

Time to full publication of studies of anti-cancer drugs for breast cancer, and the potential for publication bias: a systematic review

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Study rationale

The development of targeted therapies in recent years has led to increasing numbers of specialised anti-cancer treatments. In the United Kingdom (UK), the National Institute for Health and Clinical Excellence (NICE) has issued guidance on the use of such treatments to the NHS. This occurs through NICE's Single Technology Appraisal (STA) programme, which aims to assess their effectiveness early to allow release of guidance around the issuing of marketing authorisation.

Large clinical trials are the standard for making treatment decisions, and non-publication of the results can lead to bias in the literature, contributing to inappropriate medical decisions.¹ Increasingly oncology trials are stopping early,² with more than a doubling rate across therapeutic areas since 1990.³ This is reflected in over 78% of randomised controlled trials (RCTs) in the last three years using an interim analysis for registration purposes.² NICE has already issued guidance in the absence of full peer-reviewed trial data being available.⁴ It is therefore important to establish the pattern of full publications to inform the developing methodology for systematic reviews in this fast moving area (for full details of this review, please see Takeda *et al*, in press⁵).

Objectives

- The key objective was to identify the delay between conference abstracts and full publication of results from RCTs of new anti-cancer agents for breast cancer.
- A secondary objective was to identify whether there are any apparent biases in the publication and reporting of these trials.

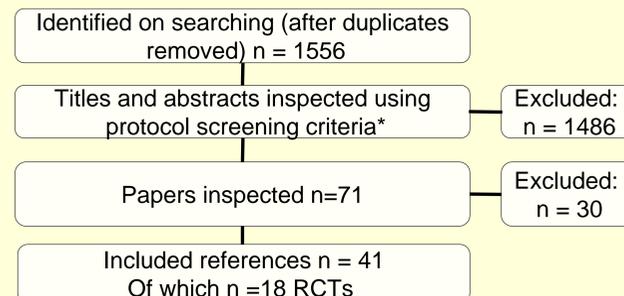
Methods

- A systematic review was conducted.
- A full search of existing NICE STA appraisals of anti-cancer drugs for breast cancer was undertaken by one reviewer and checked by a second. This included technologies which were currently in the process of being appraised or due to be by NICE.
- We identified 11 areas of NICE guidance for eight anti-cancer drugs.
- As many of the interventions had previous technology assessments for NICE, literature searches were limited to studies published after the cut-off dates of searching in the previous publications until August 2007,
- A number of electronic databases were searched, including: Ovid MEDLINE®; EMBASE; DARE, the Cochrane library and ISI Proceedings.
- The National Research Register and ClinicalTrials.gov were searched to identify RCTs in progress.
- Websites of international conferences were also searched, from 5 years prior to the date of marketing authorisation until the present date.

Inclusion criteria:

- Population:** Adults (age >18) with breast cancer (meeting specific disease stage criteria as appropriate)
 - Comparator:** Any, including placebo
 - Outcomes:** time to full publication, overall survival and any measures relating to time to disease progression
 - Study type:** Systematic Reviews and RCTs
- 6 interventions met the criteria (see Table 1).
 RCTs were quality assessed using recognised criteria (Centre for Reviews and Dissemination, 2001).

Figure 1. Flow chart of systematic review process



*Protocol amendment, limiting searches to NICE STA drugs

Methods (cont.)

- Inclusion criteria, decisions on quality criteria and data extraction were applied independently by two reviewers, with any differences in opinion resolved through discussion.
- Data were extracted from the included studies using a pre-designed and piloted data extraction template to report information on the month and year of publication of each included study, the numbers of participants in each study arm (to allow identification of linked studies), and key outcome data from each study.
- Full publications and abstracts were linked by reference to trial identifiers, trial arms, numbers of participants and any other available information.
- No statistical analysis was performed due to the small sample size.
- Mean time between publication of abstracts and full paper: for trials reporting key outcomes in abstract form but without a full publication of these results, a calculation of the mean time between publication of the abstract and the end of the search dates was made. Calculation of time to publication was restricted to abstracts and corresponding full papers which reported measures of overall survival or aspects of disease progression. Abstracts which only reported baseline characteristics, adverse events or quality of life scores were not included in the analysis.

Table 1: Interventions and NICE indications

Breast cancer drug	Indications considered by NICE
Early breast cancer	
Docetaxel	In combination with doxorubicin and cyclophosphamide for women diagnosed with operable node-positive breast cancer
Paclitaxel	As monotherapy for node-positive breast cancer
Trastuzumab	Monotherapy as second-line treatment
Advanced/metastatic cancer	
Gemcitabine	In combination with paclitaxel
Lapatinib	In combination with capecitabine
Bevacizumab	In combination with capecitabine, docetaxel, paclitaxel or cyclophosphamide and methotrexate

†Lapatinib and bevacizumab were 'appraisals in progress' at the time of our study. Indications considered here reflect those identified in the literature for bevacizumab and the combination in NICE's scope for lapatinib.

Results

- A total of 1556 publications were identified through literature searching. Of these, 1365 were excluded on title and abstract. The protocol amendment led to the exclusion of a further 121 studies.
- 71 studies were requested for more in-depth screening, leading to the exclusion of another 30 studies.
- The remaining 41 publications consisted of 18 RCTs, including at least one arm of treatment and meeting the indications noted in Table 1 (for reference list see Takeda *et al*, in press⁵). The 18 RCTs (see Takeda *et al*, in press) consisted of 2 RCTs each for paclitaxel and gemcitabine, 3 RCTs each for docetaxel, trastuzumab and lapatinib, and 5 RCTs for bevacizumab.

Results (cont.)

- The mean time delay between publication of abstracts to full publication of the RCTs was 9 months (range 5 - 19 months).
- 11 trials were without a full publication of data presented in an abstract or conference proceeding, with the duration between publication of the abstracts and the end of our searches (August 2007) varying from 3 - 38 months.
- Mean time awaiting publication (to August 2007) was 16.5 months.
- 7 trials were without full publications at least 12 months after the abstract data was presented and 4 remain unpublished after 21 months or more.

Limitations

- This review was limited to drug combinations and patient groups appraised under the NICE STA programme and resulted in a sample size too small for a statistical analysis. Only most relevant outcomes to the NICE process were data extracted.
- Strengths of this review are that the authors have no vested interest in these interventions, and that the principles of good practice in systematic reviewing have been followed.

Conclusions

- Around 40% of abstracts presented at scientific meetings are never published in full.⁶
- Breast cancer trials have been reported as having the highest proportion of unpublished studies, at 36% at 5 years after publication of the abstract, compared to 26% for all cancer.⁷
- Publication delay or failure to publish current research can lead to a biased pool of evidence.⁷
- Many new drugs will have only recently gained regulatory approval and the complete body of evidence may not be available for public scrutiny.⁸
- Rapid and full publication of trial results is not only vital for the effective appraisal of the efficacy of new technologies upon which treatment decisions are made, but also of interest to all of those concerned with new therapies, particularly in the fight against cancer.
- Future research should investigate the effect of publication delays on decision making, as well as on the availability of new drug treatments in clinical practice for these and other anti-cancer drugs.

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