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Original article

Comparison between doublet agents versus single agent in metastatic breast cancer patients previously treated with an anthracycline and a taxane: A meta-analysis of four phase III trials

Wei-Xiang Qi, Li-na Tang, Ai-na He, Zan Shen, Yang Yao*

Department of Oncology, The Sixth People's Hospital, Shanghai Jiao Tong University, No. 600, Yishan Road, Shanghai 200233, China

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ABSTRACT

Aim: To compare doublet agents with single agent as salvage treatment in metastatic breast cancer (MBC) patients pre-treated with an anthracycline and a taxane.
Methods: We systematically searched for randomised clinical trials that compared doublet agents with single agent in MBC patients pre-treated with an anthracycline and a taxane. The primary end point was overall survival (OS). Secondary end points were progression-free survival, overall response rate and grade 3 or 4 toxicity. Data were extracted from the studies by two independent reviewers. The meta-analysis was performed by Stata version 10.0 software (Stata Corporation, College Station, TX, USA).
Results: Four trials comprising 2373 patients were eligible for inclusion. Meta-analysis showed that there was significant improvement in progression-free survival (PFS) (hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.72–0.86, $P = 0.000$) and overall response rate (risk ratio (RR) 1.47, 95%CI 1.13–1.91; $p = 0.004$) in doublet agents group, though the pooled HR for OS (HR 0.96, 95%CI 0.87–1.05; $p = 0.356$) showed no significant difference. Subgroup analysis also favoured capecitabine-based doublet agents therapy in terms of PFS (HR 0.77, 95%CI 0.70–0.86; $p = 0.000$) and overall response rate (ORR) (RR 1.65, 95%CI 1.06–2.56; $p = 0.026$), but gemcitabine-based doublet agents therapy gained no clinical benefits. There were more incidences of grade 3 or 4 anaemia (RR 1.610, 1.212–2.314, $p = 0.01$), neutropenia (RR 2.239, 1.231–4.071, $p = 0.008$), thrombocytopaenia (RR 2.401, 1.595–3.615, $p = 0.000$), fatigue (RR 2.333, 1.338–4.006, $p = 0.000$) and nausea and vomiting (RR 2.233, 1.558–3.199, $p = 0.000$) in the combination group. With regard to the risk of grade 3 or 4 stomatitis (RR 1.666, 0.818–3.392, $p = 0.160$), diarrhoea (RR 0.739, 0.542–1.008, $p = 0.056$) and hand–foot syndrome (RR 1.002, 0.835–1.203, $p = 0.983$), equivalent frequencies were found between the two groups.
Conclusion: Combination chemotherapy offered a significant improvement in PFS and ORR in patients with MBC pre-treated with an anthracycline and a taxane but did not benefit OS. With present available data from randomised clinical trials, we were still unable to clearly set the role of combination therapy in the treatment of MBC in this setting.

Breast cancer is the most common cancer in women in Western countries along with a sharp increase in its incidence rate in developing countries.[1] In addition, one in every three women initially diagnosed with breast cancer eventually develops locally advanced or metastatic disease,[2,3] and the median survival time for these patients is only 2–3 years.[4] Nowadays, chemotherapy regimens containing taxanes and anthracyclines are the standard treatment for advanced or metastatic breast cancer (MBC).[5] However, MBC often progresses because of primary or acquired resistance to taxanes and anthracyclines. Furthermore, chemotherapy regimens containing taxanes and/or anthracyclines are now often used as adjuvant or neo-adjuvant treatment for early breast cancer especially in women at high risk, which limits their use in patients with MBC. As a result, there is a need to investigate new efficient agents or combination therapy for patients with MBC pre-treated with an anthracycline and a taxane.

Newer cytotoxic agents such as capecitabine, gemcitabine, ixabepilone and vinorelbine have been proven efficacy for patients

* Corresponding author.
E-mail address: qwxzlk@163.com (Y. Yao).

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with MBC who have been previously treated with anthracyclines and taxanes.[6–11] However, capecitabine is the only cytotoxic agent approved for patients with MBC who failed anthracycline and taxane treatment.[12,13] Moreover, the efficacy of single-agent capecitabine in this setting is limited with an overall response rate (ORR) of 20–26%, a median progression-free survival (PFS) of 3.0–4.6 months and a median overall survival (OS) of 10.4–15.2 months.[14–17] Clearly, further improvements are required.

One potential approach is to combine these efficient agents for patients with MBC according to different mechanisms of drug action and toxicities. In addition, several randomised controlled trials (RCTs) have been recently conducted in this setting, but the results are controversial. Therefore, we conduct this meta-analysis to give an overview of the results of all eligible randomised trials with the aim of investigating whether doublet agents are more effective than single agent in anthracycline- and taxane-pretreated women with MBC.

Materials and methods

Literature search

We searched PubMed and the Cochrane Register of Controlled Trials using various combinations of different terms 'breast cancer', 'pretreated', 'capecitabine', 'xeloda', 'gemzar', 'gemcitabine', 'vinorelbine', 'ixabepilone', 'relapesed', 'metastatic', 'randomized' and 'salvage treatment'. The last search was updated in October 2011. We looked at posters from the annual meetings of the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) in the past 10 years. We also manually searched posters of 2009, 2010 and 2011 San Antonio Breast Cancer Symposium (SABCS). The search was limited to clinical studies in the English language, and reference lists from relevant primary studies and review articles were also examined to find additional publications.

Study selection

The relevant clinical trials were manually selected carefully based on the following criteria: (1) trails comparing doublet cytotoxic agents with single agent; (2) patients were pathologically confirmed of breast cancer and previously treated with an anthracycline and a taxane; (3) phase III RCT; and (4) the study has included sufficient data for extraction. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most informative) was included.

Data extraction

Two independent investigators reviewed the publications and extracted the data. Disagreement on specific studies between the two reviewers was resolved through discussion. The following information was extracted from each article: (1) basic information from papers such as, year of publication, journal name, author name, etc.; (2) characteristics of patients such as sex, age, performance status, disease burden, type of metastasis, quality of response in previous lines of treatment, biology of the tumours including estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor-2 (HER-2) status; (3) information of study designation such as: sample size per group, study design, randomisation scheme, inclusion criteria and type of end point used; and (4) information of treatment such as treatment modality, dose of chemotherapy, withdrawals, median OS, ORR, adverse events (AEs) and so on. Available information was extracted and recorded to a data collection form and entered into electronic database.

Data analysis

The analysis was undertaken on an intention-to-treat basis: patients were analysed according to treatment allocated, irrespective of whether they received that treatment. The outcomes used were (1) OS, defined as the time from random assignment to death from any cause, censoring patients who had not died at the date last known alive; (2) PFS, defined as the time from random assignment to first documented progression; and (3) ORR, defined as the sum of partial and complete response rates according to the Response Evaluation Criteria in Solid Tumours.[18]

Statistical analysis of the overall hazard ratio (HR) for OS and PFS, the risk ratio (RR) for ORR and grade 3 or 4 AEs was calculated using Stata version 10.0 software (Stata Corporation, College Station, TX, USA). When OS could not be extracted from the original reports directly in several RCTs, we deciphered them from the survival curve as reported by Parmar et al.[19] Between-study heterogeneity was estimated using the χ^2-based Q statistic.[20] Heterogeneity was considered statistically significant when $P_{\text{heterogeneity}} < 0.05$ or $I^2 > 50\%$. If heterogeneity existed, data was analysed using a random effects model. In the absence of heterogeneity, a fixed effects model was used. Sources of heterogeneity were appraised by subgroup stratification analysis, based on several study characteristics, such as different drug combination and source of control individuals. A statistical test with a p-value less than 0.05 was considered significant. HR >1 reflects more deaths or progression in doublet agents group, and RR >1 indicates more toxicities and ORR in doublet agents group; and vice versa. The presence of publication bias was evaluated by using the Begg and Egger tests.[21,22] For the possible publication bias, we then used trim and fill method to evaluate the influence to the result. All p-values were two sided. All confidence intervals (CIs) had a two-sided probability coverage of 95%.

Assessment of study quality

An open assessment of the trials was performed using the methods reported by Jadad and colleagues,[23] which assessed the trials according to the following three questions: (1) whether reported an appropriate randomisation method (0–2 scores); (2)

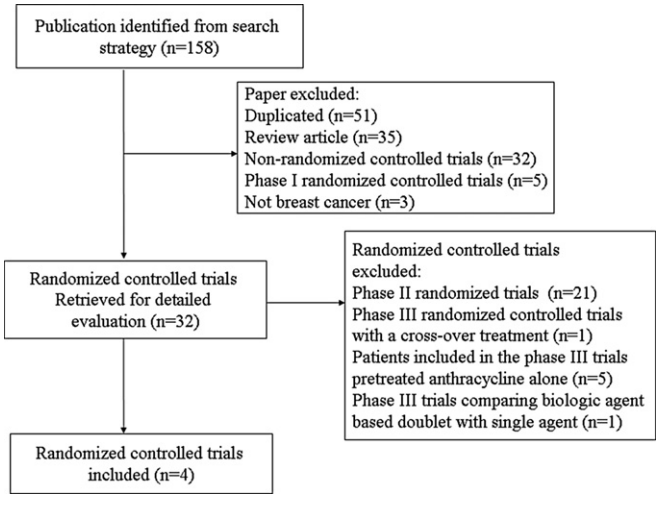

Fig. 1. Studies eligible for inclusion in the meta-analysis.