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Review

Surrogate end points for overall survival in breast cancer trials: A review

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ABSTRACT

Our aim was to review the studies which assessed potential surrogate endpoints for overall survival (OS) in breast cancer trials. A Literature search in PubMed database of studies which assessed potential surrogate endpoints for OS in breast cancer trials was conducted. The surrogacy was assessed with the German institute of Quality and efficiency in Health Care's (IWQiG) framework and the Fleming hierarchy. Thirteen studies were identified. At the neoadjuvant setting, two individual patient data (IPD) meta-analyses and one aggregate data meta-analysis assessing surrogacy of pathological complete response (PCR) were identified. Trial-level association was calculated in one study and the squared correlation was 0.24. Therefore PCR was not judged to be valid surrogate for OS at the neoadjuvant setting according to the IWQiG framework and Fleming hierarchy. At the adjuvant setting, one meta-analysis on aggregate data was identified. 2-year DFS was not judged to be valid surrogate for OS at the neoadjuvant setting according to the IWQiG framework and Fleming hierarchy. At the metastatic setting, six meta-analyses based on aggregate data, three IPD meta-analyses and one retrospective study were identified. Within the IPD meta-analyses, at the trial-level association the squared correlation between the potential surrogates and OS ranged from 0.10 to 0.57 and no endpoint was judged to be valid surrogate for OS at the metastatic setting. The level of evidence available supporting a relationship between OS and potential surrogate endpoints in breast cancer trials is low.

Introduction

As stated by the American Society of Clinical Oncology, active treatment of cancer is generally undertaken with the goal of providing improved quantity and/or quality of patient survival [1]. The selection of an appropriately valid primary end point is an important aspect of clinical trial design to achieve this objective. The Food and Drug Administration (FDA) considers overall survival (OS) benefit as the foundation for the approval of new anticancer drugs in the United States [2]. Nevertheless, the increasing number of effective salvage treatments available in many types of cancer (i.e., subsequent lines of treatments) has resulted in the need for a larger number of patients to be included and/or the need of a more prolonged observation period to attain sufficient events that can achieve planned statistical power; this increases the cost of clinical trials and requires a longer duration to obtain results [3]. Consequently, intermediate end points, such as progression-free survival (PFS), are often used as primary end points, because they are assessed earlier. However, there is a lack of consistency in their definitions [4], and they are not systematically validated as surrogate end points for OS. Many methods have been developed to validate surrogate end points. Buyse and colleagues proposed individual-data meta-analysis and calculation of both the coefficient of determination (R^2) individual and R^2 trial as the gold standard approach to the validation of statistical surrogate. On the basis of the results of previously completed trials and using individual data, this approach jointly estimates [1]: the correlation between the candidate surrogate (called "individual-level" surrogacy) and the final end points and [2] the correlation between the

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treatment effect on the candidate surrogate and its effect on OS (called "trial-level" surrogacy) [5].

In breast cancer, new treatments have improved patient survival considerably at the locally and advanced settings. Therefore, intermediate end points, such as pathological complete response (PCR) at the neoadjuvant setting, disease-free survival (DFS) at the adjuvant setting, or PFS at the metastatic setting, have been used as primary end points in phase III trials. Nevertheless, these intermediate end points have not been systematically validated as surrogate end points for OS.

We conducted a review of studies that assessed potential surrogate end points for OS in breast cancer trials. We assessed the suitability of the potential surrogates using two validation frameworks: the Fleming criteria and the German Institute of Quality and Efficiency in Health Care's (IQWiG) framework.

Methods

Search strategy and selection for studies

A search of literature published in English in PubMed database (from 1966 to March 2015) was conducted. The following strategies were used in the search: ("surrogate" [All Fields] AND "endpoints" [All Fields]) OR "surrogate endpoints" [All Fields] AND ("neoplasms" [MeSH Terms] OR "neoplasms" [All Fields] OR "cancer" [All Fields]). References of articles were also examined.

Data extraction

The following details were extracted from the studies: authors, date of publication, number of patients included, stage of breast cancer, type of treatment, details of statistical methods to assess the association between the potential surrogate and the end point, results of these analyses, and authors' conclusions. The suitability of potential surrogate end points for OS in each study was analyzed according to the Fleming criteria and the IQWiG framework.

IQWiG framework

IQWiG, an independent health technology assessment agency that assesses the benefits and harms of drug and nondrug technologies on behalf of the German Federal Joint Committee and the Federal Ministry of Health, published a framework for the validation of surrogate end points in oncology.

The IQWiG framework proposes two levels of consideration to judge the suitability of a surrogate end point: the reliability of the evidence and the strength of evidence for surrogate validation. The strength-of-evidence criterion considers the degree of correlation of effects on the surrogate and the patient-relevant end point according to predefined thresholds (i.e., high correlation, when the lower limit of the 95% confidence interval for $R \geq 0.85$; low correlation, when the upper limit of the 95% confidence interval for $R \leq 0.7$; and medium correlation otherwise) [6].

The Fleming criteria

In 2005, Fleming proposed a four-level evidence hierarchy for potential surrogate end points:

Level 1: a true clinical efficacy measure; Level 2: a validated surrogate end point (for a specific disease setting and class of interventions); Level 3: a nonvalidated surrogate end point, yet one established to be "reasonably likely to predict clinical benefit" (for a specific disease setting and class of interventions); and Level 4: a correlate that is a measure of biological activity but that has not been established to be at a higher level [2].

Results

A total of 13 studies were identified (Fig. 1). Table 1 summarizes the type of studies, potential surrogate end points, methodologies to assess surrogacy, and related results. The assessment of the validity of potential surrogate end points according to the IQWiG framework and the Fleming hierarchy as surrogate end point for OS in each study is presented in Table 2.

Neoadjuvant setting

Three studies, two individual patient data (IPD) meta-analyses and one aggregate data meta-analysis, which assessed surrogate end points for OS in trials for neoadjuvant chemotherapy, were identified.

In 2012, Von Minckwitz et al. published an individual-patient IPD meta-analysis of 6377 patients involved in seven trials. At individual-level association, PCR was associated with OS ($p < 0.001$). Trial-level association analysis was not performed. This study provides "no proof" of the surrogacy of PCR on OS according to the IQWiG framework, and the surrogacy of PCR on OS was classified as level 4 according to the Fleming hierarchy [7].

In 2015, Cortazar et al. conducted an IPD meta-analysis of 11,955 patients involved in 12 trials. At trial-level associations, coefficient of determination between PCR and OS was 0.24 (95% CI, 0.00–0.70). This study provides "no proof" of the surrogacy of PCR on OS according to the IQWiG framework, and the surrogacy of PCR on OS was classified as level 4 according to the Fleming hierarchy [8].

Adjuvant setting

One study was identified. In 2007, Ng et al. conducted a meta-analysis on aggregate data.

Two-year DFS was not considered a valid surrogate for OS according to the IQWiG framework and Fleming hierarchy.

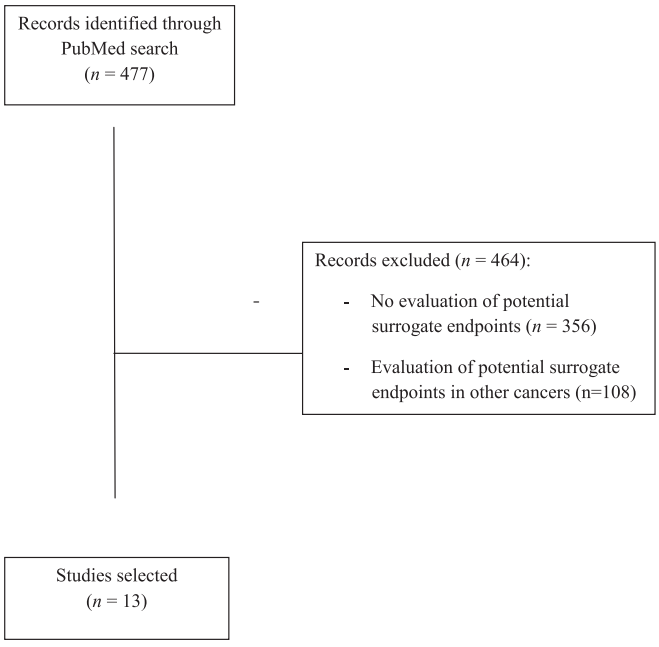

Fig. 1. Identification of studies from PubMed search.