International Journal of Technology Assessment in Health Care, **26:1** (2010), 110–116.

doi:10.1017/S0266462309990778

Time to full publication of studies of anticancer drugs for breast cancer, and the potential for publication bias

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Objectives: Nonpublication of results of clinical trials can contribute to inappropriate medical decisions. The primary aim of this systematic review was to investigate publication delays between conference abstracts and full journal publications from randomized controlled trial results of new anticancer agents for breast cancer. The review was restricted to anticancer agents previously, or due to be, appraised in the United Kingdom by the National Institute for Health and Clinical Excellence. A secondary objective was to identify whether there are any apparent biases in the publication and reporting of these trials.
Methods: We searched six electronic databases up to August 2007, including Medline and the Cochrane Library. Two reviewers independently selected studies, extracted and assessed the data.
Results: Six anticancer treatments were identified: docetaxel, paclitaxel, trastuzumab, gemcitabine, lapatinib, and bevacizumab. Of eighteen included trials, only four publications from three trials reported the same outcomes in both abstract and full publication. Time delays ranged from 5 to 19 months. Eleven trial abstracts were still without a full publication at the end of our searches, varying from 3 to 38 months since abstract publication. Observational analysis revealed no particular publishing biases.
Conclusions: Whereas delays in publication appear reasonable over a period of months, many were not published in full over a period of years and others would appear to be unlikely to ever be published. Further research should investigate the impact of publication delays on the availability of new drug treatments in clinical practice.

Keywords: Breast cancer drugs, Methodology, Publication delay, Systematic review

Large clinical trials are the standard for making treatment decisions, and nonpublication of the results can lead to bias in the literature, contributing to inappropriate medical decisions (26). Increasingly, oncology trials are stopped early (44) with rates having more than doubled since 1990 (24). In the past 3 years, over 78 percent of randomized controlled trials (RCTs) have used an interim analysis for registration purposes (44).

Positive results appear to be published quicker than null or negative results, and only 63 percent of clinical trials are published in full (33). Nearly one-third are not fully published 5 years after being presented as abstracts (26). Abstracts can only present limited information (47) and inconsistencies between conference abstracts and later published reports

We are grateful for the input to our systematic review to the following experts: Ms. Suzie Paisley, School of Health and Related Research, University of Sheffield; Dr. Stephen Johnston, Royal Marsden Hospital, Sutton; and Dr. Sally Hopewell, The UK Cochrane Centre, Oxford. We also thank the staff at the Information Resource Centre, Wessex Institute. This project was completed as part of a short systematic review funded by the NIHR Health Technology Assessment Programme (Project No. 07/55/01). It has been published in full in Health Technology Assessment 2008, Vol. 12, No. 32, and can be found on the HTA Programme Web site (www.hta.ac.uk). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health. The authors report nothing to disclose.

Table 1. Inclusion Criteria for the Systematic Review

Patients:	Adults (age over 18) with breast cancer (meeting specific disease stage criteria as appropriate)
Interventions[a] (Indications considered by NICE):	*Early 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* • Bevacizumab[b] (in combination with capecitabine, docetaxel, paclitaxel or cyclophosphamide and methotrexate) • Gemcitabine (in combination with paclitaxel) • Lapatinib[b] (in combination with capecitabine)
Comparator:	Any, including placebo
Design:	RCTs

[a]Alone or in combination according to licensed indications
[b]Lapatinib and bevacizumab were 'appraisals in progress' therefore indications considered here reflect those identified in the literature for bevacizumab, and the combination in NICE's scope for lapatinib.

have been identified, impacting on final assessment results (20).

In recent years, there have been increasing numbers of specialized anticancer 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) program, which aims to assess effectiveness early to allow release of guidance around the issuing of marketing authorization. Chemotherapy drugs have been among the first to be appraised through STAs. However, early appraisal often involves a limited evidence base, with few trials undertaken or published in full. On occasions, details of RCTs may never be fully published.

NICE has issued guidance on several drugs for breast cancer (http://www.nice.org.uk/). Many more targeted therapies, currently in the preclinical testing stage, are likely to emerge for use as combined therapies with existing cytotoxic drugs for breast cancer (6). Although these treatments may be beneficial, they could also increase the costs to the health service (34) and as such timely appraisal is required. Inevitably, such appraisals rely on the availability of good quality evidence on the benefits, harms, and costs of the intervention to allow independent assessment.

The main objective of this systematic review was to identify the delay between conference abstracts and full publication of results from RCTs of new anticancer agents for breast cancer. The secondary objective was to identify whether there are any apparent biases in the publication and reporting of these trials.

METHODS

We identified eleven separate pieces of guidance from NICE for eight anticancer drugs. These were then limited to drugs that had been, or were due to be, appraised under the NICE STA program. Six interventions fitted the criteria (Table 1). Six databases were searched including Ovid MEDLINE and the Cochrane library. Ongoing trial databases were searched for trials in progress. Bibliographies of retrieved articles were also checked (search strategy available on request). Searches for those interventions with previous technology assessment for NICE were limited to studies published after the cut-off dates of searches in these previous publications, until August 2007.

RCTs published for the six anticancer drugs for adults with breast cancer were sought. No restrictions were placed on the outcome measures or comparators used at this stage. RCTs were quality assessed using recognized criteria (7). Inclusion criteria (Table 1), decisions on quality criteria and data extraction were applied independently by two reviewers, with any differences in opinion resolved through discussion. For full details, please see Takeda et al. (42).

RESULTS

Interventions Included

Of the six breast cancer treatments, docetaxel, paclitaxel, trastuzumab, and gemcitabine have been appraised by NICE, whereas lapatinib and bevacizumab were, at the time of writing, appraisals in process. We therefore reported all of the treatment combinations identified in the literature for bevacizumab, and restricted lapatinib to the treatment combination described in the ongoing STA's scope. For docetaxel and paclitaxel, an additional criterion required the diagnosis to include node-positive disease (as per the NICE guidance).

Searches generated 1,556 references (Figure 1). Of these, seventy-one publications were retrieved and screened for inclusion. Only forty-one publications from eighteen RCTs met the inclusion criteria. The eighteen RCTs consisted of two RCTs each for paclitaxel and gemcitabine, three each for docetaxel, trastuzumab, and lapatinib, and five for bevacizumab.

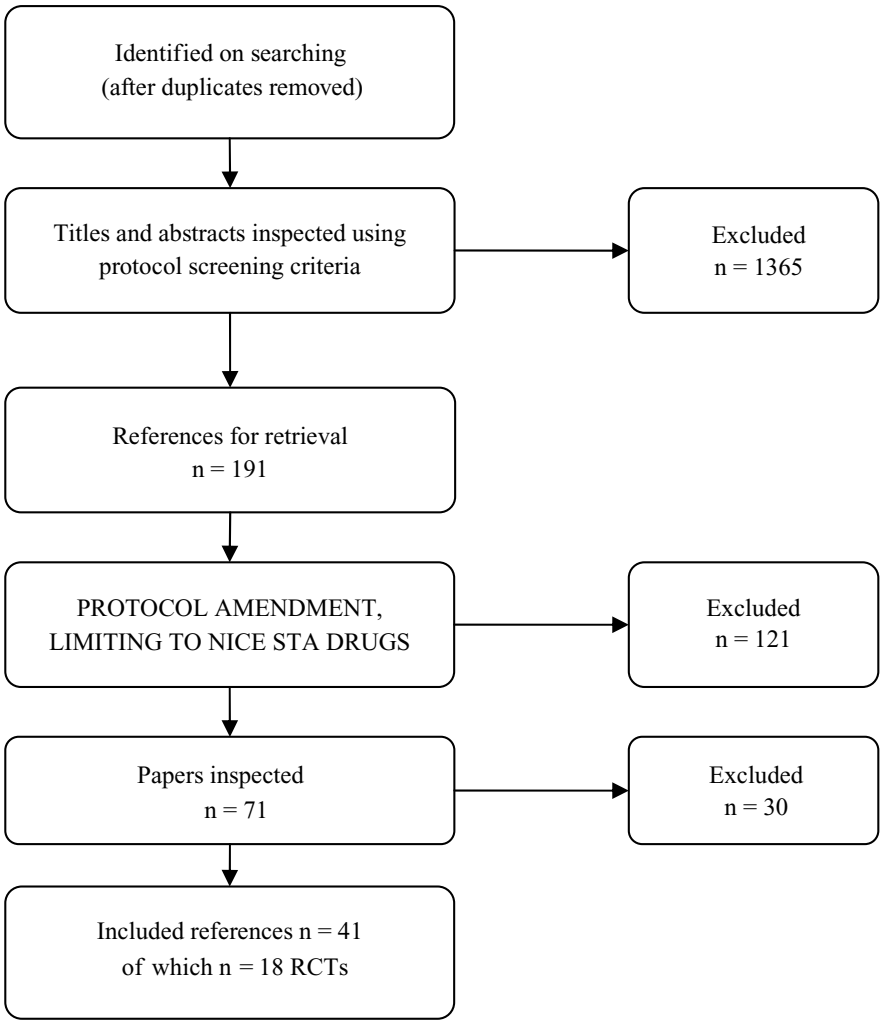

Figure 1. QUOROM flow chart of the systematic review process.

Assessment of Mean Time Between Publication of Abstracts and Full Paper

For this assessment, only those publications reporting the same outcomes were included. Calculation of time to publication was restricted to measures of overall survival (OS) or aspects of disease progression. Some trials reported outcomes in multiple abstracts and full publications. Where this has occurred, careful matching of each abstract with its respective full publication was made and a calculation undertaken. Abstracts which only reported baseline characteristics, adverse events, or quality of life scores were not included in the analysis. The mean time delay to full publication of the RCTs was 9 months (range, 5 to 19 months; Table 2).

Some trials reported key outcomes in abstract form only (i.e., no full publication of results identified). For these trials, a calculation of the mean time between publication of the abstract and August 2007 was made.

We identified eleven trials without full publication of data presented in an abstract or conference proceeding (Table 2). The duration between publication of the abstracts and the end of our searches varied from 3 to 38 months. The mean time awaiting publication to the end of August 2007 was 16.5 months; however, this estimate is based on a small sample with a large range. The calculation does not account for any differences in the interventions, manufacturers, trial sponsors, or any publication bias. Seven trials were without full publications at least 12 months after the abstract data were presented, and four of these remain unpublished after 21 months or more.

For those studies reporting a full publication, this occurred between 5 and 19 months after the abstract; however, the majority of studies had still not published data in a full publication after at least 12 months.

Comparison of Results of Abstracts and Full Papers

Of the eighteen RCTs, only three had a conference abstract and full publication sharing a common outcome

https://doi.org/10.1017/S0266462309990778 Published online by Cambridge University Press

Table 2. Abstracts with and without Full Publications

Abstracts without full publication (per treatment)		
Trial identifier	*Time since publication*[a]	*Statistical significance of trial results*
Docetaxel for early breast cancer		
GEPARDUO: Blohmer et al. (2006) (3)	18 months	Not significant
Trastuzumab for early breast cancer		
BCIRG 006: Slamon et al. (2005; 2007) (37;38)	5 months	Significant
PACS 04: Spielmann et al. (2006) (41)	15 months	No overall survival data
Gemcitabine for advanced/metastatic breast cancer		
JHQG: Albain et al. (2004) (2)\ O'Shaughnessy et al. (2003) (27)\ Moinpour et al. (2004) (23)	38 months	Significant
Lapatinib for advanced/metastatic breast cancer		
NCT00078572: Geyer et al. (2006; 2007) (10;11)	3 months	Not significant
Sherrill et al. (2007) (35)	3 months	Significant
Cameron et al. (2006) (5)	9 months	Not reported
Bevacizumab for advanced/metastatic breast cancer		
Lyons et al. (2006) (16)	15 months	Not reported
E2100: Miller et al. (2005) (21)\ Wagner et al. (2006) (46)	21 months	Significant
Burstein et al. (2005) (4)	21 months	Not reported
Overmoyer et al. (2004; 2004) (28;29)	33 months	Not reported
Abstracts with full publication (per treatment)		
Trial identifier	*Time delay*[a]	*Full publications*
Docetaxel for early breast cancer		
GEPARDUO: Von Minckwitz et al. (2002) (45)	5 months	Jackisch et al. (2002) (14)
Trastuzumab for early breast cancer		
HERA: The HERA study team (2005) (43)	5 months	Piccart-Gebhart et al. (2005) (30)
HERA: Smith et al. (2006) (40)	7 months	Smith et al. (2007) (39)
Paclitaxel for early breast cancer		
INT 0148: Sartor et al. (2003) (31)	19 months	Sartor et al. (2005) (32)

[a]as of August 2007.

(14;30;32;39;40;43;45). Of these, two sets of publications from the HERA trial, with two different abstracts (40;43) linked to two full publications (30;39), reported data on OS and time to disease progression (TTP). Of the other two linked studies, one was a publication of a secondary outcome (GEPARDUO—pathological complete response) (14;45) and one a subgroup analysis of radiotherapy delivery (INT 0148) (31;32). However, this review only considered data extracted from primary outcomes. Trials usually reported interim analyses of their data in an abstract and full analysis in another linked publication. The interim analysis of data in the HERA trial for OS and for TTP was the same in the abstract (43) and the linked full publication (30). The 2-year follow-up analysis of data from patients in the HERA trial, was also included in both the abstract (40) and the corresponding full publication (39). In general, very few studies appear to report the same outcomes in both abstract and full publication, but for those that do, results are the same.

Trials Reporting Interim Results in Abstracts and Final Results in Full Publication

It may not be meaningful to compare interim and final results, however, it is meaningful to consider if the direction of the results is similar. Three trials reported interim data in an abstract and final data in a full publication, two trials for paclitaxel (12;13;17;18) and one for docetaxel (19;25). Although the docetaxel trial reported a second interim rather than a full final analysis, it has been included here as it reports the same outcome measures as the abstract. Data presented for OS in the INT0148 trial was positive for treatment with paclitaxel in both the abstract (12) and the full results (13), with a better effect on survival in the interim analysis. Although the abstract stated that the addition of paclitaxel had a significant impact on disease-free survival (DFS), data for TTP was only reported in the full publication. The NSABP-B28 trial reported no statistically significant differences between treatment arms in survival or death at the interim analysis

https://doi.org/10.1017/S0266462309990778 Published online by Cambridge University Press

(17), while the full publication (18) reported a nonstatistically significant reduction in the death rate. DFS in this trial was reported as not statistically significantly different in the interim analysis, but statistically significant in favor of paclitaxel at the full analysis.

For docetaxel, the BCIRG 001 trial reported data for OS and TTP as interim data (25) and the second interim analysis in a peer review publication (19). For OS, the risk ratio (adjusted for node status) was not statistically significant in the abstract (25), but had reached statistical significance by the 5-year results reported in the full publication (19). The risk ratios for DFSl (adjusted for node status) presented in both the abstract (25) and full publication (5-year data) (19) were statistically significant.

A mixed picture appears when assessing the direction of effect between interim analyses and subsequent final analyses. In some trials, the direction of effect was the same, while it was not so for others.

Likelihood of Publication in Relation to Outcome

Only six of the eleven trial abstracts reported OS or an outcome measuring TTP. In this small sample of RCTs, the statistical significance of results did not appear to affect the likelihood of full publication of data previously reported in a conference abstract.

DISCUSSION

Overall, very few of the identified trials had both a conference abstract and a full publication which reported the same outcomes. Only three of eighteen RCTs had one or more full papers which reported the same outcome measures and stage of analysis as earlier conference abstracts. Selective reporting of outcomes in abstracts has been put as high as 76 percent (1), creating a biased picture of the efficacy of the treatment. Abstracts or conference presentations are not subject to a detailed and formal peer review, and provide insufficient evidence to allow for rigorous appraisal of their methods (36). They generally do not include all the information needed to assess the trial, are sparse on study characteristics and offer generalized results (22). The absence of full trial details makes it difficult to determine the value of the research and without all the evidence, could lead to erroneous conclusions being drawn. Furthermore, the rising trend of oncology trials being stopped prematurely increases the potential for unreliable findings to be transferred into clinical practice.

Docetaxel, paclitaxel, and trastuzumab all had at least one full publication reporting OS before NICE guidance being issued, although the OS data for the HERA trial appears to have been only an interim analysis. For gemcitabine, no fully published data on OS was publically available before NICE guidance being produced. At the time of the review, NICE had not issued any guidance on the use of bevacizumab or lapatinib.

This review only considered evidence available in the public domain, while the NICE Appraisal Committee has an additional submission from the manufacturer. Such submissions may contain unpublished data of trials only available publicly as conference abstracts. Although the evidence reviewed by NICE extends beyond that in the public domain, there is still the issue of whether or not such data is of the same quality as that published in peer reviewed journals.

There did not appear to be any particular biases in terms of whether positive results were more likely to be fully published than negative ones. While this is based on a small number of studies and consequently lacks statistical analysis, this is in line with findings by Dickersin et al. (9).

We found a mean time of 9 months for trials that had fully published results, and for those not yet published in full, a longer mean delay of 16.5 months. An average delay of 2 years between study termination and the publication of reports has been reported (44). However, breast cancer trials have been found to have the highest proportion of unpublished studies at 36 percent at 5 years after publication of the abstract, compared with 26 percent for all cancer (15). Publication delay or failure to publish current research can lead to a biased pool of evidence, creating problems for systematic reviewers of new health technologies (15). As systematic reviews are generally the starting point for the development of evidence-based guidelines, this bias impacts on their validity (22) and subsequent technology appraisals. While it may be important to include abstracts in systematic reviews, they should be treated with greater caution to counter for evidence of inconsistencies between abstracts and full publications (44).

The most frequent reason given by authors for not publishing in full are a lack of time, funding or resources (15). Publication bias can cause detrimental effects on the scientific progress and there are implications for human health if only half of scientific results are communicated (36). Furthermore, authors have a responsibility to their participants and failure to publish violates that trust and is considered by some as scientific misconduct (8).

Many new technologies, including drugs, will have only recently gained regulatory approval and the complete body of evidence may not be available for public scrutiny (22). 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.

This review was limited to drug combinations and patient groups appraised under the NICE STA program and resulted in a small sample size. Due to this, no statistical analysis was performed. Only the 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.

Future research may consider other anticancer drugs and should investigate the effect of publication delay on decision making.

POLICY IMPLICATIONS

The NICE STA program is designed to provide an assessment of therapies around the time of license. It is essential that the correct decision is arrived at after consideration of the full evidence base; albeit there is a risk that nonpublication or publication delays of evidence will produce a biased assessment. Nationwide-recommendations may be based on an incomplete evidence base and here we provide evidence used in six historical appraisals, which show that delays in publication appear to be common.

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