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Abstract (298)

Background: The gold standard endpoint in randomized clinical trials in metastatic breast cancer is overall survival. Although therapeutics have been approved based on progression-free survival, its use as a primary endpoint is controversial. We aimed to assess to what extent progression-free survival may be used as a surrogate for overall survival in randomized trials of anti-HER2 agents in HER2+ metastatic breast cancer.

Methods: Eligible trials accrued HER2+ metastatic breast cancer patients in 1992-2008. A correlation approach was used: at the individual level, to estimate the association between investigator-assessed progression-free and overall survival using a bivariate model and at the trial level, to estimate the association between treatment effects on progression-free and overall survival. Correlation values close to 1.0 would indicate strong surrogacy.

Results: We identified 2545 eligible patients in 13 randomized trials testing trastuzumab or lapatinib. We collected individual patient data from 1963 patients and retained 1839 patients from 9 trials for analysis (7 first-line trials). During follow-up, 1072 deaths and 1462 progression or deaths occurred. The median survival time was 22 months (95% CI 21-23 months) and the median progression-free survival was 5.7 months (95% CI 5.5-6.1 months). At the individual level, the Spearman correlation was equal to $\rho=0.67$ (95% CI 0.66 to 0.67) corresponding to a squared correlation value of 0.45. At the trial level, the squared correlation between treatment effects (log hazard ratios) on progression-free and overall survival was provided by R2=0.51 (95% CI 0.22 to 0.81).

Conclusions: In trials of HER2-targeted agents in HER2+ metastatic breast cancer, progression-free survival moderately correlates with overall survival at the individual level and treatment effects on progression-free survival correlate moderately with those on overall mortality, providing only modest support for considering progression-free survival as a surrogate. Progression-free survival does not completely substitute for overall survival in this setting.

Key words: surrogate, progression-free survival, HER2, metatastic breast cancer, trastuzumab, lapatinib

Introduction

Worldwide, approximately 1.68 million new cases of female breast cancer are diagnosed each year and this rate is increasing globally[1]. Approximately 15-30% of these tumors overexpress HER2/neu (human epidermal Growth factor receptor type 2), which is associated with aggressive tumor behavior and poor prognosis[2-4]. Trastuzumab, a monoclonal antibody directed against the extracellular domain of the HER2 tyrosine kinase receptor, has revolutionized HER2-positive (HER2+) breast cancer treatment since its approval by the U.S. Federal Drug Administration in 1998. It is approved for use in both adjuvant[5, 6] and metastatic settings[7] and has been investigated in clinical trials in the neoadjuvant setting[8]. Despite this, a substantial proportion of women will experience a recurrence or progression of their disease, suggesting the presence of de novo resistance or the development of resistance to trastuzumab. This has led to the pursuit and successful development of other molecules, used alone or in combination with trastuzumab or chemotherapy: lapatinib (approved by the Food and Drug Administration (FDA) in 2007) and more recently, pertuzumab (2012) and Trastuzumab-DM1 (2013).

The gold standard endpoint for the evaluation of new therapies in oncology is overall survival (OS). But OS, although simple to measure, easy to interpret and clinically meaningful, has the disadvantage of requiring extended follow-up, and of being confounded by unrelated causes of death or the successive lines of effective therapy now available in common solid tumors. An endpoint that is reached more rapidly may answer the question posed by clinical trials more quickly and, potentially, expedite drug approval. For example in colorectal cancer, disease-free survival (DFS) has been validated as a surrogate for OS in the adjuvant setting[9] and progression-free survival (PFS) has been validated as a surrogate for OS in advanced disease[10]. It should be noted, however, that surrogate endpoints may be specific to a class of agents. In colorectal cancer, DFS and PFS have only been validated for first-line fluoropyrimidine-based regimens, and the extrapolation of surrogacy to other classes of agents having substantially different mechanisms of action may not be warranted.

The preferred approach for surrogate endpoint evaluation is the use of individual patient data (IPD), the reference method against which other forms of systematic review should be measured. Within this framework, a surrogate endpoint may be assessed both at the individual (correlation between endpoints) and trial level (correlation between treatment effects on endpoints). Besides colorectal cancer, this approach has been tested in advanced breast cancer[11], lung cancer[12, 13], head and neck cancer[14], gastric cancer[15, 16] and leukemia[17].

In the advanced setting, PFS has been shown to be an appropriate surrogate for evaluation of chemotherapy effects in several malignancies, but in metastatic breast cancer (MBC), PFS was shown not to be a valid surrogate for overall survival when reanalyzing 3,953 patients in 11 trials that compared an anthracycline (alone or in combination) with a taxane (alone or in combination with an anthracycline)[11]. A literature-based study of 67 trials in MBC of various chemotherapy regimens also suggested an insufficiently high correlation [18]. However, a more recent meta-analysis of the literature found a stronger correlation between treatment effects in trials of HER2-positive MBC, as compared to the HER2-negative population ([19]) so that further evaluation of PFS as a surrogate endpoint of OS is warranted. This study, the first IPD meta-analysis of anti-HER2 agents in MBC, aimed to assess to what extent PFS correlates with, and may be used as a surrogate for OS.

Methods

Protocol
We assessed the endpoints according to the preplanned objective of PFS as a surrogate for OS in MBC patients in trials studying the effect of anti-HER2 treatments and wrote a study protocol (available upon request), which was approved by the medical ethics committee of Jules Bordet Institute. Briefly, a previously conducted electronic literature search[20] was updated using PubMed -using terms 'trastuzumab', 'Herceptin' 'lapatinib', 'Tykerb', 'pertuzumab', 'neratinib', 'Trastuzumab-DM1' and the exploded MeSH term 'breast neoplasms' and search line [(breast or mammary) and (cancer* or tumour* or tumor* or neoplas* or metastas* or carcinoma)]-, clinicaltrials.gov and conference proceedings in April 2011. Eligible publications consisted of randomized controlled trials (phase II or III) that accrued HER2+ MBC patients in 1992-2008. At least one of the study arms had to investigate a HER2-targeted agent. A collaboration was sought with industrial partners (Roche, GSK) for access to IPD from industry-led studies. The protocol requested IPD on survival outcomes and key prognostic factors and prespecified the statistical analysis outlined below.

Statistical analysis
Investigator-assessed PFS was defined as the time from randomization to clinical or radiological progression, or death. Patients who had no documented evidence of events were censored at the date of last follow-up. OS was defined as the time from randomization to death, irrespective of cause.

A correlation approach was used: at the individual level, the rank correlation coefficient ρ between distributions of PFS and OS was assessed with a bivariate survival model that takes censoring into account (Hougaard copula)[21]; at the trial level, the correlation between treatment effects (log hazard ratios) on PFS and OS were quantified through a linear regression model, weighted by trial size. Treatment effects were estimated by Cox regression and by the copula model.

The squared correlation coefficients or coefficients of determination—ie, ρ^2 at the individual level and R^2 at the trial level—were calculated to investigate the amount of variation explained by the surrogate. The candidate surrogate endpoints were deemed acceptable only if both correlation coefficients were close to 1·00. We used a leave-one-trial out strategy to study the sensitivity of the trial-level squared correlation when leaving each trial out once.

The surrogate threshold effect was calculated as the minimum treatment effect on the surrogate that would be necessary to predict a non-zero effect on OS[22]. A future trial would require an upper limit of the confidence interval (CI) for the estimated surrogate treatment effect to fall below the surrogate threshold effect to predict a non-zero effect on OS.

The Kaplan-Meier method was used to construct survival curves. Median follow-up times were calculated by the reversed Kaplan-Meier method. Statistical analyses were done with SAS (version 9.3) and R (version 3.1). All randomized patients were analyzed according to intention to treat.

Results

The search strategy resulted in 2545 eligible patients included in 13 randomized clinical trials testing trastuzumab or lapatinib (see flow chart in supplementary figure 1). Four trials were still in progress or did not have available data so that we collected

and checked individual patient data from 1963 HER2-positive patients included in 9 trials[7, 23-29]. One phase II trial did not have sufficient follow-up data for OS beyond progression[30] leading to a total of 1839 patients included in 8 trials that were retained for analysis. Details of the treatment arms evaluated are provided in Table 1. One trial was a four-arm trial leading to a total of 2 treatment comparisons for targeted HER2-treatments. We will denote the total of 9 treatment comparisons as 'trials' from now on, of which 6 tested trastuzumab and 3 lapatinib. The majority of trials were conducted in the first-line setting (7 out of 9 trials, 1198 patients). The description of the patients included in the 9 trials is provided in Supplementary table 1. A small majority (55% in control, 56% in anti-HER2 arm) of patients were ER-negative. Of note, 552 patients (30%) had been previously exposed to trastuzumab before inclusion in the trials, while the majority of patients had been exposed to chemotherapy.

The median follow-up for OS and PFS were given by respectively 33 months (95% CI 32-34 months) and 28 months (95% CI 26-32 months). During follow-up, 1072 deaths and 1462 PFS events occurred. The median OS was estimated to be 22 months (95% CI 21-23 months) and the median PFS was 5.7 months (95% CI 5.5-6.1 months). PFS and OS curves are shown in Figure 1, according to treatment arm. The 1-year PFS probabilities were estimated by 18% (95% CI 16-21%) in the control arm and 30% (95% CI 28-34%) in the anti-HER2 agent arm; while 2-year OS probability estimates were 42% (95% CI 39-46%) in the control arm and 51% (95% CI 47-54%) in the anti-HER2 agent arm.

At the individual level, PFS was moderately correlated with OS (Spearman ρ=0.67, 95% CI 0.67-0.68, or equivalently an R^2 value of 0.45, 95% CI 0.44-0.45). In an exploratory analysis, we restricted the data to those 583 patients included in first-line trials before 1998, the year of FDA approval of trastuzumab. The individual level correlation was estimated to be the same (ρ=0.67, 95% CI 0.67-0.68).

At the trial level, treatment effects on PFS correlated moderately with treatments effects on OS: R^2=0.51 (95% CI 0.22 to 0.81) using log hazard ratios from Cox models (Figure 2, see also Supplementary figure 2 for forest plots of hazard ratios on PFS and OS). Thus only about half of the variation in weighted treatment effects on OS can be explained by effects on PFS. The surrogate threshold effect, the minimum treatment effect that is necessary on PFS to be able to predict a non-zero effect on OS is provided by 0.72 (graphically this value is the abscissa of the intersection of a horizontal line at hazard ratio of OS equal to 1 and the upper bound of the 95% prediction interval of the regression line). The slope of the weighed linear regression equation is estimated by 0.44 (standard error 0.16) and the intercept by 0.04 (0.08), so that estimated treatment effects on OS are largely attenuated. When using the treatment effects as estimated by the copula model, the weighted R^2 was estimated by R^2=0.65 (95% CI 0.40 to 0.90).

In the leave-one-out analysis in which each trial was left out once, the trial-level R^2 values were very sensitive to the exclusion of single trials and ranged from 0.05 to 0.71, with a median R^2 of 0.53. Some additional unplanned exploratory subgroup analyses restricting the data to the set of first-line trials, to ER-positive patients, to ER-negative patients, or excluding borderline HER2+ patients defined by 2+ immunochemistry only, did not lead to substantially better trial-level correlation (data not shown).

Discussion

In the past, surrogate endpoints evaluations of PFS in metastatic breast cancer have revealed mixed results. The interpretation of the findings of 3 studies is limited as they extracted data from published literature[18, 19, 31]. In contrast, one study evaluated individual patient data from 3953 patients included in 11 randomized clinical trials that compared an anthracycline with a taxane[11]. PFS was shown not to be a valid surrogate for OS (individual level ρ=0.69 and trial-level squared correlation R^2=0.23). However, it is known that a surrogate endpoint needs to be evaluated for classes of drugs since the mechanism of action can be different.

In this study we explored whether in a more biologically homogenous defined group of patients (HER2+) the surrogacy of PFS for OS may be higher for targeted anti-HER2 cancer therapies. Using the gold standard method to study trial-level surrogacy - i.e. through collection of individual patient data- we included 1839 patients from 9 trials in the analyses. PFS was shown to be moderately correlated with OS at the individual level (Spearman correlation ρ=0.67, 95% CI 0.67 to 0.68) and treatments effects (log hazard ratios) on PFS correlated moderately with treatment effects on OS (R^2=0.51, 95% CI 0.22 to 0.81). Of note, our estimated individual level correlation (0.67) was almost identical to the estimated individual level correlation in the metastatic trials of anthracycline vs. taxane (0.69). As far as treatment effects were concerned, to the best of our knowledge there is no formal consensus on the minimum trial-level R2 value needed to validate a surrogate endpoint and several authors have used different cut-offs (from 0.60 ([32, 33]) to 0.72 ([34]) and 0.75 ([13, 35]). No matter what cut-off is chosen, based on the current results we cannot accept PFS as validated surrogate for OS.   Similarly, the surrogate threshold effect is estimated to be 0.72 so that a very strong treatment effect on PFS needs to be obtained before a non-zero effect on OS can be predicted.

The lack of stronger correlation between PFS and OS for HER2-targeted agents in HER2+ MBC could be related to the crossover that was allowed in several of the included trials, the administration of 2nd or 3th-line treatments and the relatively long post-progression time[36], a feature not common to the studies of other malignancies where PFS has been validated as surrogate for OS (i.e. advanced colorectal cancer[10], locally advanced lung cancer[13], locally advanced head and neck cancer[14]). In the trials included in the current study, only scarce information on crossover was collected excluding a potential trial-level evaluation taking crossover into account. Just as in colorectal cancer where several strategy trials have already been conducted[37], the objective of future trials in MBC could consist in identifying the optimal treatment sequence across lines of therapy instead of the best first-line treatment. For this purpose, crossover has to be incorporated in the design of the trial.

It may seem important to highlight the controversies on the effect of bevacizumab on PFS and OS in MBC. In a re-analysis of the individual patient data of 3 phase III trials in the first-line setting (*n*=2447), adding bevacizumab to standard chemotherapy prolonged PFS (HR=0.64, 95% CI 0.57-0.71) but did not significantly improve OS (HR=0.97, 95% CI 0.86–1.08)[38]. In 2011, the FDA withdrew its authorization for bevacizumab in MBC after the initial accelerated approval of 2008. The use of surrogate endpoints in trials should not be used as an excuse for not performing long-term follow-up, which is necessary to control unexpected adverse reactions and also to get sufficient power to analyze OS. The use of the surrogate ndpoint would allow one to conclude more rapidly on the treatment effect, but this should not lead to prematurely stop patient follow-up.

Recently, some additional phase III trials studying the effect of HER2-targeted agents in this setting have been conducted (in particular with pertuzumab, trastuzumab-DM1 but also a couple of studies with lapatinib or trastuzumab)[39-42]. These were not eligible when our protocol was set-up and accrued patients after our cut-off date of 2008. It may thus be of interest to update the current analysis in a future research collaboration. However, it seems rather unlikely that the degree of surrogacy of PFS for OS would increase because there likely were more effective 2nd-and 3th-line options available in the recent trials as compared to the historical ones. The recent trials may potentially have more precise recordings of treatments received after progression for fine-tuned analyses of crossover, although it is still not the norm in oncology clinical trials to systematically collect this information.

In summary, the current findings provide only modest support for considering PFS as a surrogate for OS in HER2+ metastatic breast cancer; PFS does not completely substitute for OS in this setting. It can however be problematic to use OS as primary endpoint for a first-line therapy trial in metastatic breast cancer because of crossover, 2nd-line treatments and competing risk of deaths.

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JS: research funding/honorarium for Roche and GSK
ADL: consultancy honoraria for GSK
GvM: research grants by Roche and GSK
MC: DSMB member for 2 GSK studies and chair the SystHERs steering committee (Roche)
All remaining authors have declared no conflicts of interest

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Table 1: Retained randomized clinical trials evaluating trastuzumab (T) or lapatinib (L) in HER2-positive metastatic breast cancer of which individual patient data was analyzed, in chronological order

Reference	Treatment comparison	Accrual Period	Phase	# HER2-positive patients	Line of treatment
Slamon et al[43]	Ctl: A+C or P Exp: A+C+T or P+T	1995-1997	III	469	First-line
Vogel et al[44]	Ctl: T (schedule 1) Exp: T (schedule 2)	1995-1998	II	114	First-line
Marty et al[45]	Ctl: D Exp: D+T	2000-2002	II	188	First-line
Kaufman et al[46]	Ctl: Anas Exp: Anas+ T	2001-2004	III	208	First-line
Johnston et al[47]	Ctl: Let+Placebo Exp: Let + L	2003-2006	III	219	First-line
von Minckwitz et al[48]	Ctl: X Exp: X+ T	2003-2007	III	151	Second or subsequent line
Cameron et al[49]	Ctl: X Exp: X + L	2004-2005	III	399	Second or subsequent line
Di Leo et al[50]	Ctl: P Exp: P+L	2004-2005	III	91	First-line

Ctl: Control arm; Exp: Experimental arm
A; Anthracycline; C: Cyclophosphamide; P: Paclitaxel; T: Trastuzumab; D: Docetaxel; Anas: Anastrazole; Let: Letrozole; L: Lapatinib; X: Capecitabine

Figure legends

Fig1: Kaplan-Meier curves of progression-free and overall survival in in HER2-positive metastatic breast cancer according to treatment arm.
Number of patients still at risk below the figure correspond to overall survival.

Fig2: Correlation between treatment effects on progression-free survival (PFS) and overall survival (OS) in the assessment of targeted HER2-agents in metastatic breast cancer
Each trial is represented by a circle, with a size proportional to the number of patients. A logarithmic scale is used on both axes. The plot displays the treatment effects estimated by Cox models. The regression line is weighted by trial size.

Figure 1
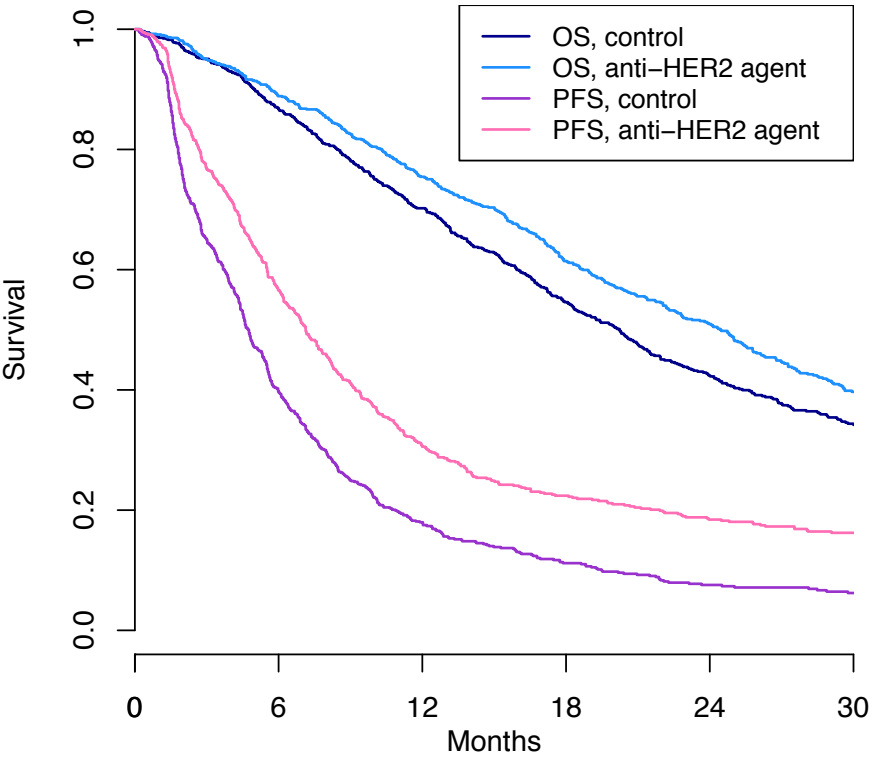
No. At Risk						
OS, control	926	717	519	371	266	196
OS, anti−HER2 agent	913	735	561	420	312	215

Figure 2