Phase II study with lapatinib (L) and capecitabine (C) in patients with brain metastases (BM) from HER2-positive (L+2) metastatic breast cancer (MBC) before whole-brain radiotherapy (WBRT). Presented at: 2011 ASCO Annual Meeting. Chicago, IL, USA, 4–8 June 2011.


Website
