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Hot Topic

# If there is no overall survival benefit in metastatic breast cancer: Does it imply lack of efficacy? Taxanes as an example

Birgit E.P.J. Vriens [a,d], Dorien J.A. Lobbezoo [a,b,e], Joep P.J. de Hoon [a,d], Jürgen Veeck [a,d], Adri C. Voogd [c,f], Vivianne C.G. Tjan-Heijnen [a,*,d]

[a] Division of Medical Oncology, Department of Internal Medicine, GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands
[b] Department of Internal Medicine, Máxima Medical Centre, Eindhoven, The Netherlands
[c] Department of Epidemiology, GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands

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ABSTRACT

In recent years, new drugs have shown activity in metastatic breast cancer, but not always resulting in an overall survival benefit. This has led to discussions if such drugs, mainly expensive drugs, should be reimbursed especially when also not leading to improvement in quality of life. For that reason, we decided to systematically review taxane-based chemotherapy studies in early and metastatic breast cancer, to assess which factors may have caused the differential outcome. Taxanes did not improve survival in metastatic breast cancer trials, whereas they did so in early breast cancer trials. We questioned if the differential outcome of taxanes in metastatic breast cancer might be caused by the chosen comparator and study design. We noticed that in the majority of metastatic breast cancer studies taxanes were used as a substitute for other active cytotoxic drugs, mainly cyclophosphamide, whereas in early breast cancer studies taxanes were generally delivered in addition to a standard regimen. We conclude from our analyses that use of taxanes instead of other active drugs explains the lack of overall survival benefit in metastatic breast cancer trials. Further, our results suggest that cyclophosphamide is an important drug in the treatment of breast cancer, being as effective as optimally dosed taxanes and anthracyclines. By studying the different study designs and comparators in both settings, we were able to demonstrate their impact on efficacy endpoints. We conclude, therefore, that re-assessment of studies of drugs both assessed in metastatic and early breast cancer provides a new tool for improved understanding.


## Introduction

Taxanes are approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in metastatic and early breast cancer. Despite registration, it was concluded in the most recent Cochrane review that there was no evidence of a survival benefit in metastatic breast cancer for single-agent taxanes versus anthracyclines.[1] And, although an overall survival benefit was seen in favour of taxane containing regimens, the superiority of taxane regimens over non-taxane containing regimens was not seen if the non-taxane regimens were largely limited to optimally-dosed anthracycline-based regimens.[1] In a second review on taxanes in metastatic breast cancer, it was concluded that single-agent taxane was even less effective than single-agent anthracycline, based on the EORTC study 10923.[2] On the other hand, it was concluded that first-line anthracycline–taxane combinations seemed slightly better than anthracycline-based regimens with regard to tumor response and progression-free survival, although not with regard to overall survival. However, the conclusions from meta-analyses on adjuvant taxane breast cancer trials were remarkably different, showing an improvement in both disease-free and overall survival.[3–5]

In recent years, new drugs have shown activity in metastatic breast cancer, but not always resulting in an overall survival benefit.[6] In the oncology community this has led to discussions on whether such drugs should be reimbursed. A thorough analysis of drugs without a clear survival gain in metastatic breast cancer

* Corresponding author. Address: Division of Medical Oncology, Department of Internal Medicine, Maastricht University Medical Centre, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands. Tel.: +31 43 3877025; fax: +31 43 3876281.
*E-mail addresses:* b.vriens@mumc.nl (B.E.P.J. Vriens), D.Lobbezoo@mmc.nl (D.J.A. Lobbezoo), joep.dehoon@maastrichtuniversity.nl (J.P.J. de Hoon), jurgen.veeck@path.unimaas.nl (J. Veeck), adri.voogd@maastrichtuniversity.nl (A.C. Voogd), vcg.tjan.heijnen@mumc.nl (V.C.G. Tjan-Heijnen).
[d] Division of Medical Oncology, Department of Internal Medicine, Maastricht University Medical Centre, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands. Tel.: +31 43 3877025; fax: +31 43 3876281.
[e] Department of Internal Medicine, Maxima Medisch Centrum, P.O. Box 90052, 5600 PD Eindhoven, The Netherlands. Tel.: +31 40 8885320; fax: +31 43 3876281.
[f] Department of Epidemiology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands. Tel.: +31 (0) 43 3882387; fax: +31 43 3876281.

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but with a survival gain in early breast cancer may help clarify this apparent discrepancy, and may prevent premature conclusions on the value of new drugs in this field. For that reason, we decided to systematically review taxane-based chemotherapy studies in early and metastatic breast cancer, to assess which factors may have caused the different outcomes between these patient groups.

## Methods

### *Search strategy and selection criteria*

A detailed search strategy, consisting of numerous MeSH heading and text word combinations, "breast cancer", "chemotherapy", "taxanes", "docetaxel" and "paclitaxel", was used to search the PubMed database. Publications of clinical phase III trials between 1995 and November 1, 2010 in the English language were included. Abstracts of the annual meetings of the American Society of Clinical Oncology (ASCO) and of the San Antonio Breast Cancer Symposium (SABCS) were searched for relevant trials (and replaced by full papers if published before November 1, 2011).

Trials with the taxanes docetaxel and paclitaxel in combination with or compared to anthracyclines, and used within its licensed indications, as well as comparator regimens which are considered as standard of care, were eligible. Consequently, we excluded trials that used first generation chemotherapy schemes, other combinations with no licensed indication, as well as trials including pegylated doxorubicin or nab-paclitaxel or comparing different taxanes.

### *Study categories and endpoints*

Our primary research question was whether we could identify factors that contributed to the differential outcome of taxanes in metastatic versus early breast cancer setting. For that, we categorized the studies by disease setting, by choice of taxane and by study design, i.e., substitution of another active drug or addition of a taxane without substitution. Finally, we addressed the most optimal use of taxanes, sequential or concurrent use. Studies in which both arms either used concurrent or sequential taxanes were excluded.[7]

### *Data and statistical methods*

Data on the outcomes of interest were: response rate and progression-free survival in metastatic breast cancer, disease-free survival in early breast cancer and overall survival in both settings. Because of immature follow up we mainly report on disease-free survival in early breast cancer studies. Trials were not consistent in the way they defined progression-free or disease-free survival; out of convenience we analysed all these as if they reported on progression-free and disease-free survival in a similar way. If odds ratios or hazard ratios were not provided, they were obtained using the available summary statistic.[8] If insufficient data were available the trials were not included in the pooled analysis.

We performed a pooled analysis using the Review Manager software (RevMan 5) provided by the Cochrane Collaboration. We used the fixed or random effect model, based on observed minus expected number of events and the variance of each trial. Chi-square tests were used to test for heterogeneity over all trials included in the pooled analyses. Due to the limited number of trials in each pooled analysis, no sensitivity analysis could be performed when significant heterogeneity occurred among the trials.

## Results

### *Overall efficacy of taxanes in metastatic and early breast cancer*

In total 10 trials in the metastatic breast cancer setting were included, comparing taxane containing chemotherapy schemes with anthracycline containing schemes (Table 1). We calculated the pooled hazard ratio and found no significant difference for progression-free survival with a hazard ratio of 0.94 (95% CI 0.88–1.01) and for overall survival with a hazard ratio of 0.98 (95% CI 0.91–1.05) (Fig. A, Appendix).

In total 21 trials in the adjuvant breast cancer setting were included, comparing chemotherapy schemes with and without taxanes (Table 2). We were able to calculate pooled hazard ratios for 14 trials, with regard to overall survival. The pooled analysis showed a hazard ratio for disease-free survival of 0.85 (95% CI 0.80–0.91) in favour of adding a taxane. Moreover, a significant difference in favour of taxanes was seen in overall survival (hazard ratio 0.85; 95% CI 0.79–0.91) (Fig. B, Appendix).

### *Efficacy according to the choice of taxane in metastatic and early breast cancer*

In our pooled analysis of metastatic breast cancer studies, there was a trend for improved overall survival with a hazard ratio of 0.88 (95% CI 0.76–1.01) when only including studies using docetaxel (Fig. A, Appendix). In contrast, overall survival was not improved in metastatic breast cancer studies using paclitaxel with a hazard ratio of 1.01 (95% CI 0.93–1.10) (Fig. A, Appendix).

On the other hand, in early breast cancer docetaxel and paclitaxel resulted in similar improvements in overall survival both with a hazard ratio of 0.85 (95% CI 0.77–0.94) (Fig. B, Appendix). In all but one study on paclitaxel a 3-weekly schedule was used.[9]

### *Substitution or addition of taxanes in metastatic breast cancer*

In metastatic breast cancer most studies investigated substitution, either by use of taxanes as single-agent versus single-agent anthracyclines or by use of taxanes in combination with anthracyclines versus anthracycline-cyclophosphamide combinations.

#### *Substitution: taxanes versus anthracyclines as single–agent*

The registration of single-agent docetaxel was based on the TAX 303 trial. Patients received either 3-weekly docetaxel 100 mg/m$^2$ or adriamycin 75 mg/m$^2$ (Table 1).[11] With respect to response rate docetaxel was superior. Progression-free survival and overall survival were not improved. There are two studies comparing paclitaxel with anthracyclines (Table 1).[10,12] In the EORTC 10923 trial, patients were randomized to receive either 3-weekly paclitaxel 200 mg/m$^2$ or adriamycin 75 mg/m$^2$.[12] In the North-American ECOG E1193 trial patients were randomized to receive single-agent paclitaxel (3-weekly 175 mg/m$^2$) or single-agent adriamycin (3-weekly 60 mg/m$^2$).[10] Compared with a relative low dose adriamycin, 3-weekly paclitaxel showed similar efficacy.

Our pooled analysis shows a hazard ratio for overall survival of 1.02 (95% CI 0.89–1.16), showing that single-agent taxanes are equally effective as single-agent anthracyclines in first and second line treatment of metastatic breast cancer (data not further shown). It is noted that the taxane choice and anthracycline dose both may have influenced the individual study outcomes.

#### *Substitution: anthracycline-taxane combinations versus AC or FAC*

There are five phase III trials that report on the comparison between an anthracycline–taxane combination regimen (AT) and an anthracycline–cyclophosphamide (AC) combination regimen, two of