

RESEARCH ARTICLE

Lack of Prognostic Value of Human Epidermal Growth Factor-Like Receptor 2 Status in Inflammatory Breast Cancer (IBC): a Meta-analysis

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Abstract

Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer which is more likely to be her-2/neu amplified. While the her-2/neu status has been utilised to predict prognosis, the published data are inconsistent. The present meta-analysis was conducted to determine whether the her-2/neu status predicts outcomes. Papers were selected from the PubMed database based on defined inclusion and exclusion criteria. Parameters such as total patients, follow-up time and outcome statistics (i.e. overall survival (OS), relapse-free survival (RFS) were collected. The analysis included 6 studies with 2,838 IBC patients. The summary hazards ratio (HR) estimating the association of OS with HER-2-positive disease was 0.96 (95% confidence interval (95%CI: 0.85-1.10)), with similar findings for RFS (HR=0.81, 95%CI: 0.61-1.09). No obvious statistical heterogeneity was detected. This meta-analysis suggests that HER-2-positive status is not an independent adverse prognostic factor for survival among IBC patient cases.

Keywords: Human epidermal growth factor-like receptor 2 - inflammatory breast cancer - meta-analysis - prognosis

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Introduction

Inflammatory breast cancer (IBC) is the most aggressive form of primary breast cancer with poor 5-year rates of disease-free survival (DFS) and overall survival (OS). Clinically, IBC is characterized by diffuse erythema and edema of the skin of the breast, called 'peau d'orange', with or without associated palpable mass. IBC is a relatively rare form of breast cancer, and chemotherapy plays the primary role in their treatment. Although the survival of patients with IBC has been improved greatly by the use of combined treatment modalities, people with IBC still have far lower survival rates than those with other types of breast cancer. Advances in the treatment of IBC have been hampered by absence of prognostic factors, in part because the rarity of IBC has made it difficult to conduct clinical trials.

Human epidermal growth factor-like receptor 2 (HER2) is a proto-oncogene located on chromosome 17. It is overexpressed in about 30% of breast cancer and is associated with a more aggressive breast cancer phenotype (Slamon et al., 1987). Although studies have reported an increased incidence of HER-2 amplification in patients with IBC, the prognostic significance of HER-2 amplification in this cohort has not been clearly defined,

and due to the rarity of this disease the prognostic impact of HER-2 status on survival outcomes of patients with IBC is not well known (Turpin et al., 2002). Unfortunately, there are limited high quality prospective data and the current publications have not been consistent in their conclusions. We performed a meta-analysis aiming to analyse the existing data to determine if HER-2 status predicts for outcomes in IBC patients.

Materials and Methods

Literature search

We conducted a systematic literature search of PubMed and EMBASE through April 2013 by using the following key words: Inflammatory breast cancer, human epidermal growth factor-like receptor 2, HER-2, prognosis and survival. References from identified studies were also reviewed. The search was limited to English language. The eligible studies should meet the following criteria: (1) We have restricted our analyses to inflammatory breast cancer. (2) Only original papers evaluating the association between HER-2 status and overall survival (OS), relapse-free survival (RFS) or disease free survival (DFS) were selected. (3) Hazard ratio (HR) for OS, RFS or DFS according to HER-2 status either had to be reported or

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Table 1. Characteristics of the Studies Included in the Meta-analysis

Study	T	HER-2	Duration	No. of Patients	CT Regimen	TNM Stage	No. of H-positive	Survival
Sawaki et al	therapy	detection	of follow-up	46	A-based	III	23	Data OS, DFS
Dawood et al	No	IHC+FISH	Median 35 m	179	AT-based	III	68	OS, RFS
Zell et al	Yes	IHC+FISH	1999-2007	2104	AT-based	III, IV	477	OS
Sutherland et al	Yes	IHC+FISH	1990-2007	155	AT-based	III, IV	59	OS, RFS
Li et al	Yes	IHC+FISH	Median 35 m	316	AT-based	III	62	OS, RFS
Chaher et al	No	IHC+FISH	2005-2009	117	AT-based	III, IV	20	OS

*A, Anthracycline; T, taxane; IHC, immunohistochemical; FISH, fluorescent in situ hybridization; m, months; T, Trastuzumab; CT, Chemotherapy; H, HER-2

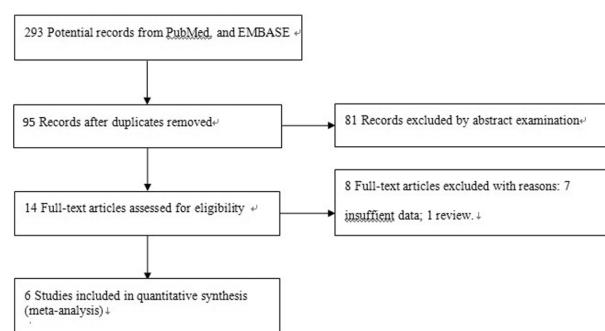


Figure 1. Flow Chart of the Selection of Publications Included in the Meta-analysis

could be calculated from the paper. Furthermore, abstracts were excluded because of insufficient data.

Data Extraction

The following data from eligible publications was extracted respectively by two reviewers (Li XJ and Ren ZJ) with a standardized data collection form: first author's last name, duration of follow-up, sample size, number and of patients with HER-2-positive, disease stage, chemotherapy regimen, inclusion of trastuzumab therapy, the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). When both univariate and multivariate analysis were used to adjust for covariates, only survival data from multivariate analysis were included in our meta-analysis. If HRs and 95%CIs were not provided directly, estimated value was obtained indirectly by using the methods described by Tierney et al (Tierney et al., 2007). Disagreement was resolved by discussion and consensus, and where required through discussion with, or independent extraction by two authors with content expertise (Tang JH and Gong JP).

Statistical analysis

Summary statistics of patients with HER-2-positive disease for survival outcome with HRs and 95%CI were calculated using the fixed effect model/Mantel-Haenszel method when there was no significant heterogeneity in the variables amongst studies and the DerSimonian-Laird method (random effect model) when there was significant heterogeneity. Heterogeneity between trials was evaluated by I-squared (I^2) statistic (Higgins et al., 2003). Statistical heterogeneity was considered significant if p value less than 0.10 or $I^2 > 50\%$. Publication bias was assessed by Begg's funnel plots and Egger's regression test (Begg et al., 1994). Additionally, we also conducted a sensitivity analysis to investigate the influence of a single trial on the overall risk (Tobias et al., 1999). All reported P values were two-sided and P values less than 0.05 were regarded

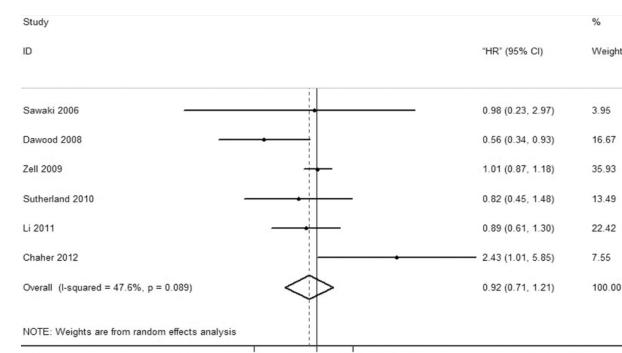


Figure 2. Forest Plots of Hazard Ratio (HR) for Overall Survival (OS) from Eligible Studies of IBC with HER-2-positive. The combined HRs and 95%CIs were calculated using the random-effects model

as statistically significant. Statistical analyses were carried out using STATA 12.0 (Stata Corporation, USA).

Results

Literature search

We initially reviewed 293 relevant citations using search strategies as described previously. Of these, the majority were excluded after the first screening based on abstracts, because they were not relevant to our analysis, or the primary outcome was not OS, RFS, or DFS. After full-text review of 14 papers, 7 studies (Low et al., 2004; Panades et al., 2004; Labidi et al., 2008; Mehta et al., 2008; Ellis et al., 2011; Gianni et al., 2012; Rehman et al., 2012) were excluded because of poor data for meta-analysis. Another one study was excluded because it was a review (Kim et al., 2006). Finally, 6 studies (Dawood et al., 2008; Zell et al., 2009; Sutherland et al., 2010; Li et al., 2011; Chaher et al., 2012) were included in our meta-analysis. Flow diagram of selecting eligible trials was shown in Figure 1.

Study Characteristics

The characteristics of these 6 studies are listed in Table 1. The sample size of the included studies ranged from 46 to 2041 patients. The number of patients with HER-2-positive disease ranged from 20 to 477 patients. HER2 status was determined by fluorescent in situ hybridization (FISH) and immunohistochemical (IHC) analysis in 5 of the 6 eligible studies, and patients were categorized as having HER-2-positive disease if their tumor samples exhibited overexpression (2+) by IHC technique in one study. All systemic therapy delivered typically consisted of an anthracycline and/or taxane with other chemotherapeutic agents, in accordance with

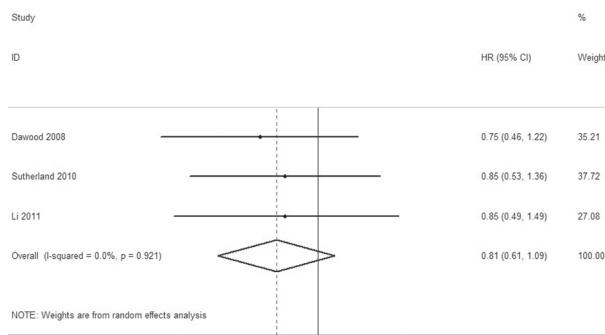


Figure 3. Forest Plots of Hazard Ratio (HR) for Relapse-free Survival (RFS) from Eligible Studies of IBC with HER-2-positive. The combined HRs and 95% CIs were calculated using the random-effects model

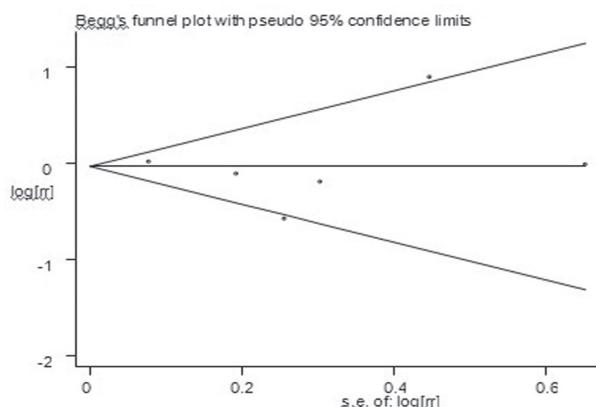


Figure 4. Funnel Plot Detect Publication Bias in the Study of Relationship between HER-2 Status and Overall Survival (OS). The vertical line indicated the pooled estimate of the overall HR, with the sloping lines representing the expected 95%CI for a given SE

the standard of care for IBC. Detailed information from each trial was listed in Table 1.

Meta analysis

Data for OS were available from all 6 studies (Sawaki et al., 2006; Dawood et al., 2008; Zell et al., 2009; Sutherland et al., 2010; Li et al., 2011; Chaher et al., 2012) with 2838 patients reported. The HER-2-positive group was not associated with a statistically significant improvement in OS when compared with the HER-2-negative group ($HR=0.96$, 95%CI 0.85-1.10; $I^2=47.6\%$) (Figure 2) under a random-effect model. RFS was reported in 3 papers [15, 16, 18], including 650 patients with similar findings ($HR=0.81$, 95%CI: 0.61-1.09; $I^2=0.0\%$) (Figure 3). There was only one study which reported DFS, The efficacy of HER-2-positive on the DFS was $HR=1.19$, (95%CI 0.76-1.84, random-effects model).

Publication bias

Visual assessment of the funnel plot did not provide evidence of publication bias for studies (Figure 4 and Figure 5). The Begg rank correlation test and Egger linear regression test also indicated no evidence of publication bias (Begg, $p=0.851$ for OS; and, $p=0.602$ for RFS);(Egger's test $p=0.878$, for OS; and, $p=0.833$ for RFS).

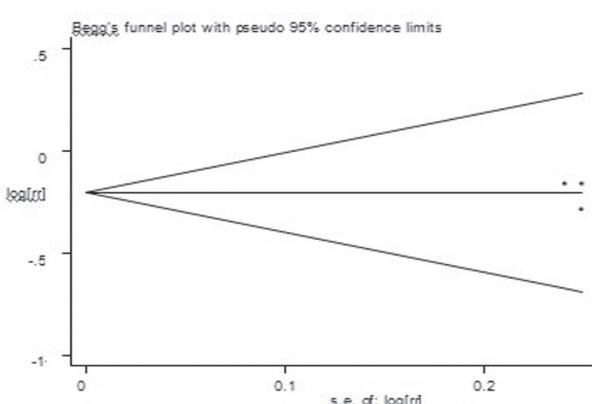


Figure 5. Funnel Plot Detect Publication Bias in the Study of Relationship between HER-2 Status and Relapse-free Survival (RFS). The vertical line indicated the pooled estimate of the overall HR, with the sloping lines representing the expected 95%CI for a given SE

Discussion

The clinical researches of IBC are hampered because of the rarity of the disease and the reliance on nonspecific clinical diagnostic criteria to identify cases. IBC is more likely than other breast cancers to be her2/neu amplified (Turpin et al., 2002; Hance et al., 2005). While her2/neu status has been utilised to predict prognosis(Abdul et al., 2013), the published data are inconsistent. Dawood et al. (2005), reported that, IBC patients with HER-2-positive disease had increased OS compared with HER-2-negative disease, presumably because of the use of trastuzumab for their recurrent disease. Sawaki et al. (2006), did not find HER-2 positivity to be a significant prognostic factor in IBC; Zell et al. (2009), also did not observe statistically significant difference in survival outcome for IBC patients with HER-2-positive disease. The present meta-analysis was conducted to determine the her2/neu status predicts for outcomes. Based on the combined data of 6 eligible published studies with 2838 IBC patients, our findings suggest that the summary hazards ratio (HR) estimating the association of OS with HER-2-positive disease was 0.96 (95%CI: 0.85-1.10), with similar findings for RFS ($HR=0.81$, 95%CI: 0.61-1.09). No obvious statistical heterogeneity was detected (Begg, $p=0.851$ for OS; and, $p=0.602$ for RFS); (Egger's test $p=0.878$, for OS; and, $p=0.833$ for RFS). This meta-analysis suggests that HER2+ status is not prognostic for survival among IBC patient cases.

To our knowledge, HER-2 amplification in primary breast cancers was associated with shorter OS and RFS compared with tumors that did not exhibit HER-2 amplification (Slamon et al., 1987). The introduction of a monoclonal antibody, trastuzumab, that targeted the HER-2 receptor, significantly improved survival outcomes in primary breast cancers with HER-2 amplification (Romond et al., 2005).

However, our meta-analysis concluded that HER-2 status was not a significant prognostic factor in patients with IBC, despite the finding that HER-2 amplification is common in this disease. There are several possible explanations for why HER2 is not prognostic for survival

in IBC. Many other molecules may contribute to IBC's aggressive behavior, including chemokine receptors such as CCR7 (Cabioglu et al., 2007), EGFR (Cabioglu et al., 2007), E-cadherin (Colpaert et al., 2003), Rho proteins, and WISP3 (Van Golen et al., 2000; Kleer et al., 2002). Future studies should attempt to identify which molecular target was specific to IBC. It has been reported that an anthracycline-based chemotherapy regimen may be more effective in HER2-positive patients compared with HER2-negative ones because HER2-positive patients often overexpress topoisomerase II, which is the target of anthracyclines (Tanner et al., 2006). It may possibly come to a conclusion that anthracycline-based chemotherapy regimen eliminates HER2 positivity's impact on survival outcome in these HER2-positive patients.

Potential limitations of this study should be considered. First, although most of studies adjusted for a series of key covariates, we still cannot rule out the possible residual confounding variables. Second, it is unknown how many people received trastuzumab and their survival outcome. Third, the total number of included studies and the total sample size were relatively small, which may influence the accuracy of meta-analysis to some extent.

It is thus clear that more specific prognostic and predictive markers, with the subsequent development of novel therapeutic regimens, are needed to individualize treatment and thus improve survival outcomes.

Monoclonal antibody, trastuzumab, is an important variable known to have a favorable prognostic impact in breast cancer, and it calls into question whether trastuzumab may improve survival in these HER2-positive IBC patients. In this meta-analysis, there were 2 included studies without addition trastuzumab to patients with HER-2-positive and other 4 studies restricted their analyses to the period prior to 2005, when trastuzumab became widely used in the adjuvant setting for treatment of breast cancer (Romond et al., 2005). Further studies are warranted to evaluate the effect of trastuzumab on HER2-positive IBC. It is interesting that HER-2 status is not an adverse prognostic factor for survival in IBC patients, and yet trastuzumab may still benefit IBC patients, a finding that needs further research.

In summary, we conclude that HER-2 status is not an independent adverse prognostic factor for survival among IBC patients. The aggressive biology of IBC and other unknown prognostic factors may explain the poor OS for IBC.

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