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Systemic Treatment Options for HER2-Positive Breast Cancer Patients with Brain Metastases beyond Trastuzumab: A Literature Review

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Keywords

Brain metastases · Breast cancer · HER2 · Therapy resistance

Summary

Background: The incidence of brain metastases (BM) in breast cancer patients has increased. Many retrospective analyses have shown that first-line treatment with trastuzumab prolongs survival in patients with HER2-positive BM. In contrast, the evidence for other therapies targeting HER2 for patients with BM is rare. **Methods:** The aim of this review is to update the reader about current systemic treatment options in patients with HER2-positive metastatic breast cancer with BM who had already received trastuzumab. A literature search was performed in the PubMed database in June 2016. 30 relevant reports concerning the efficacy of trastuzumab emtansine (T-DM1), lapatinib and its combination with other cytotoxic agents, pertuzumab and novel HER2-targeting substances were identified. **Results:** There is limited but promising evidence for the use of T-DM1 and pertuzumab in the treatment of BM. Up to now, most reported studies used lapatinib as treatment of HER2-positive breast cancer with BM, a treatment with only a modest effect and a high toxicity profile. The combination of lapatinib with cytotoxic agents seems to result in better response rates. **Conclusion:** Further prospective investigations are needed to investigate the efficacy of the established and novel HER2-targeting agents on BM in HER2-positive breast cancer patients.

Introduction

The incidence of brain metastases (BM) in breast cancer patients has increased. Up to 40% of patients with metastatic HER2-positive breast cancer will develop BM during the course of the disease [1, 2]. The standard local therapies are surgery and/or radiotherapy. However, it is unclear which systemic treatment should be applied in addition to local therapies. Most data have shown that first-line treatment with trastuzumab prolongs survival in patients with HER2-positive BM [3]. In contrast, there are only few studies evaluating other therapies targeting HER2 [1]. The aim of this review is to present an update about available data on current systemic treatment options beyond trastuzumab in patients with HER2-positive metastatic breast cancer with BM.

Material and Methods

A literature search was performed in the PubMed database in June 2016. The aim was to identify trials investigating HER2-targeting agents, such as pertuzumab, trastuzumab emtansine (T-DM1) and lapatinib, as treatment options for patients with HER2-positive breast cancer and BM who showed trastuzumab resistance. The included trials were identified according to abstract or full-text information. The abstracts from relevant international meetings (e.g. ASCO, San Antonio Breast Cancer Symposium until December 2016) were also considered. 30 reports were found.

Results

Trastuzumab Emtasine

Trastuzumab emtansine (T-DM1) is a second-line evidence-based treatment according to the guidelines in the metastatic setting, or first-line treatment in patients with early progression

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after adjuvant trastuzumab therapy [4, 5]. Although it was hypothesized that its molecular size was too large to penetrate the blood-brain barrier, there is some evidence for the treatment of BM of breast cancer with T-DM1 in the case of trastuzumab resistance.

The results for 4 clinical cohorts have been published describing treatment with T-DM1. The EMILIA study group retrospectively evaluated the efficacy of T-DM1 (3.6 mg/kg i.v. every 21 days) versus lapatinib/capecitabine (LC) (1,250 mg days 1–21, 1,000 mg/m^2 twice daily days 1–14 in a 21-day cycle) for patients with BM [6]. The identified subgroup of patients had either asymptomatic central nervous system (CNS) metastases at baseline (n = 95) or developed CNS metastases post baseline. The T-DM1 group with CNS metastases at baseline showed a significantly higher overall survival (OS) rate compared with the LC group (hazard ratio 0.38, p = 0.008, median 26.8 vs. 12.9 months) in multivariate analysis. However, this result must be interpreted with caution as no significant difference in progression-free survival (PFS) between both groups was observed, and the reported OS difference might also result from different subsequent treatments strategies.

The second cohort, published by Bartsch et al. [7], evaluated the efficacy of T-DM1 in 10 patients with BM of breast cancer and trastuzumab pretreatment. An intracranial PFS of 5 months was observed; 3 patients had partial remission of BM, 4 had stable disease, and 3 progressed under the treatment.

A third retrospective analysis by Jacot et al. [8] evaluated 39 patients with BM of HER2-positive breast cancer under T-DM1 treatment and showed a partial response rate of 44% and a clinical benefit rate of 59%. Concerning survival, a PFS of 6.1 months (95% confidence interval (CI) 5.2–18.3) was achieved.

The largest cohort of patients with CNS metastases treated with T-DM1 was reported by Montemurro and coworkers [9], who analyzed a subgroup of 399 patients with CNS metastases at baseline from the KAMILLA trial, a phase IIIb study investigating T-DM1 in patients with HER2-positive metastatic breast cancer. Patients with untreated, asymptomatic CNS metastases or controlled CNS disease previously treated with radiotherapy were also eligible. Of the 236 patients with disease progression in the brain, 65 (28%) continued treatment with T-DM1 post progression. The median duration of T-DM1 treatment post progression was 6.0 months. Median time to progression in the brain was 11.3 months (95% CI 8.6–13.7).

Although we have evidence for the efficacy of T-DM1 on BM, the side effects of radiotherapy might be worsened during concomitant T-DM1 therapy. Carlson et al. [10] published a clinical observation in 4 patients treated with stereotactic radiosurgery and concomitant therapy with T-DM1, who showed clinically significant brain edema and radionecrosis at sites of treated BM.

Therefore, clinicians should be aware of possible side effects of simultaneous T-DM1 application and cranial radiotherapy, even though it is unclear whether T-DM1 was responsible for the increased rate of radionecrosis.

Lapatinib

Lapatinib is a small molecule and it was presumed that it might cross the blood-brain barrier [11]. This feature made the substance an interesting compound for treating BM of HER2-positive breast cancer. Despite its high toxicity, more evidence exists for its use either as monotherapy or as combination therapy in BM compared with other anti-HER2 agents.

Lapatinib Monotherapy

Lapatinib monotherapy in cases of trastuzumab resistance and after cranial radiotherapy has been described in 3 phase II trials. Lin et al. 2008 and 2009 and Iwata et al. showed a moderate effect of lapatinib in the treatment of BM and extracranial metastases [12–14].

Lapatinib in Combination with Other Cytotoxic Agents

Concerning the blood-brain barrier penetration of lapatinib, Morikawa et al. [11] published results based on evaluation of lapatinib and capecitabine levels in patients with surgically resected BM. This analysis showed a penetration of both drugs to a significant degree in the BM. The critical point of this study was a small sample size and unclear rate of the patients who had been given radiotherapy of the brain, as radiotherapy might lead to higher penetration rates in the brain.

Two retrospective and 2 prospective studies analyzed the combination of lapatinib and capecitabine in cases with trastuzumab resistance and, usually, prior cranial radiotherapy [15–18]. A median PFS of 5.6–7 months and a median OS of 13–27.9 months were shown in these studies. In the phase II study of Lin et al. 2011 [18], which was stopped prior to full enrollment, an objective response rate as high as 38% was detected.

In the LANDSCAPE-trial, Bachelot et al. [19] investigated the role of LC in 45 patients without prior radiotherapy and with performance status (ECOG) 0–2 and a median number of BM at baseline of 3: an objective partial CNS response of 65.9% was seen, 84% of patients had a reduction in tumor volume from baseline, and 58% of patients had improvement in neurological symptoms. An efficacy on extracranial metastases was also observed: 44% of patients had an objective extra-CNS response, 47% had stable disease, and 9% progressed. Median time to CNS progression was 5.5 months; median survival was 17 months.

Combination of Lapatinib with Other HER2-Targeted Agents

A dual blockade with lapatinib and trastuzumab was examined by 2 research groups: a prospective trial by Lin et al. [20] (n = 28) and a retrospective analysis by Bartsch et al. [21] (n = 15). Both showed a moderate effect on BM. Lin et al. [20] reported an objective CNS response rate of 79%, a median PFS of 4.8 months and a median OS of 19 months. Bartsch et al. [21] showed a significant prolongation of OS in the group with additional lapatinib over trastuzumab-based treatment (p = 0.002).

Although the reported response rates seem encouraging, patients in the study of Lin et al. received whole brain radiation and

some also stereotactic radiosurgery, and it was not possible to differentiate whether the good response rates were achieved due to radiation or due to systemic treatment.

Combination of Lapatinib with Other Compounds

Lin et al. 2011 [18] examined the combination of lapatinib with topotecan (n = 9) and showed no efficacy but high toxicity in the L-topotecan group. In the investigation of Azambuja et al. [22], a combination of temozolomide and lapatinib was administered and showed a moderate efficacy in 16 heavily pretreated patients with multiple BM of breast cancer (PFS 2.6 months, 95% CI 1.82–3.37, stable disease rate 67%, progressive disease rate 33%). A combination of lapatinib, trastuzumab and bevacizumab showed promising results in the analysis of Falchook et al. [23] in 10 patients with BM of breast cancer pretreated with trastuzumab and lapatinib. The HER2-reintroduction therapy in the combination with anti-vascular endothelial growth factor (VEGF) treatment showed a stable disease rate (≥ 6 months) and partial or complete remission in 60% of patients.

Pertuzumab

There is only limited evidence about the efficacy of pertuzumab in BM. In a subgroup analysis of the CLEOPATRA trial (first-line pertuzumab/trastuzumab/docetaxel vs. placebo/trastuzumab/docetaxel), a similar percentage of patients developed BM (12.6% vs. 13.7%). Notably, patients receiving pertuzumab developed BM 3 months later compared with the placebo group. Patients with BM had a significantly better OS in the docetaxel, trastuzumab and pertuzumab group in comparison to docetaxel and trastuzumab (Wilcoxon test p = 0.0449, n = 106) [24].

Trastuzumab Reintroduction

There is some evidence about the reintroduction of trastuzumab in the case of progressive disease. Gori et al. [25] evaluated 16 patients with BM under trastuzumab reintroduction after previous therapy with trastuzumab and lapatinib. The median OS for patients with BM in this setting was 17.3 months (95% CI 3.4–32.2).

Novel Compounds

Several novel HER2-targeting agents were recently investigated in a clinical setting. Deva et al. [26] provided first efficacy data of a novel EGFR/HER2 inhibitor S-222611 (phase I trial) for 6 patients with BM and breast cancer, and observed intracranial response (n = 1) and prolonged stable diseases (n = 2) (≥ 6 months).

In the evaluation by Murthy et al. [27], a HER2-selective tyrosine kinase molecule inhibitor ONT-380 showed CNS activity when administered in combination with either T-DM1, trastuzumab, capecitabine or trastuzumab + capecitabine in patients with BM of HER2-positive breast cancer. Results from a phase Ib trial applying ONT-380 in combination with capecitabine and trastuzumab [28], including patients with BM who had received both pertuzumab and T-DM1, showed evidence of responses and long-term disease control. A phase II study (HER2CLIMB) is now also enrolling patients with BM to evaluate the activity of ONT-380 further [29].

Two further tyrosine kinase inhibitors have been recently investigated. Tesevatinib seems to be a promising compound as it has the ability to cross the blood-brain barrier [30]. Neratinib (in combination with paclitaxel) showed a benefit concerning the CNS progression rate compared to trastuzumab/paclitaxel (8% vs. 16% CNS progression rate, p = 0.0037) [31].

The BEACON trial (phase III) with etirinotecan pegol (NKTR-102) has demonstrated a superior efficacy of the drug compared with treatment of physician's choice in heavily pretreated breast cancer patients with BM [32]. Although patients with HER2-positive breast cancer were included, they comprised only 7% of the total cohort.

Discussion

Unfortunately, in most large clinical trials patients with BM were excluded. Therefore, evidence about BM is mostly limited to retrospective analysis and case reports. The EMILIA trial evaluating T-DM1 in comparison to LC was 1 of the few trials that also included patients with BM. Further retrospective evaluations and prospective trials are needed to identify the best treatment option for HER2-positive breast cancer patients with BM.

The aim of this review was to present the evidence about HER2-targeted therapies beyond trastuzumab, as trastuzumab resistance is a challenging problem in the treatment of HER2-positive BM patients. The systemic treatment of HER2-positive patients with BM of breast cancer should be performed according to the current guidelines for patients with HER2-positive metastatic breast cancer. Novel agents that might have activity in the brain are being investigated.

To gain further information about outcomes in breast cancer patients with BM, we have established a national clinical data registry and registry of tumor tissue in Germany [33]. Similar efforts are under way in other countries. Work is also required to detect biomarkers that can predict response to HER2-targeted therapy in the brain, as these are currently lacking. Finally, further clinical trials involving HER2-positive breast cancer patients with BM are urgently needed. This will be a challenge for clinical and translational research in the next few years.

Disclosure Statement

The authors declare no conflict of interest.

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