Time to publication of studies of medicines for breast cancer and the potential for publication bias

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

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Executive summary

Health Technology Assessment 2008; Vol. 12: No. 32

Health Technology Assessment
NIHR HTA Programme
www.hta.ac.uk

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Background

In recent years the development of targeted therapies has led to an increase in the number of specialised anti-cancer treatments. The National Institute for Health and Clinical Excellence (NICE) has issued guidance on many such treatments and continues to assess new drugs as they become licensed. Because the technologies are often undergoing market authorisation or have only recently been licensed, the evidence base is usually limited. Often there will be only one randomised controlled trial assessing efficacy, and this may not be fully published at the time of appraisal. It is therefore important to establish the pattern of full publications to inform the developing methodology for reviews in this fast moving area.

Methods

The methodology for this project was constrained by the tight timescales and limited resources allowed for a short report (i.e. approximately one-third of that allowed for a full technology appraisal). A full search of existing NICE technology appraisals of anti-cancer drugs for breast cancer was undertaken by one reviewer and checked by a second. Because of time constraints these were then restricted to those that had been, or were due to be, appraised under the Single Technology Appraisal (STA) programme at NICE.

A comprehensive search strategy was developed to identify RCTs of the selected interventions for the treatment of breast cancer. The following databases were searched for published RCTs: Ovid MEDLINE; EMBASE; Database of Abstracts of Reviews of Effectiveness; Cochrane Database for Systematic Reviews; the Cochrane Central Register of Controlled Trials; and ISI Proceedings. As there were previous NICE technology assessments for many of the interventions, the searches were limited to studies published after the cut-off dates of searching in the previous publications until August 2007. Dates were therefore from 2002 for capecitabine, from 2005 for docetaxel, from 2006 for paclitaxel, and from 2000 for trastuzumab and vinorelbine. For those technologies that are currently in the process of being appraised by NICE, searches were undertaken from 5 years before the date of the first license of the technology up until August 2007.

The National Research Register and a US National Institutes of Health register (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.

Titles and abstracts of identified references were screened systematically against the inclusion criteria by one reviewer and checked by a second. Inclusion criteria detailed the patient groups, interventions and comparators defined by NICE, with no restriction on the outcome measures used. Full manuscripts of all selected citations were retrieved and assessed by one reviewer and checked by a second reviewer against the inclusion criteria. Disagreements over study inclusion were resolved by consensus or if necessary through arbitration by a third reviewer. Data were extracted from the included studies by one reviewer and checked by a second reviewer. Any disagreements were resolved by consensus, if necessary involving a third reviewer.

Results

Six anti-cancer treatments for breast cancer were included in the review. Interventions for early breast cancer were docetaxel, paclitaxel and trastuzumab and interventions for advanced or metastatic breast cancer were gemcitabine, lapatinib and bevacizumab. The literature searches and checking of reference lists generated 1556 references, of which 71 publications were retrieved and screened for inclusion. Screening identified 41 publications of 18 RCTs with at least one arm of treatment meeting the inclusion criteria for the review.

Of the 18 included RCTs, only four publications (from three RCTs) reported the same outcomes in both an abstract and a full publication. Time between the abstract and full publications was 5

months in two cases, 7 months in one case and 19 months in one case (overall mean delay = 9 months).

Eleven trials were identified that have not currently published in a full publication the data presented in an abstract or conference proceeding. The duration between publication of the abstracts and the end of August 2007 varied from 3 months to 38 months (mean delay 16.5 months). The longest delays in publication were for trials investigating gemcitabine (38 months) or bevacizumab (33 months).

Conclusions

Given that the searches identified 18 relevant RCTs it was rather surprising that only three of these had one or more full papers which reported the same outcome measures (and stage of analysis) as an earlier conference abstract. Observational analysis of the published and unpublished trials did not indicate any particular biases in terms of whether positive results were more likely to be fully published than non-significant ones. However, a limitation here was the small number of studies included in this report.

Publication

Takeda A, Loveman E, Harris P, Hartwell D, Welch K. Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review. *Health Technol Assess* 2008;**12**(32).

NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

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Third, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 07/55/01. The protocol was agreed in October 2007. The assessment report began editorial review in April 2008 and was accepted for publication in May 2008. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NCCHTA.

Printed on acid-free paper in the UK by the Charlesworth Group.