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Original article

Correlation between overall survival and other endpoints in metastatic breast cancer with second- or third-line chemotherapy: Literature-based analysis of 24 randomized trials

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Corrélation entre taux de survie globale et autres critères dans le cancer du sein métastatique traité par 2e et 3e ligne de chimiothérapie : analyse de la littérature basée sur 24 essais randomisés

Keywords
Breast cancer
Subsequent chemotherapy
Progression-free survival
Time to progression
Objective response rate

Summary

Background and objective > Correlations between overall survival (OS) and other endpoints have been evaluated in patients with metastatic breast cancer (MBC) who received first-line chemotherapy. However, no corresponding analysis has been accomplished for patients who have undergone second- or third-line chemotherapy.

Methods > We evaluated the potential of progression-free survival (PFS)/time to progression (TTP) and objective response rate (ORR) as surrogates of OS when OS data were not available. Correlations were evaluated by Spearman's rank correlation coefficient (r_s) and weighted linear regression model. Subgroup analyses were performed for previous chemotherapy, regimen, study endpoint, study period and HER2 status.

Results > Twenty-four randomized trials involving 8617 patients were included for analysis. The correlation between PFS/TTP and OS was 0.7824 (95% CI: 0.6034–0.8702), whereas ORR did not strongly correlate with OS (r_s = 0.5398, 95%CI: 0.2942–0.7233). Further, the association between hazard ratios (HRs) of PFS/TTP and OS of the 22 randomized studies showed a moderate correlation (r_s = 0.5725, 95%CI: 0.1735–0.8277); the slope of the regression model (β) was 0.5366 (95%CI: 0.3479–0.7253). In particular, the PFS/OS correlation for HER2-positive MBC patients was stronger (r_s = 0.9515, 95%CI: 0.7009–1.0000; β = 0.8728, 95%CI: 0.0795–1.6661).

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Conclusions > These results suggest that PFS/TTP is a useful early endpoint for patients with MBC who have undergone second- or third-line chemotherapy, especially for those who are HER2-positive.

Mots clés
Cancer du sein
Chimiothérapie
Survie globale
Survie sans progression
Taux de réponse

Introduction

Among women, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death worldwide, accounting for 23% of total cancer cases and 14% of cancer deaths [1]. For breast cancer detected early, the prognosis is good, but breast cancer is often incurable once cancer cells spread to other parts of the body (metastatic breast cancer [MBC]). The median overall survival (OS) of patients with MBC treated with first-line combination chemotherapy regimens is between 20 and 45 months [2].

Over the last decade, significant achievements have been made in first-line chemotherapy for MBC [3–5]. Although there may be clinical remission or disease stabilization in many MBC patients with first-line chemotherapy, most will ultimately experience disease progression and be candidates for further chemotherapy. For patients who have experienced disease progression either during or after first-line chemotherapy for MBC, effective second-line chemotherapy is essential. A phase III randomized controlled trial (RCT) showed that lapatinib plus trastuzumab significantly delayed progression of the disease and improved the OS relative to lapatinib alone [6]. However, a RCT of lapatinib plus capecitabine compared with capecitabine alone has resulted in no improvement of OS [7]. In recent years, post-progression survival (PPS) has became increasingly prominent due to the availability of more effective treatments as further chemotherapy, which affects estimation of OS and makes it a less useful endpoint. From this point, clinical trials with application of an effective surrogate endpoint may be more likely to make a positive conclusion. Additionally, clinical trials with application of a validated, short-term surrogate endpoint would shorten development cycles and save research costs [8]. In previous reviews, the correlation between progression-free survival (PFS)/time to progression (TTP) and OS has been estimated for patients with MBC who have undergone first-line chemotherapy [2,8–10]. To our knowledge, no corresponding analysis has been accomplished for MBC patients with second- or third-line chemotherapy. Therefore, we conducted a meta-analysis to determine if PFS or other endpoints correlate with OS in MBC patients who have undergone second- or third-line chemotherapy.

Glossary

MBC	**Metastatic breast cancer**
NSCLC	**Non-small cell lung cancer**
RCT	**Randomized controlled trial**
OS	**Overall survival**
PFS	**Progression-free survival**
PPS	**Post progression survival**
TTP	**Time to progression**
ORR	**Objective response rate**
HR	**Hazard ratio**
rs	**Spearman's rank correlation coefficient**
WLS	**Weighted linear regression**
CI	**Confidence interval**
R^2	**Coefficient of determination of WLS**
β	**Slop of WLS**

Materials and methods

Literature search and eligibility criteria

Randomized clinical trials of second- or third-line chemotherapy for MBC published from January 1999 to March 2014 were identified through a systematic search of PubMed. The keywords included "randomized clinical trial," "breast cancer," "advanced or metastatic," and "chemotherapy." We used Google Scholar and PubMed to conduct a citation search of identified studies and reference lists of original and review articles were checked for additional citations. To avoid publication bias, we also checked unpublished articles that listed abstracts from conference proceedings of the American Society of Clinical Oncology, the European Cancer Conference, and the European Society for Medical Oncology. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines in designing, performing, and reporting the systematic review [11]. The search was limited to articles published in English. Trials designed to assess first-line chemotherapy, surgery, radiotherapy, vaccine therapies, or endocrine therapies alone were also excluded.