Critical Reviews in Oncology / Hematology 143 (2019) 20–26

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

The evolving role of trastuzumab emtansine (T-DM1) in HER2-positive breast cancer with brain metastases

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ARTICLE INFO

Keywords:
Breast cancer
Trastuzumab emtansine (TDM1)
Brain metastases
HER2

ABSTRACT

Approximately 30–50% of advanced human epidermal growth factor receptor 2 (HER2) positive breast cancer patients will develop brain metastases (BMs) during the disease course. Brain metastases may become a main limitation of life expectancy and a half of them will die from brain progression. Even in patients with early HER2-positive breast cancer managed with curative therapy, the risk of brain metastases is also increased. Central nervous system (CNS) may usually present as the first site of recurrence in HER2-positive breast cancer. Local treatments including radiotherapy and surgery are essential while new chemotherapy and biological agents appear to contribute a significant role in the future treatment field of CNS metastases. This article will review recent progresses in HER2-positive breast cancer with BM, with a focus on the efficacy of the HER2 targeted agents-trastuzumab emtansine (T-DM1).

1. Introduction

In the United States, up to 268,670 new cases will be diagnosed with breast cancers in 2018, which is the most common cancer and becomes the second leading cause of cancer death in females (Siegel et al., 2018). Approximately 10–20% of breast cancers present as human epidermal growth factor receptor 2 (HER2) overexpression which is associated with shorter disease-free and overall survival (OS) (Ross et al., 2009). Breast cancers with HER2-overexpression appear prone to occur BM and nearly 50% of advanced breast cancers with HER2-positive will die from brain progression (Lin and Winer, 2007). This makes the management of HER2-positive breast cancers with BM (BCBM) a critical issue. The high incidence of BM in HER2-positive breast cancer may attribute to several factors. These contain the success of anti-HER2 targeted therapies, leading to a substantial survival gain of breast cancer to develop CNS metastases, the activity of anti-HER2 therapy in brain microenvironment is limited, and the propensity of HER2-positive breast cancer to the CNS.

Surgical removal of resectable lesions and radiotherapy for multiple lesions are the current standard managements for breast cancer with BM leading to median survival up to 23.5 months for good performance patients (Sperduto et al., 2013). However, the subsequent management for those with intracranial progression and effective drugs for this indication have not reach a consensus and remain an area of unmet need (Ramakrishna et al., 2018). For the majority of BCBMs, local management usually follows systemic HER2-targeted therapy. Current recommendations regarding the treatment of HER2-positive breast cancer demonstrate that for these patients with extracranial disease progression at the time of BM diagnosis, HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer should be offered. In turn, anti-HER2 therapy should continue for patients subjected to neurosurgery or radiotherapy whose extracranial disease is stable at the time of diagnosis of BM (Ramakrishna et al., 2018). The abilities of newer anti-HER2 therapies to penetrate the blood–brain barrier (BBB) to either prevent BCBM or control existing disease, suggest that HER2-targeted treatment may have a positive impact on the survival of HER2-positive BCBM and the recurrence rates in brain. However, due to the paucity of data from randomized clinical trials, the optimal proposals of chemotherapy and targeted therapy for BCBMs, as well as their sequence in relation to local therapy have not formed.

Expression of HER2 has been confirmed to be highly concordant between the primary and CNS metastatic lesions (Shen et al., 2015), which makes anti-HER2 therapy possible for the HER2-positive BCBM. Additionally, multiple trials have evaluated the role of anti-HER2 therapy in patients with CNS metastases. Accumulating evidence has demonstrated that lapatinib—as a single agent or combined with capecitabine (XL) could make some activity in HER2-positive CNS

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https://doi.org/10.1016/j.critrevonc.2019.07.010
Received 8 September 2018; Received in revised form 23 June 2019; Accepted 10 July 2019

metastases (Bachelot et al., 2013; Tomasello et al., 2010). Another large monoclonal antibody- trastuzumab is commonly considered to be too large to penetrate the BBB, has been demonstrated to access BBB in a recent positron emission tomography imaging study using 89Zr-trastuzumab in HER2-positive metastatic breast cancers (Dijkers et al., 2010). Retrospective studies have shown that trastuzumab can delay the BM and improve the survival after the development of BM in HER2-positive breast cancers (Lewis et al., 2017; Stemmler et al., 2007). Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate, incorporating the microtubule-inhibitory agent DM1 with trastuzumab via a stable linker, and has the ability to deliver DM1 to HER2-overexpressing tumor cells (Lewis et al., 2008). Recently, TDM1 has been proved to be more effective in the treatment of breast cancers with metastatic lesions than the lapatinib-capecitabine (Verma et al., 2012) and has the same diffusion characteristic with trastuzumab. Therefore, the assessment of its features in HER2-positive BCBM appears interesting. This review will highlight recent advances in the HER2-positive BCBM, with a focus on the emerging role of T-DM1 for the treatment of BM.

2. HER2-positive breast cancer with brain metastases

Younger age (< 50 years), more than 2 metastatic lesions at diagnosis, hormone receptor-negative tumors, large tumors, positive lymph node, previous bone, lung, or liver metastasis, elevated lactate dehydrogenase levels, and HER2-positive disease are identified as risk factors to develop BM for breast cancers.

Previous researches have shown that patients with HER2-positive metastatic breast cancer are 2–4 times more likely to develop CNS tumors than those with HER2-negative disease (Brufsky et al., 2011; Liu et al., 2006). The increased risk of brain metastases in HER2-overexpression breast cancer may attribute to multifactorial effects. Several possible explanations have been mentioned. The first one is that HER2-positive breast cancer is aggressive and more prone to spread to organs outside the breast (Kallioniemi et al., 1991). Another explanation has been a preferential homing of HER2-positive cells to CNS sites (Montagna et al., 2009), however, clinical studies have not confirmed this kind of hypothesis. Finally, the higher incidence of BM in HER2-positive breast cancer may reflect the fact that those patients treated with trastuzumab live longer due to extra cranial disease control, therefore, more likely to develop brain metastases (Brufsky et al., 2011; Mehta et al., 2013).

In order to explore the role of HER2 in the development of BM, the International Breast Cancer Study Group enrolled 10 adjuvant trials and evaluated a total of 9524 women with early breast cancer who were absent of anthracyclines, taxanes, or trastuzumab treatment (Pestalozzi et al., 2006). After a median follow-up of 13 years, the 10-year cumulative incidence of CNS involvement (as first recurrence) accounted for 2.7% in HER2-positive patients compared with 1% in patients with HER2 negative ($p < 0.01$). The 10-year cumulative incidence of CNS disease as either the first or subsequent metastasis was 6.8% for HER2-positive primary tumor, while 3.8% for HER2-negative ones ($p < 0.01$). Among the breast cancers, node-positive disease (2.2% for > 3 positive nodes), ER-negative (2.3%), tumor size > 2 cm (1.7%), tumor grade 3 (2.0%), age < 35 years old (2.2%), and HER2-positive (2.7%) were identified as risk factors to develop BM. For HER2-positive breast cancer, a retrospective analysis demonstrates that age ≤40, tumor size > 2 cm, nodal positive, absence or late start (≥6 months after initial diagnosis) of adjuvant anti-HER2 treatment and the development of lung metastases as first site of relapse may contribute to develop BM (Maurer et al., 2018).

Moreover, expression of HER2 between the paired tumors and brain tumors is proved to be high concordant (Shen et al., 2015). Shen et al. (2015) identified 140 patients of breast cancer with brain metastases who underwent craniotomy for BCBM at the University of Texas MD Anderson Cancer Center between 2002 and 2009. They found HER2 status was highly concordant between the paired primary and brain tumors (97% concordance by immunohistochemistry and FISH; 35 of 36 paired breast and brain tumors). Discordance in HER2 status was observed in only 1 (3%) of these 36 patients. By contrast, some studies indicated that the expression of HER2 in brain metastases presents amplification compared to primary tumors. Additionally, some studies indicated that BCBM may acquire alterations in clinically actionable genes, with metastasis-acquired ERBB2/HER2 alterations in ERBB2/HER2-negative cases (Priedigkeit et al., 2017). To explore changes in expression levels of HER2 and its truncated form p95HER2 (P95) between primary tumor and brain metastases, Duchnowska et al. (2015) assayed 75 pairs of formalin-fixed paraffin-embedded samples from paired primary breast cancers and corresponding CNS disease for quantitative p95 and HER2-total (H2T) protein status by using the p95 VeraTag and HER mark assays, respectively. Finally, they found that there was a significant increase in p95 and H2T expression in brain metastases relative to the matched primary tumors (median1.5-fold, $p = 0.0007$ and 2.1-fold, $p < 0.0001$, respectively). In order to establish precise biological explanation for the propensity of HER2-positive breast cancer cells to metastasize to CNS, Zhang et al. (2013) showed that circulating tumor cells (CTCs) isolated from patients with BCBM appeared to overexpress specific “brain metastasis selected markers” containing EGFR, HER2, Heparanase, and Notch1. Expression of these proteins in breast cancer CTCs presents as an invasive phenotype and obtains ability to colonize in the brain.

However, a recently retrospective study indicated that it was the HR status, but not the HER2 status, affected the kinetics of BM occurrence for breast cancers (Darlix et al., 2018). The study revealed that the time from stage IV disease to BM was shorter in HR-negative breast cancers compared with HR-positive ones (8.5 vs. 15.1 months, $p < 0.001$). While it was not different between HER2+ and HER2− tumors (14.2 vs. 9.6 months). When it came to the 2-year BM-free survival rate, HR-positive tumors was higher compared with HR-negative ones (80.5% vs. 58.3%, $p < 0.001$), HER2-positive was lower than the negative one (68.9% vs. 70.7%, $p = 0.039$). Therefore, more research is needed to confirm this issue.

3. Prognostic score for HER-2 positive breast cancer with brain metastases

In order to accurately predicting the outcome and adapt effective managements for BCBMs, it is significant to develop effective prognostic scores. Several types of scoring systems have been devised for clinical use to guide treatment decision-making, such as the breast recursive partitioning analysis (Breast RPA), the Breast-Graded Prognostic Assessment Index (Breast GPA), the Modified Breast-GPA score, basic score for BM (BS-BM), Le Scodan's Score and a clinic-biological score developed in a phase I study (P1PS), whose constituting parameters are detailed in Table 1 (Braccini et al., 2013; Griguolo et al., 2018). In order to obtain the optimal prognostic indexes for BCBM, Braccini et al. (2013) compared the clinical relevance of the major scoring systems. They claimed that the RPA was the most accurate score to identify patients with long and short life expectancy and appeared to be the most appropriate and simplest available tool to help clinicians select breast cancer patients with BM at the time of BM diagnosed. However, the RPA does not consider the breast cancer subtype, a factor highly associated with prognosis, and is unable to distinguish brain metastatic number (Zindler et al., 2013). Given the significant clinical relevance of the number of BMs with regard to treatment decisions, investigators validated Modified Breast-GPA in breast cancer patients diagnosed with BM, and evaluated its value as a prognostic scoring tool for survival as compared to the Breast-GPA score. They concluded that Modified Breast-GPA can be considered as a prognostic tool to BM in clinical practice and as a patient selection tool for prospective clinical trials (Griguolo et al., 2018; Subbiah et al., 2015). However, for the prognosis evaluation, a scoring system may be only a statistic model.

Table 1
Clinical parameters used for prognostic indexes.

RPA	
Class 1	Age < 65 years, KPS ≥70, controlled primary tumor, no extracranial metastases
Class 2	All patients not in Class I or III
Class 3	KPS < 70
Breast RPA	
Class 1	1–2 BMs and extracranial disease absent or controlled and KPS 100
Class 2	All patients not in Class I or III
Class 3	Multiple BMs and KPS ≤ 60

	Breast GPA				
	0	0.5	1	1.5	2
Age	≥60	< 60			
KPS	≤50	60	70–80	90–100	
Genetic subtype	Basal		Luminal A	HER2	Luminal B

	Modified breast-GPA				
	0	0.5	1	1.5	2
Age	≥60	< 60			
KPS	≤50	60	70–80	90–100	
Genetic subtype	Basal		Luminal A	HER2	Luminal B
No. of BMs	> 3	1–3	–	–	–

	P1PS	
	0	1
Sites of metastases	0–2	> 2
Serum LDH	< ULN	> ULN
Albumin, g/L	≥35	< 35

Le Scodan score	
Class I	HER2+ tumors treated with trastuzumab
Class II	All patients not in Class I or III
Class III	Tumors not treated with trastuzumab and lymphopenia at BM diagnosis or KPS < 70 and ≥50 years old at BM diagnosis or KPS ≥70 and triple negative tumors

RPA: recursive partitioning analysis; GPA: graded partitioning Analysis; BS-BM: basic score for brain metastases; BM: brain metastases; P1PS: phase 1 prognostic score; KPS: Karnofsky performance status; BM: brain metastases; LDH: lactate dehydrogenase; ULN: upper limit of normal.

The patient's performance status and expectation may remain important issues in the selection of appropriate managements.

4. Current therapy in HER2-positive breast cancer with established brain metastases

To provide optimal management to HER2-positive BCBM, the American Society of Clinical Oncology (ASCO) 2018 Clinical Practice Guideline reaffirms and summarizes the updated recommendations (Ramakrishna et al., 2018) (Table 2). Local approaches such as radiation therapy with or without surgery are current treatment options for BM. Indications of each local therapy are described in Table 2.

The data on the efficacy of novel systemic therapies in HER2-positive BCBM is limited for these patients have usually been excluded from clinical trials. It is generally assumed that therapeutic agents may not achieve effective anti-tumor function in the CNS because of the BBB. Its importance may be overthrowed in case of neoangiogenesis surrounding macroscopic metastases or relapsed disease, because, at this stage, the BBB has already been disrupted by the metastases and local therapy. Thus, the newly developed blood vessels do not present the physiological properties of the common BBB. In such a setting, chemotherapeutic agents, known hardly to cross the BBB initially, appear to penetrate the metastatic tissue (Dijkers et al., 2010). HER2-targeted drugs may efficiently control systemic extracranial disease; their efficacy against BM remains, however, limited (Bendell et al., 2003). Even small-molecule HER2 inhibitors with improved delivery into brain lesions show a deficiency in penetrating the BBB (Bachelot et al., 2013). The dominant concepts acknowledged to explain drug resistance in HER2-positive BCBMs include: (a) inadequate drug delivery to the tumor for the presence of BBB; (b) brain-specific molecular alterations involving the PI3K-AKT-mTOR pathway underlie BCBM resistance to HER2-targeted therapy (Kabraji et al., 2018); (c) changes in brain microenvironment of BCBM, which is confirmed by Kodack and his colleagues. They claimed that the resistance to PI3K inhibition when growing in the brain is mediated by enhanced activity of the HER3 signaling pathway (Kodack et al., 2017); (d) diverse genomic alterations emerged in brain environment after the continued suppression of PI3Kα, such as PTEN loss, can be as an alternate mechanism of PI3K activation (Juric et al., 2015). Therefore it is necessary to explore new treatments and combination therapies.

However, standard systemic management regiments for BCBM remain unclear. For HER-2 positive patients with BCBM, local management is usually followed by systemic anti-HER2 treatments (Ramakrishna et al., 2018). According to the ASCO guidelines, patients who subjected to neurosurgery or radiotherapy (whole brain radiotherapy [WBRT], stereotactic radiosurgery, stereotactic radiation therapy) and their extracranial disease is not progressive at the time of diagnosis of brain metastases, HER2-targeted therapy should not be switched (Arvold et al., 2016). For patients whose systemic disease is progressive at the time of BM diagnosis, HER2-targeted therapy should be offered according to the algorithms for treatment of HER2-positive metastatic breast cancer (Ramakrishna et al., 2018).

Hitherto, there are no established standards for assessment of intracranial response to systemic therapies. In clinical trials, RECIST (Response Evaluation Criteria in Solid Tumors; version 1.0 and 1.1), or RANO (Response Assessment in Neuro-Oncology) are the two most

Table 2
Recommendations on disease management for HER2-positive breast cancer and brain metastases.

- For patients with a favorable prognosis for survival and a single brain metastasis, treatment options include surgery with postoperative radiation, stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT; 6 SRS), fractionated stereotactic radiotherapy (FSRT), and SRS (6 WBRT), depending on metastasis size, resectability, and symptoms. After treatment, serial imaging every 2–4 months may be used to monitor for local and distant brain failure.
- For patients with a favorable prognosis for survival and limited (two to four) metastases, treatment options include resection for large symptomatic lesion(s) plus postoperative radiotherapy, SRS for additional smaller lesions, WBRT (6 SRS), SRS (6 WBRT), and FSRT for metastases > 3 to < 4 cm. For metastases > 3 to > 4 cm, treatment options include resection with postoperative radiotherapy. In both cases, available options depend on resectability and symptoms.
- For patients with diffuse disease/extensive metastases and a more favorable prognosis and those with symptomatic leptomeningeal metastasis in the brain, WBRT may be offered.
- For patients with poor prognosis, options include WBRT, best supportive care, and/or palliative care.
- For patients with progressive intracranial metastases despite initial radiation therapy, options include SRS, surgery, WBRT, a trial of systemic therapy, or enrollment in a clinical trial, depending on initial treatment. For patients in this group who also have diffuse recurrence, best supportive care is an additional option.
- For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched.
- For patients whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2- targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer.
- If a patient does not have a known history or symptoms of brain metastases, routine surveillance with brain magnetic resonance imaging should not be performed.
- Clinicians should have a low threshold for performing diagnostic brain magnetic resonance imaging testing in the setting of any neurologic symptoms suggestive of brain involvement.

commonly used system. Currently, the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group is widely used to evaluate the response to new systemic therapies for brain metastases (Alexander et al., 2018). Those kinds of assessments contain composite of radiographic CNS target and non-target lesion responses, corticosteroid use, and clinical status. In the updated recommendation, a routine active magnetic resonance surveillance for asymptomatic brain metastases should be avoided, since there is no evidence that this strategy may have positive impacts on survival or quality for breast cancers. However, there is a recommendation for performing diagnostic brain magnetic resonance imaging testing in the setting of any neurologic symptoms suggestive of brain involvement (Ramakrishna et al., 2018).

T-DM1 is an antibody-drug conjugate which composed of the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine); trastuzumab and DM1 are conjugated by means of a non-reducible thioether link set, called N-maleimidomethyl cyclohexane-1-carboxylate (MCC). This bond reduces the side effects of DM1, an extremely powerful microtubules stabilizer (Lewis et al., 2008; Poon et al., 2013). T-DM1 is a large, hydrophilic molecule with the ability to bind the extracellular domain of HER2, followed by internalization of the HER2/T-DM1 complex into lysosomes. Then the complex is proteolytically degraded and releasing lysine-MCC-DM1 into the cytoplasm, where it could inhibit microtubule polymerization and induce cell death. Lys-MCC-MD1 is unable to diffuse to bystander normal cells for it is positively charged, thus further limiting the potential for non-specific toxicity and contributing to overall safety profile of T-DM1. In T-DM1, conjugated trastuzumab also retains its effector functions, including Fcg receptor-mediated activation of antibody dependent cell-mediated cytotoxicity and inhibition of HER2 mediated signal transduction.

4.1. Trastuzumab emtansine (T-DM1)

The mechanism of T-DM1 might be independent of HER2 signaling for trastuzumab may act mainly as a targeted delivery of DM1 to the HER2-positive cancer cell. The main efficacy of T-DM1 in CNS may be attributed to the cytotoxic agent DM1, which is known to inhibit microtubule, disrupt cell cycle and induce cell apoptosis (Poon et al., 2013; Junttila et al., 2011). Therefore, the effect of T-DM1 will not be impaired entirely by anti-HER2 agents resistance mechanisms related to HER2 downstream signaling (Kabraji et al., 2018) (Fig. 1), such as PI3K mutation or PTEN downregulation which has been reported in approximately 32% and 19–48% of patients with HER2-positive metastatic breast cancer (Baselga et al., 2014; Park et al., 2014). There are also researches shown that the PI3K-AKT-mTOR pathway is frequently activated as a brain-specific mechanism of drug resistance to HER2-targeted therapies (Kabraji et al., 2018). T-DM1 is active against both trastuzumab- and lapatini-resistant HER2-positive cancer models (Lewis et al., 2008; Junttila et al., 2011), as well as in patients with breast cancer progressing on trastuzumab and/or lapatinib therapy (Verma et al., 2012; Krop et al., 2012, 2014). In a phase III EMILIA study (Verma et al., 2012), for patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxane, T-DM1 treatment improved progression-free survival (PFS) and OS significantly compared with the combination of capecitabine and lapatinib. Then Braccini et al. (2013) further explored the relationship between treatment efficacy and PIK3CA mutation status in patients from the EMILIA trial. They indicated treatment benefits in terms of PFS, OS, and overall response rate were observed with T-DM1 relative to capecitabine and lapatinib.

On February 22, 2013, the FDA licensed T-DM1 for using as a single agent to patients with HER2-positive metastatic breast cancer who have already received trastuzumab and a taxane and who have received previous treatment for metastatic breast cancer or have developed disease recurrence within 6 months of completing adjuvant therapy (Amiri-Kordestani et al., 2014). Retrospective analysis of the phase III EMILIA trial revealed that patients, previously treated with trastuzumab and taxanes, T-DM1 achieved a statistically significant survival improvement compared with lapatinib/capecitabine (Verma et al., 2012; Dieras et al., 2017; Welslau et al., 2014). Moreover, in the phase III TH3RESA study for patients with progressed disease after at least two HER2-targeted agents, T-DM1 significantly improved PFS compared with treatment of physician's choice (Krop et al., 2014, 2017). At the period of the final OS analysis of the phase III TH3RESA study, T-DM1was associated with significant improvement of OS compared with treatment of physician's choice (median OS 22.7 months (95% CI 19.4–27.5) versus 15.8 months (13.5–18.7); HR 0.68 [95% CI 0.54–0.85]; $p = 0.0007$). The OS benefits of T-DM1 reported in both TH3RESA and EMILIA confirm the role of T-DM1 in the treatment of recurrent and metastatic breast cancer. Moreover, T-DM1 also displayed to confer clinically relevant benefits for patients previously treated with trastuzumab and pertuzumab in a real-word study (Vici et al., 2017).

The integrity of the local BBB could be comprised in the presence of tumor. In the brain parenchym when metastatic tumors grow beyond 1–2 mm, the BBB becomes structurally and functionally compromised (Mehta et al., 2013). T-DM1 is a large, hydrophilic molecule and has been prove to achieve anti-tumor concentration in CNS by a preclinical animal model. Askoxylakis et al. (2016) treated mice bearing BT474-Gluc and MDA-MB-361-Gluc BM, which are HER2-amplified but also harbor an activating PIK3CA mutation, with T-DM1, trastuzumab, or control IgG at the same dose (15 mg/kg). Results showed that T-DM1 could delay the growth of HER2-positive BCBM and overcome resistance of trastuzumab therapy in HER2-driven or PI3K-driven brain

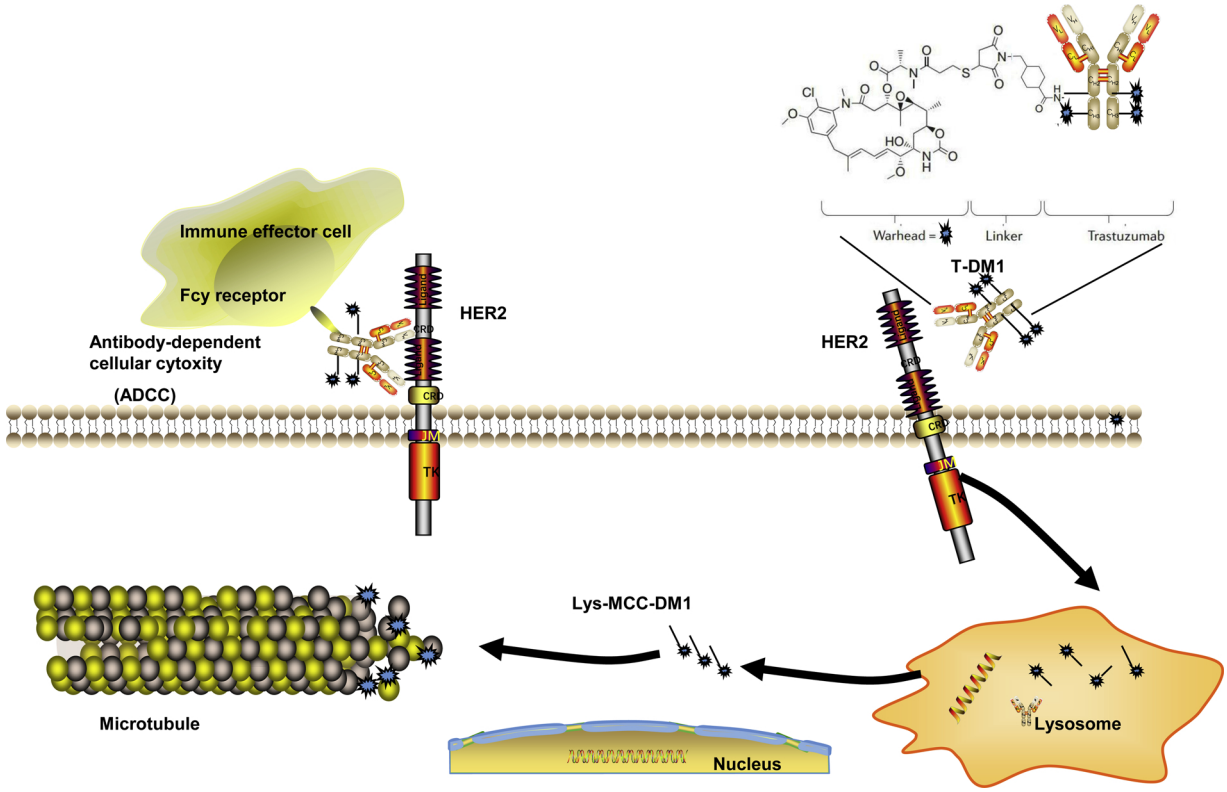

Fig. 1. Structure of T-DM1 and mechanisms of action. After T-DM1 binds HER2, the HER2/T-DM1 complex undergoes internalization, followed by lysosomal degradation. DM1-containing catabolites are released and bind to tubulin to prevent microtubule polymerization as well as suppress microtubule dynamic instability. T-DM1 has also been shown to retain mechanisms of action of trastuzumab.

lesions of breast cancer. The activity of T-DM1 resulted in a survival benefit and led to a statistically significant increase in tumor cell apoptosis. Published clinical cohorts also described advantages of T-DM1 for BCBM. The EMILIA study group retrospectively evaluated the efficacy of T-DM1 versus lapatinib plus capecitabine for HER2-positive patients with BMs (Krop et al., 2014). In this trial, patients who had been previously treated and with stable CNS metastases at baseline were randomized to T-DM1 arm (45/495) and lapatinib plus capecitabine arm (50/496). The T-DM1 was associated with significantly improved OS compared with lapatinib plus capecitabine (HR 0.38, $p = 0.008$, median 26.8 vs. 12.9 months) in multivariate analysis without increasing risks for CNS progression. Although, the estimated median PFS was no statistically significant differences between T-DM1 (5.9 months) and lapatinib plus capecitabine (5.7 months) (HR = 1.00; 95% CI 0.54–1.84; $p = 1.000$). When considering the safety, T-DM1 was associated with lower incidence of grade ≥3 and serious adverse events compared with lapatinib plus capecitabine.

The second cohort was a case-series including 10 HER2-positive breast cancer patients of newly diagnosed or progressive BMs (Bartsch et al., 2015). The efficacy and safety of T-DM1 was evaluated in this study. T-DM1 yielded intracranial PFS of 5 months (95% CI 3.69–6.32) with well tolerated; 3 patients had partial remission of brain metastases, 4 experienced stable disease, and 3 progressed under the treatment.

Another retrospective study analyzed 39 uncontrolled BCBM treated with T-DM1 (Jacot et al., 2016). T-DM1 treatment demonstrated an overall response rate of 44% and a clinical benefit rate of 59%. Concerning survival, a median OS cannot reach after a median follow-up of 8.1 months while T-DM1 treatment achieved a median PFS of 6.1 months (95% CI 5.2–18.3). Moreover, unexpected toxicity was not observed and dose delay or reduction was rare.

The latest cohort of patients with BCBMs treated with T-DM1 was conducted by Montemurro et al. (2017). Investigators analyzed a subgroup of 399 patients with CNS metastases from the KAMILLA trial, a phase IIIb global safety study of T-DM1 in patients with HER2-positive locally-advanced or metastatic breast cancer. Patients with asymptomatic CNS metastases were eligible and were given T-DM1 3.6 mg/kg every 3 weeks. A decrease in the size of CNS target lesions during T-DM1 treatment in 84 of 126 patients was observed. Of the 236 patients with disease progression in the brain, 65 (28%) experienced with T-DM1 post progression. A 6-month median duration of T-DM1 treatment post progression was achieved and median time to progression in the CNS was 11.3 months (95% CI 8.6–13.7).

4.2. Prospect of combined therapies

Radiosurgery combined with lapatinib for breast cancer with CNS involvement has been shown to achieve better response rates than radiosurgery alone with a response rate of 86 versus 69% ($p < 0.001$) (Yomo et al., 2013). Adams et al. (2016) reported that potent anti-tubulin drugs conjugated to anti-ErbB antibodies; one of them, namely as T-DM1 selectively radiosensitize tumors based on surface receptor expression. Recently, in a preliminary series, 12 patients were treated for BMs with T-DM1 and concurrent or sequential radiosurgery with or without WBRT (Geraud et al., 2017). They reported that the T-DM1 and concomitant SR combination appeared to be well tolerated and feasible in BCBM but could increase the risk of radiation necrosis. Moreover, radiotherapy has potential to disturb the BBB and enhance the expression of HER2/neu in the surface of breast cancer. These changes may improve antibody-dependent cell-mediated cytotoxicity and sensitize anti-proliferative effects of anti-HER2 therapy (Wattenberg et al., 2014). Case studies have verified that concurrent use of T-DM1 with radiotherapy prolongs tumor control in HER2-overexpressive tumor and T-DM1 could provide potent and tumor selective radiosensitization (Wattenberg et al., 2014).

Focused ultrasound (FUS) with systemic microbubble infusion is a

minimally invasive and transient physical technique opening the BBB, and has been proposed to enhance the retention and permeability of drugs or gene therapy materials within targeted regions in the brain (Kovacs et al., 2017). Arvanitis and his colleagues examined the impact of FUS in combination with microbubbles on the transport of chemotherapy-based anticancer agents in BCBM at cellular (Arvanitis et al., 2018). Their animal experiment model indicated that FUS in combination with microbubbles can overcome vascular and cellular transport barriers in the brain tumor microenvironment by altering the drug delivery toward convective transport, resulting in increased tumor tissue penetration. Their study also demonstrated that FUS in combination with microbubbles increased early extravasation and penetration of T-DM1 in HER2-amplified BT474 breast cancer BMs.

The brain microenvironment plays a key role in metastatic tumor progression. Research showed that astrocytes and brain endothelial cells could protect tumor cells from chemotherapy-induced damage through an endothelin pathway-mediated mechanism (Kim et al., 2014). Interesting, the expression of endothelins (ET) in astrocytes will increase due to the interaction between metastatic cancer cells and brain stromal cells, which will activate the endothelin pathway in cancer cells and promote their survival. Previous studies indicated that treatment with macitentan, a dual inhibitor of ETA and ETB receptors destroyed the astrocyte- and endothelial cell-mediated chemoprotection and stimulated apoptosis of tumor-associated endothelia cells after paclitaxel chemotherapy in brain metastasis models from breast and lung cancer (Lee et al., 2016). Subsequently, Askoxylakis et al. (2019) demonstrated that dual ETA and ETB inhibitor could enhance the activity of T-DM1 against BM from HER2-positive breast cancer. Surprisingly, their data showed that the combination of the macitentan and neratinib – a small molecule inhibitor of HER2/EGFR delayed tumor growth in brain environment minimally and did not improve survival of HER2-positive BCBM mice. Such result can attribute to the fact that brain-specific molecular alterations involving the PI3K-AKT-mTOR pathway underlies BCBM resistance to HER2-targeted therapy (Kabraji et al., 2018). While T-DM1 was effective against brain metastases from HER2- amplified breast cancer independent of the PIK3CA mutation status.

Tyrosine kinase inhibitors (TKIs) have been approved for metastatic breast cancer. Tucatinib, an oral, reversible HER2-specific TKI, is being developed as a novel treatment for ERBB2/HER2-positive breast cancer and can selectively inhibit ERBB2/HER2. In an open-label multidose phase 1b trial, 57 HER2-positive breast cancers including 32 brain metastases were enrolled who were T-DM1-naïve and had undergone a median of 2 earlier HER2 therapies (Borges et al., 2018). Investigators found that the combination of T-DM1 and tucatinib provided dual inhibition of ERBB2/HER2, improved the efficacy of single-agent therapy with T-DM1 through use of an alternative mechanism of receptor inhibition. Among the maximum tolerated dosage group, 21 of 30 patients (70%) progressive brain metastases at study entry. Median progression free survival among those patients was 6.7 months (95% CI, 4.1–10.2 months) which was encouraging compared with other systemic therapies used to treat a similar patient population, and a median duration of overall response according to RECIST 1.1 was 6.9 months (95% CI, 1.45–19.48 months) (Laakmann et al., 2017). The tolerance tucatinib combined with T-DM1 was well at the study-derived maximum tolerated dosage and schedule.

5. Conclusion

Today, breast cancer patients with HER2-positive are surviving longer. However, the development of novel systemic therapies for brain metastases faces many daunting obstacles as most of initial clinical trials for new drugs exclude patients with BCBM. Recently, the clinical guidelines of ASCO for the management of HER2-overexpressive BCBMs emphasized the use of HER-2 targeted therapy, especially in those with extracranial progression of disease (Ramakrishna et al., 2018). T-DM1 is independent of HER2 signaling pathway and may overcome several anti-HER2 resistance mechanisms. Additionally, T-DM1 could penetrate the BBB which is disrupted by metastatic lesion or local therapy and is a well-tolerated therapeutic option. Furthermore, the combination of T-DM1 and other therapy will improve the efficacy of T-DM1. Taken together, these data suggest that T-DM1 may be efficacious for HER2-positive breast cancer with BMs and may challenge the traditional concept of the monoclonal antibodies in the treatment of BCBMs.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

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