RESEARCH ARTICLE

Role of HER2 in Brain Metastasis of Breast Cancer: a Systematic Review and Meta-Analysis

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Abstract

Background: Breast cancer is one of the most common cancers among women worldwide and the HER2 receptor plays an important role in its development and progression. This systematic review aimed to summarize the role of HER2 in brain metastasis in patients with breast cancer. Materials and Methods: We conducted a literature search by advanced search in title field using the Scopus, Pubmed, and Google scholar databases until the end of June 2014. With metastasis, metastatic, HER2, brain, and breast cancer, as terms of search we selected 31 articles, which were reviewed by two independent and blinded expert reviewers. The studies were first selected according to their titles and abstracts. Quality of the studies were then assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) protocol for observational studies and CONSORT(Consolidation of Standards for Reporting Trials) protocol for clinical trials. For statistical analyses, we used STATA, version 11.0 software. Forest and funnel diagrams were drawn and for heterogeneity, index was also considered. Also we used meta regression analysis. Results: Finally, we reviewed 10 studies. The prevalence of brain metastasis in HER2- positive breast cancer patients was 24.9%. There was publication bias in the reviewed studies. Meta regression analysis showed that follow up time had no significant effect (p=0.396) on the prevalence of brain metastasis. Conclusions: The results showed a high prevalence of brain metastasis in HER2 positive breast cancer patients.

Keywords: HER2 - brain metastasis - breast cancer

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Introduction

Breast cancer is one of the most common cancers among women worldwide (Taghavi et al., 2012). Brain metastasis occurs when cancerous cells come from a primary tumor to the brain and implant and grow there. This event is potentially lethal and causes neurologic symptoms and signs. These patients are treated in order to decrease their neurologic problems, increase quality of life and overall survival (Akhavan et al., 2014). In 2001, Yarden et al. stated that the human epidermal growth factor receptor family, or ErbB family, includes four transmembrane tyrosine kinase receptors, HER1 (ErbB-1), HER2 (ErbB-2), HER3 (ErbB-3), and HER4 (ErbB-4), with a high degree of homology to each other, and that they regulate cell growth and survival, attachment, migration, differentiation, and other cellular responses (Yarden, 2001). Moreover, Lu et al. (2005) declared that ErbB receptors play an important role in the development and progression of breast cancer (Lu et al., 2005). Also, Salmon et al. reported that over-expression of HER2 was strongly associated with the pathogenesis and prognosis of the breast cancer, i.e. tumor invasion and metastasis. They reported HER2 over-expression in 20 to 25 percents of invasive breast cancers (Slamon et al., 1987). Brain metastasis, in particular, is one of the most prevalent complications of the breast cancer, since 100,000-170,000 cases are diagnosed each year in the US (Lin and Winer, 2007), and breast cancer is responsible for about 15-20% of all cases of brain metastasis (Duchnowska and Szczylik, 2005) (Tomasello et al., 2010). Given the high geogrophical variations in the field of cancer (Ajami et al., 2009), and few published systematic reviews and meta-analyses in this field, this systematic review aimed to summarize the role of HER2 in brain metastasis in patients with breast cancer.

Materials and Methods

Search strategy

This is a systematic review and meta-analysis on the role of HER2 in brain metastasis in patients with breast

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cancer. We conducted a literature search by advanced search in title filed using the Scopus, Pubmed, and Google scholar databases until the end of June 2014. We used Google Scholar for search, since this database includes both local and international journals. Searching terms, including metastasis, metastatic, HER2, Brain and Breast cancer, retrieved 31 articles.

Study selection and data extraction

The articles imported into ENDNOTE software, and duplicates and similar files were deleted. They were then reviewed by the two independent and blinded expert reviewers. The information was recorded on particularly designed sheets. Reviewers checked all potentially relevant studies and reached a consensus on all items. The evaluation was performed on the title and abstracts for the selection of studies. Any disagreement between the two reviewers was deleted after talking with a third reviewer. Data were recorded on special designed forms containing general information about each article: author names, publication date, country, number of samples, and percentage of HER2 positive metastatic brain cancer. For assessing the quality of studies, we used STROBE protocol for observational studies and CONSORT for clinical trials (Holloway and Worthington, 2002) (von Elm et al., 2007). These programs provide a simple and unique method for evaluation and clarification. The study selection process (according to the PRISMA guidelines) is shown in Figure 1.

Eligible criteria

Inclusion criteria were all English articles determining the role of HER2 in breast cancer with brain metastases. Other studies, such as letters to the editor and non-English papers were excluded.

Statistical tools

For the statistical analyses, we used STATA, version 11.0 software (Stata Corporation, College Station, TX, USA). Forest and Funnel diagrams were drawn and for heterogeneity, I^2 index was also considered. Meta

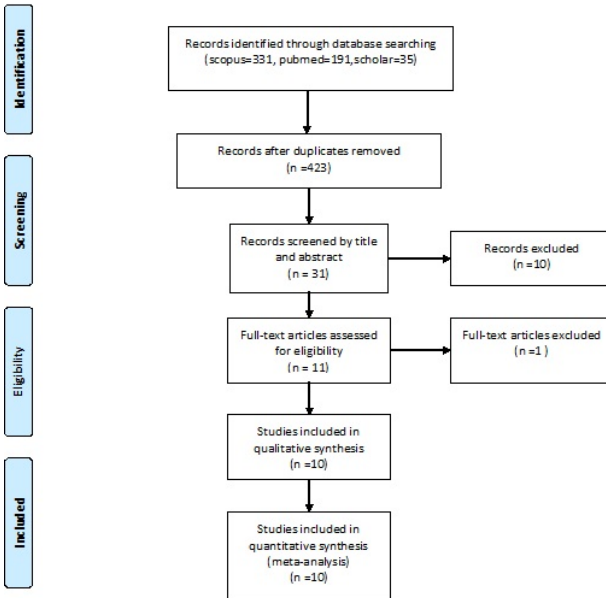

Figure 1. PRISMA Flow Diagram for the Meta-analysis

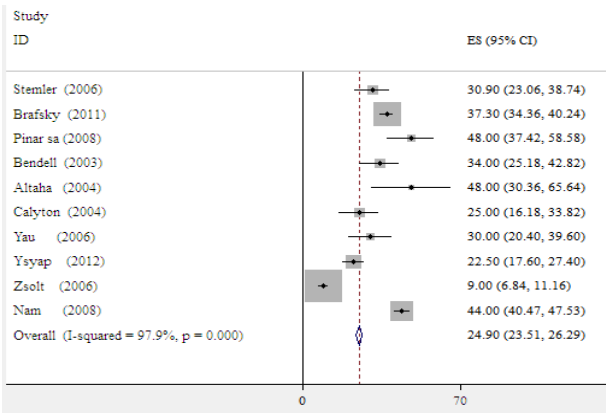

Figure 2. Forest Plot of Brain Metastasis in HER2+ Breast cancer

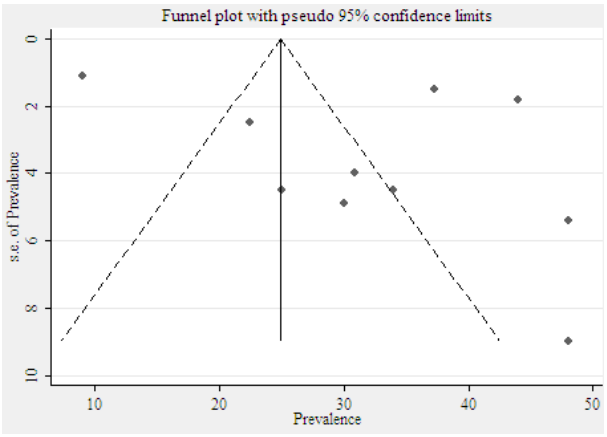

Figure 3. Funnel Plot of Eligible Studies Included in this Meta-analysis

Table 1. Characteristics of Eligible Studies Included in this Meta-analysis

Author	Country	Type of study	Grading				Follow up time	N	Prevalence (%)
			G1	G2	G3	unknown			
Stemler et al. 2006	Germany	Cohort		64.3	33.5	2.4	13	136	30.9
Brafsky et al. 2011	USA	Clinical trial					29	1012	37.3
Pinar saip et al. 2008	Turkey	Clinical trial		61	31	3	60	86	48
Bendell et al. 2003	USA	Cohort					24	112	34
Altaha et al. 2004	USA	Cohort					60	31	48
Calyton et al. 2004	UK	Cohort					36	93	25
Yau et al. 2006	UK	Cohort					48	87	30
Ys yap et al. 2012	Asian Multicenter	Cohort	26.4	43.9	27.1	2.5	24	280	22.5
Zsolt et al. 2006	Canada	Cohort	3.3	64.8	26.2	5.6	47	664	9
Nam et al. 2008	Korea	Survival analysis					45.1	800	44

Table 2. Meta Regression Results of Follow up Time Effect on the Prevalence Rate of Brain Metastasis in HER2, Positive Breast Cancer Patients

	Coef	Std. Err	P
Follow-up	0.244	0.272	0.396
Cons	22.935	11.066	0.072

*tau2= > 144.1; I-squared_res= > 97.86%; Adj R-squared= > -5.39%

regression analysis was also used to measure the effect of follow up time on the prevalence of brain metastasis in HER2 positive breast cancer.

Results

A total of 31 articles were found, articles that were unsuitable were excluded. Finally, 10 articles were accessed by the two independent reviewers.

Finally, we enrolled 10 studies, characteristics are shown in Table 1. As shown in Figure 2, the prevalence of brain metastasis in HER2+ breast cancer patients was 24.9%. Figure 3 shows the publication bias in the reviewed studies. Meta regression analysis showed that follow up time had no significant effect (p=0.396) on the prevalence of brain metastasis (Table 2).

Discussion

Human epidermal growth factor receptor status is an important prognostic factor in breast cancer (Pazhoomand et al., 2013) and the aim of this review was to combine the results of other studies to produce more precise results. The results showed a prevalence of 24.9% for the brain metastasis in HER2+ breast cancer patients suggesting that a considerable number of HER2+ breast cancer patients develop brain metastasis. Concurrently, Brufsky et al. and Saip et al. separately reported that several risk factors have been associated with the development of central nervous system (CNS) lesions in patients with metastatic breast cancer (MBC), including younger age (<50 year), having more than 2 metastatic sites at MBC diagnosis, hormone receptor-negative tumors, large tumors, positive lymph node status, previous lung, liver, or bone metastasis, elevated lactate dehydrogenase levels, and HER2-positive disease. They also showed that patients with HER2-positive MBC tumors are 2 to 4 times more likely to develop CNS tumors than those with HER2-negative diseases (Saip et al., 2008) (Brufsky et al., 2011). In 2001, Yarden, et al. (2001) stated that the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases can activate a complex signal transduction cascade that modulates cell proliferation, survival, adhesion, migration, differentiation and growth of tumor cells (Yarden, 2001). Moreover, Lin et al. (2007), reported HER2 is a predisposing factor for brain metastasis in patients with breast cancer (Lin and Winer, 2007). This ratio in early breast cancer was reported 10 to 30% during follow-up period (Demircioglu et al., 2013). Gabos et al. also mentioned that activation of HER-2 tyrosine kinase receptor triggers a complex array of signaling pathways that regulates normal cell growth and promotes tumorigenesis via cell proliferation, survival, migration, differentiation, and angiogenesis (Gabos et al., 2006). In other words, HER2 over-expression has been shown to be a predictive factor for CNS metastases in advanced breast cancer (Yau et al., 2006). In fact, HER2 over-expression is an important risk factor for brain metastasis in breast cancer patients.

The follow up time of patients was different between studies, because some of the evaluated studies were observational while others were clinical trials. For all included studies the mean follow up time was 38.6±15.9 months and meta regression analysis show that the follow up time had no effect on the prevalence of brain metastasis in HER2 positive breast cancer

In conclusion, The present study showed a high prevalence of brain metastasis in breast cancer which is suggested to be noted in planning for the diagnostic and therapeutic strategies.

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