Trastuzumab containing regimens for early breast cancer (Protocol)

Moja L, Brambilla C, Compagnoni A, Pistotti V

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 3

http://www.thecochranelibrary.com

TABLE OF CONTENTS

Trastuzumab containing regimens for early breast cancer (Protocol)

Moja L, Brambilla C, Compagnoni A, Pistotti V

This record should be cited as:
Moja L, Brambilla C, Compagnoni A, Pistotti V. Trastuzumab containing regimens for early breast cancer. (Protocol) *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD006243. DOI: 10.1002/14651858.CD006243.

This version first published online: 18 October 2006 in Issue 4, 2006.
Date of most recent substantive amendment: 20 August 2006

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
1. To evaluate the efficacy of trastuzumab (a monoclonal antibody against HER-2), given together with or following chemotherapy, in the adjuvant treatment of women with HER-2 positive early breast cancer.
2. To evaluate the toxicity of trastuzumab when used as a adjuvant treatment of women with HER-2 positive early breast cancer.

BACKGROUND

The antibody trastuzumab (Herceptin®) was developed as a means of blocking the tyrosine kinase-linked human epidermal growth factor receptor-2 (HER-2) (Coussens 1985). The gene encoding the HER-2 is amplified and the protein over expressed in 20 to 25% of women with early breast cancer (EBC) (Slamon 1987). The study by Baselga et al. provided the first clinical evidence of the anti-tumor activity of recombinant human monoclonal antibody against HER-2 with trastuzumab in patients with HER-2 overexpressing breast carcinomas (Baselga 1996). This and other follow-up studies have documented an important difference between trastuzumab and most standard chemotherapy agents due to its tolerability, with a favorable risk-benefit profile in patients with metastatic breast cancer (Cobleigh 1999; Vogel 2001). Following these findings, the potential efficacy in early breast cancer has been investigated and two large clinical trials of trastuzumab in women with early breast cancer were reported on 2005 (Piccart-Gebhart 2005; Romond 2005). The most common adverse events were fever, chills and other acute, self-limiting symptoms that may accompany the initial infusion of trastuzumab. Cardiac dysfunction, an important side effect reported in patients with metastatic breast cancer (MBC) when trastuzumab was used with or after anthracyclines, seems to be of less concern in neoadjuvant or adjuvant chemotherapy (Tan-Chiu 2005). Another concern that has been raised is that isolated central nervous system (CNS) progression is seen more commonly in patients with HER-2 overexpressing EBC who received trastuzumab (Piccart-Gebhart 2005), probably resulting from surviving systemic disease. Due to possible improvements in time-to-disease progression and survival, the US Food and Drug Administration (FDA) rapidly approved trastuzumab, in 1998, for the treatment of women with metastatic breast cancer (MBC) (FDA 1998). Other drug regulatory agencies have approved trastuzumab after a longer scrutiny of evidence (NICE 2002) and there has been increasing pressure on regulatory bodies to fast track its approval for women with EBC, although there is uncertainty about the true effects of trastuzumab on survival.

The current available evidence supporting trastuzumab regimens mostly relies upon surrogate end-points (for example, disease free-survival in patients with EBC). The strength of these evidences has been questioned (Apolone 2005; Joppi 2005; The Lancet 2005). The debate surrounding the decision to make trastuzumab available for women with early breast cancer has received great attention by the media (Collier 2006). Given the consequent increasing pressure by patients for its wide availability, the benefits, and above all, potential harms of trastuzumab, must be fully elucidated.

The purpose of this review is to systematically evaluate the evidence for the efficacy and safety of trastuzumab, given either with, or following chemotherapy, as part of the adjuvant treatment of women with HER-2 positive EBC.

This systematic review shares the section dedicated to ad-

verse effects with another Cochrane systematic review entitled 'Trastuzumab containing regimens for metastatic breast cancer'.

OBJECTIVES

1. To evaluate the efficacy of trastuzumab (a monoclonal antibody against HER-2), given together with or following chemotherapy, in the adjuvant treatment of women with HER-2 positive early breast cancer.
2. To evaluate the toxicity of trastuzumab when used as a adjuvant treatment of women with HER-2 positive early breast cancer.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

1. Randomised controlled clinical trials.
2. The following additional studies will be included in the search for all available toxicity information:
a. observational studies reporting suspected trastuzumab related adverse events (parallel-group controlled trials, cohort and case-control studies);
b. case series and single case reports describing suspected adverse effects that may be due to trastuzumab. The findings from these studies will be primarily used to point out practical 'implications for research'.

Types of participants

Women with HER-2 positive operable early breast cancer of any age, menopausal status, nodal or hormone receptor status.

Types of intervention

Intervention group: trastuzumab given following, or in combination with chemotherapy.
Comparator: the same chemotherapy regimen but without trastuzumab.

Trials may or may not specify recommended treatment upon disease progression or initial treatment failure. Trials where patients cross over to the other treatment arm at the time of progression or receive other treatment off-study will be included in this review and analysed according to the treatment they were originally randomised to receive. Trials which aim to compare different dosage, duration or treatment schedules of trastuzumab, alone or in combination with other chemotherapy, will be included only for side effects.

Types of outcome measures

Primary outcome measures
1. Overall survival using intention-to-treat analysis.
2. Disease-free survival.

Secondary outcome measures
3. Cardiac toxicity per protocol analysis (all patients who received the experimental treatment regardless of compliance).
4. Recurrence rates.
5. Other toxicities (defined and graded according to the WHO and NCIC criteria).
6. Treatment-related deaths.
7. Quality of life.

The following outcome definitions apply:
1. Overall survival (OS): time from the date randomised to date of death (by any cause).
2. Disease-free survival (DFS): time from randomisation to date of recurrence of tumor or death from any cause.
3. Cardiac toxicity: any grade of severity.
4. Recurrence rates: the proportion of patients with a local breast cancer recurrence or development of metastatic disease. Time to recurrence (also referred to as disease-free interval): time from the date randomised to date of first recurrence. The site of recurrence will be also recorded (i.e. skeletally distant recurrence). Within distant recurrences we will consider the risk of disease progression due to metastasis to the CNS.
5. Other toxicities: we will restrict our analysis to serious side effects classified by WHO or NCIC grading as greater than two.
6. Treatment-related death: death due to drug toxicity not disease progression. If an individual trial did not include the definition used by that trial but used the terms 'toxic death' or 'lethal toxicity' then this information will be included in the review.
7. Quality of life: an expression of well-being and measured through a validated scale (i.e. SF-36, EORTC, FACT).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Breast Cancer Group methods used in reviews.

Our search is limited to publications after January 1, 1996; this is the date Baselga et al first presented data about the efficacy of trastuzumab in humans (Baselga 1996).

For randomised controlled trials (RCTs)
See: Cochrane Breast Cancer Group search strategy

The Cochrane Breast Cancer Group (CBCG) Specialized Register will be searched. Details of the search strategy applied to create the register and the procedure used to code references are described in the Group's module on The Cochrane Library. The register includes both published and unpublished (including ongoing) trials. The CBCG codes "early" and "immunotherapy" will be applied to the specialised register and combined with the following keywords (imported with the references from MEDLINE) "trastuzumab" [Substance Name], and a search of all non-indexed fields for the following text words: Trastuzumab, Herceptin or monoclonal antibod* AND HER2.

To retrieve observational studies that report adverse events, we designed separate search strategies (as outlined below) and will consider additional sources of information.

Databases
MEDLINE (host: PubMed), January 1996 to May 2006;
EMBASE (host: Embase.com), January 1996 to May 2006;
BIOSIS (host: ISI Web of Knowledge), January 1996 to May 2006;
Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2006);
TOXNET, National Library of Medicine;
ASCO Annual Meetings, American Society of Clinical Oncology, 1996 to 2005.

We will also check bulletins from regulatory agencies (Loke 2006):
UK, Current Problems in Pharmacovigilance (http://www.mhra.gov.uk/home/);
Australia, the Australian Adverse Drug Reactions Bulletin (http://www.tga.gov.au/adr/aadrb.htm);
European Public Assessment Reports from the European Medicines Evaluation Agency (http://www.emea.eu.int/#);
US, MedWatch, the Food and Drug Administration Safety information and Adverse Events Reporting Program (http://www.fda.gov/medwatch/elist.htm).

We will search CENTRAL, MEDLINE, EMBASE, TOXNET (1996 to May 2006) using the medical subject headings 'Breast Neoplasms', 'Antineoplastic Agents', 'Adverse effects' and 'Toxicity', and the text words 'Trastuzumab', 'Herceptin', 'Adverse effect', 'Side effect', 'Toxic effect', 'Drug toxicity', 'Dug tolerance', 'Causality', 'Risk', 'Adverse event', 'Adverse drug reaction', 'Breast cancer', 'Breast tumour', 'Breast tumor' and 'Breast neoplasm'. We will include reports irrespective of the language in which they were reported.

MEDLINE search strategy (PubMed)
1."Breast Neoplasms"[MeSH]
2.(breast OR mammary) AND (cancer* OR tumour* OR tumor* OR neoplasm* OR metastas* OR carcinoma) Field: Title/Abstract
3.#1 OR #2
4.trastuzumab OR herceptin
5."Antineoplastic Agents/adverse effects"[MeSH] OR "Antineoplastic Agents/controindications"[MeSH] OR "Antineoplastic Agents/toxicity"[MeSH]
6."Drug Hypersensitivity"[MeSH]
7."Drug Toxicity"[MeSH]
8."Drug Tolerance"[MeSH]
9."Causality"[MeSH]
10."Risk"[MeSH]
11."Product Surveillance, Postmarketing"[MeSH]
12.#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13.safe* OR adr OR adrs OR tolerabilit* OR toxicit* OR "undesirable effect*" OR "adverse reaction*" OR hypersensitivit* Field: Title/Abstract
14.toxic effect* OR complication* OR causalit* OR risk* Field: Title/Abstract
15.(side OR adverse) AND (effect* OR event* OR outcome*) Field: Title/Abstract
16.postmarketing OR "post marketing" Field: Title/Abstract
17.#13 OR #14 OR #15 OR #16
18.#12 OR #17
19.#3 AND #4 AND #18
Our search will not be limited to human in the free-text to include PubMed's in-process records.

EMBASE search strategy
1.'breast cancer'/exp AND [humans]/lim AND [embase]/lim AND [1996-2006]/py
2.(breast:ti,ab OR mammary:ti,ab OR mammaries:ti,ab) AND (cancer*:ti,ab OR tumour*:ti,ab OR tumor*:ti,ab OR neoplasm*:ti,ab OR metastas*:ti,ab OR carcinoma*:ti,ab) AND [humans]/lim AND [embase]/lim AND [1974-2006]/py
3.#1 OR #2
4.'trastuzumab'/exp AND [humans]/lim AND [embase]/lim AND [1996-2006]/py
5.(trastuzumab:ti,ab OR herceptin:ti,ab) AND [humans]/lim AND [embase]/lim AND [1974-2006]/py
6.#4 OR #5
7.'antineoplastic agent'/exp/dd_ae,dd_to AND [humans]/lim AND [embase]/lim AND [1974-2006]/py
8.'drug hypersensitivity'/exp AND [humans]/lim AND [embase]/lim AND [1974-2006]/py
9.'drug toxicity'/exp AND [humans]/lim AND [embase]/lim AND [1974-2006]/py
10.'drug tolerance'/exp AND [humans]/lim AND [embase]/lim AND [1974-2006]/py
11.'risk'/exp AND [humans]/lim AND [embase]/lim AND [1974-2006]/py
12.'postmarketing surveillance'/exp AND [humans]/lim AND [embase]/lim AND [1975-2006]/py
13.(safe*:ti,ab OR adr:ti,ab OR adrs:ti,ab OR tolerability*.:ti,ab OR toxicit*:ti,ab OR undesirable:ti,ab AND effect*:ti,ab OR adverse:ti,ab AND reaction*:ti,ab OR hypersensitivit*:ti,ab OR toxic:ti,ab AND effect*:ti,ab OR complication*:ti,ab OR causalit*:ti,ab OR risk:ti,ab OR postmarketing:ti,ab OR post:ti,ab AND marketing:ti,ab) AND [humans]/lim AND [embase]/lim AND [1974-2006]/py
14.(side:ti,ab OR adverse:ti,ab) AND (effect*:ti,ab OR event*:ti,ab OR outcome*:ti,ab) AND [humans]/lim AND [embase]/lim AND [1974-2006]/py
15.#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16.#3 AND #6 AND #15

CENTRAL

1.MeSH descriptor Breast Neoplasms, this term only in MeSH products
2.MeSH descriptor Adverse Drug Reaction Reporting Systems, this term only in MeSH products OR MeSH descriptor Drug Toxicity, this term only in MeSH products
3.trastuzumab OR herceptin in All Fields in all products
4.#2 AND #3
5.#1 AND #4
6.breast AND (cancer* OR tumour* OR tumor* OR neoplasm*)
7.#6 AND #3
8.adverse effect* OR side effect* OR toxic effect* OR adverse event* OR adverse drug reaction*
9.#7 AND #8
10.#9 OR #5

BIOSIS

1. Text words 'breast cancer*', 'breast neoplasm*', 'breast tumour*' and 'breast tumor*' were searched.
2. Text words 'trastuzumab' and 'herceptin' were searched and linked to the major concept 'oncology' (definition: clinical studies of the characteristics, diagnosis, and treatment of human tumors and cancers) and concept code 'toxicology-pharmacology' (definition: studies of toxic effects of drugs).
3. Search 1 and 2 (above) were linked and limited to publication year (1996 to 2006) and humans.

A copy of the full article for each reference reporting a potentially eligible trial will be obtained.

METHODS OF THE REVIEW

Study selection

The titles and abstracts of articles found in the search will be independently screened for inclusion by two reviewers (LPM and CB). For unpublished trials, available information from conference proceedings will be assessed. Disagreements will be resolved by discussion. Further information will be sought from the authors where papers contain insufficient information to make a decision about eligibility. The selection criteria described above will be applied to each trial. Reasons for exclusion will be recorded.

Data extraction methods and their reliability

Two reviewers (from LPM, AC and CB) will independently extract information using the pro forma process piloted on a random sample of papers investigating other chemotherapy agents. We will record details of study design, participants, setting, interventions, follow-up, quality components, efficacy outcomes and side effects. The extraction form will be available from the authors upon request. Details of previous therapy given to patients (including endocrine or systemic therapy) will be recorded. A third review author will resolve any discrepancies regarding the extraction of quantitative data or the quality assessment of RCTs. When a trial is presented in abstract form, further information will be searched for (from the internet, contacting the authors, checking for the next best available resource or publication).

Where possible, any missing data will be sought from the authors. For studies with more than one publication, we will extract data from all the publications; however, the final or updated version of each trial will be considered to be the primary reference. We will contact the trastuzumab manufacturers (Genentech Inc and Roche Holding Ltd) for additional data.

Quality assessment for RCTs

We will assess separately the methodological quality of the trials based on five components: patient randomisation (both generation of the allocation sequence and allocation concealment), blinding, completeness of follow-up and if a multicenter study (Schulz 1995; Moher 1998; Kjaergard 2001; Juni 2001; Balk 2002). We will use the following definitions in the assessment of the methodological quality.

Generation of the allocation sequence

1. Adequate: if the allocation sequence is generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing die is considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
2. Unclear: if the trial is described as randomised but the method used for the allocation sequence generation is not described.
3. Inadequate: if a system involving dates, names, or admittance numbers are used for the allocation of patients. These studies are known as quasi-randomised and will be excluded from the present review for efficacy data. Trials with alternating allocation will be excluded also.

Allocation concealment

1. Adequate: if the allocation of patients involved a central, independent unit; on-site locked computer; identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator; or sealed, opaque envelopes.
2. Unclear: if the trial is described as randomised but the method used to conceal the allocation is not described.
3. Inadequate: if the allocation sequence is known to the investigators who assigned participants, the envelopes are unsealed or transparent, or if the study is quasi-randomised.

Blinding (or masking)

1. Adequate: if the trial is described as double blind and the method of blinding involves identical placebo or active drugs. Particularly:
- double blind (method described and use of a placebo(s) or dummy technique meant neither the participant nor the care provider or assessor knew which treatment was given);
- single blind (participant or the care provider or assessor aware of the treatment given).
2. Unclear: if the trial is described as double blind or single blind but the method of blinding is not described.

3. Not performed: if the trial is open label (all parties aware of treatment).

Follow-up

1. Adequate: if the numbers and reasons for dropouts and withdrawals in all intervention groups were described and if 90% or more of the participants randomised were included in the analysis; or if it is specified that there were no dropouts or withdrawals.
2. Unclear: if the report gives the impression that there were no dropouts or withdrawals but this was not specifically stated.
3. Inadequate: if less than 90% of participants randomised into the trial were included in the analysis or the number or reasons for dropouts and withdrawals were not described.

Multicentre

1. Adequate: if the study includes more than one site and the recruitment is well balanced between participating centres.
2. Unclear: if the report gives the impression that there was more than one site but this is not specifically stated.
3. Inadequate: if the study includes only one site or the recruitment is not balanced between participating centres.

Authors of the primary trial reports will be contacted when necessary to clarify data and to obtain missing information. Two reviewers (from LM, AC, CB) will independently assess trials according to the predefined quality criteria. Any disagreements will be resolved by consulting a third party. The characteristics and outcomes of the included trials and details of the excluded trials will be entered into our database. Sensitivity analysis or meta-regression to assess the effect of methodological quality is planned.

Quality assessment for observational studies

We will separately assess the methodological quality of observational studies by using a component approach considering: concurrent, concomitant treatment; how allocation occurred; any attempt to balance groups by design; blinding of outcome assessment; completeness of follow-up; identification of prognostic factors (ie cardiovascular risk factors) and case-mix adjustment. These components are part of a list of quality items identified through a systematic review of the literature (Deeks 2003). Overall, the review team judged seven quality items to be potentially useful for some of the secondary outcomes (i.e. cardiac toxicity) of this systematic review.

We will not evaluate the quality of case series or single case reports.

Statistical Analysis

Effectiveness

We will extract the hazard ratio (HR) and associated variances for overall survival and disease-free survival directly from the trial publications. If not reported, we will obtain these data indirectly, using the methods described by Parmar 1998, employing either other available summary statistics or data extracted from published Kaplan-Meier curves. To allow for immature follow-up, we will adjust the numbers at risk based upon estimated minimum and maximum follow-up times. If these are not reported in any of the reports available, we will estimate minimum follow-up using the estimated time taken to complete treatment. We will estimate maximum follow-up using the last event reported in the relevant time-to-event curve. We will present these follow-up estimates in the 'Characteristics of included studies' table, under 'Notes'.

We will obtain a pooled HR through the generic inverse variance approach from the log HR and the standard error of the log HR, using the fixed-effect and random-effect models, along with assessments of heterogeneity (Deeks 2006). The pooled HR represents the overall risk of an event on chemotherapy regimens containing trastuzumab versus those not containing trastuzumab.

We will report ratios of treatment effects for time-to-event outcomes so that HRs less than 1.0 favour regimens containing trastuzumab and values greater than 1.0 favour regimens that do not contain trastuzumab. The forest plots for overall survival and progression-free survival will present the hazard ratio (HR) and 95% confidence intervals.

If all arms in a multi-arm trial are to be included in the meta-analysis and one treatment arm is to be included in more than one of the treatment comparisons, then we will divide the number of events and the number of participants in that arm by the number of treatment comparisons made. This method will avoid the multiple use of participants in the pooled estimate of treatment effect while retaining information from each arm of the trial. It will compromise the precision of the pooled estimate slightly.

Heterogeneity

We will include all outcomes available from the individual studies in the meta-analysis, with heterogeneity reported by the Q (Chi-squared) and the I-squared statistics (see the Cochrane Handbook). Statistical significance of the Q (Chi-squared) statistic will be judged by $P < 0.10$ because of the low statistical power of the test. The I-squared statistic indicates the percent variability due to between-study (or inter-study) variability, as opposed to within-study (or intra-study) variability. An I-squared value greater than 50% will be considered to be large (Higgins 2002). If there is no statistical evidence for heterogeneity effect sizes, we will use the fixed-effect model. Where statistically significant heterogeneity exists, we will conduct careful clinical review of the data for the source of such heterogeneity. Based on this review, the reviewers will make a decision to either: (1) redo the analysis using the homogenous subgroup (only if a clear and compelling reason to exclude the heterogeneous data can be made); (2) abandon statistical combining of the trials in favor of a narrative review of the literature; or (3) redo the analysis using the random-effects model (DerSimonian 1986).

It is likely that we will collect quality of life data using a variety of instruments across trials. If data are expressed using continuous data, we will present results as weighted mean differences (WMD).

However, when different scales are used, we will use standardised mean differences (SMD). If it is not possible to pool the results for clinical or methodological heterogeneity, we will not statistically synthesise data but will summarise and evaluate qualitatively.

We have pre-specified three subgroup analyses: 1. analysis by type of adjuvant chemotherapy regimen (cyclophosphamide, methotrexate, 5-fluorouracil (CMF); anthracycline combinations, other combinations, single agents); 2. sensitivity analysis using high-quality methodological components (high-quality trials versus other); 3. status of nodal involvement (lymph node (LN) positive versus LN negative, four or more LNs involved versus three or fewer LNs involved).

Toxicity

We will report toxicity data as death related to treatment and as grade III or grade IV events of any toxicities: dyspnea, leukopenia, thrombocytopenia, anemia, infection, fever, chills, nausea, vomiting, nausea and vomiting, alopecia, diarrhea, fatigue, asthenia, constipation, dermatitis, skin, pain, stomatitis, hand-foot syndrome. We will extract all adverse events related to cardiotoxicity irrespective of grade or severity. We expect that data about toxicities will be not consistently reported across the included trials and that different scales and definitions will have been used (heart failure, left ventricular ejection fraction, symptoms, etc). When adverse effects have been reported with explicit definitions, we will extract for any harm and combine with data from other trials with similar definitions. We will make a decision about which definition and scale to include in the final analysis by consensus after the data have been collected, with a preference for standardised and validated scales (for example World Health Organization toxicity criteria or New York Heart Association criteria for cardiac symptoms). A potential list of cardiac toxicities is presented in Table 01. We will consider possible disparities in adverse effects due to different schedules of trastuzumab (that is during anthracycline, before anthracycline, immediately after anthracycline, delayed after anthracycline or without anthracycline).

We will pool and summarise adverse events noted in the course of the randomised trials, and discuss their causal relationship to trastuzumab.

We will screen, summarise and discuss reports of adverse events linked with trastuzumab in other studies, such as outside RCTs. We cannot anticipate if it will be possible to pool these studies and calculate combined estimates. Any risk of bias in attempting to produce combined estimates will be seriously taken into consideration (Egger 2001).

We also cannot anticipate if it will be possible to evaluate adverse events, particularly cardiotoxicity, for distinct care phases (for example during chemotherapy treatment or follow-up).

When we examine the possible harmful side effects of trastuzumab, we will adopt a higher type-I error ($\alpha = 0.10$) for some pre-specified adverse events (Shadish 2002): cardiotoxicity, death related to treatment and dyspnea. For the remaining analyses we will adopt the same type-I error ($\alpha = 0.10$) with a Bonferroni correction for the number of comparisons (Pocock 1997); these will be exploratory data analyses and will not be over interpreted.

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Su Golder and Carol Lefebvre for valuable suggestions about bibliographic researches; Deirdre Price, Jessica Thomas and Andrew Herxheimer for valuable suggestions about methodological issues in analysing adverse events; Davina Ghersi, Sharon Parker, Nancy Owens and Nicholas Wilcken for their helpful assistance during all the phases of the preparation of the protocol.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Mario Negri Institute ITALY

REFERENCES

Additional references

Apolone 2005

Apolone G, Joppi R, Bertele V, Garattini S. Ten years of marketing approvals of anticancer drugs in Europe: regulatory policy and guidance documents need to find a balance between different pressures. *British Journal of Cancer* 2005;**93**(5):504–9.

Balk 2002

Balk EM, Bonis PA, Moskowitz H, Schmid CH, Ioannidis JP, Wang C, et al.Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA* 2002; **287**(22):2973–82.

Baselga 1996

Baselga J, Tripathy D, Mendelsohn J, Baughman S, Benz CC, Dantis L, et al.Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. *Journal of Clinical Oncology* 1996;**14**(3):737–44.

Cobleigh 1999

Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, et al.Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *Journal of Clinical Oncology* 1999;**17**(9):2639–48.

Collier 2006

Collier J. Panorama: Herceptin: Wanting the Wonder Drug. *BMJ* 2006;**332**(7537):368–.

Coussens 1985

Coussens L, Yang-Feng TL, Liao YC, Chen E, Gray A, McGrath J, et al.Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science* 1985;**230** (4730):1132–9.

Deeks 2003

Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al.Evaluating non-randomised intervention studies. *Health Technology Assessment* 2003;**7**(27):iii-x, 1-173.

Deeks 2006

Deeks JJ, Higgins, JPT, Altman DG, editors. Analysing and presenting results. *Cochrane Handbook for Systematic Reviews of Interventions 4.2.5. In: The Cochrane Library Issue 2, 2006*. Chichester, UK: John Wiley & Sons, Ltd, 2006.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88.

Egger 2001

Egger M, Davey Smith G, Schneider M. Systematic reviews of observational studies. *Systematic reviews in health care: meta-analysis in context*. 2001:211–27.

FDA 1998

U.S. Food and Drug Administration. FDA Oncology Tools Approval Summary for Trastuzumab for HERCEPTIN. http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=284 (accessed 9 Feb 2006).

Higgins 2002

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539–58.

Joppi 2005

Joppi R, Bertele V, Garattini S. Disappointing biotech. *BMJ* 2005; **331**(7521):895–7.

Juni 2001

Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;**323**(7303): 42–6.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982–9.

Loke 2006

Loke YK, Price D, Herxheimer A. Including adverse effects. *Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]; Appendix 6b. In: The Cochrane Library Issue 2, 2006*. Chichester, UK: John Wiley & Sons, Ltd, 2006.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al.Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**(9128):609–13.

NICE 2002

NICE. Breast cancer - trastuzumab (No. 34). http://www.nice.org.uk/page.aspx?o=29274 (accessed 9 Feb 2006).

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815–34.

Piccart-Gebhart 2005

Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al.Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New England Journal of Medicine* 2005;**353**(16):1659–72.

Pocock 1997

Pocock SJ. Clinical trials with multiple outcomes: a statistical perspective on their design, analysis, and interpretation. *Controlled Clinical Trials* 1997;**18**(6):530–45.

Romond 2005

Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, et al.Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New England Journal of Medicine* 2005; **353**(16):1673–84.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12.

Shadish 2002

Shadish WR, Cook TD, Campbell DT. Statistical conclusion validity and internal validity. *Experimental and quasi-experimental designs for*

generalized causal inference. Boston New York: Houghton Mifflin Company, 2002.

Slamon 1987
Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;**235**(4785): 177–82.

Tan-Chiu 2005
Tan-Chiu E, Yothers G, Romond E, Geyer CE Jr, Ewer M, Keefe D, Shannon RP, et al.Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *Journal of Clinical Oncology* 2005;**23** (31):7811–9.

The Lancet 2005
The Lancet editorial. Herceptin and early breast cancer: a moment for caution. *Lancet* 2005;**366**(9498):1673.

Vogel 2001
Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, et al.First-line Herceptin monotherapy in metastatic breast cancer. *Oncology* 2001;**61 Suppl 2**:37–42.

ADDITIONAL TABLES

Table 01. Potential list of cardiac adverse events

Cardiac toxicity

Left ventricular ejection fraction (LVEF) abnormal by multiple-gated acquisition (MUGA) or echocardiogram

Uncontrolled arterial hypertension

Myocardial infarction

Unstable angina or angina pectoris

Congestive heart failure

Serious cardiac arrhythmia

QTc interval greater than 440 msec

Rhythm abnormalities requiring permanent therapy

Prolonged PR interval or atrioventricular block on electrocardiogram (ECG)

Second or third-degree heart blocks

Peripheral vascular disease

Cardiomyopathy

Signs and symptoms of cardiac dysfunction (such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema)

Other clinically significant cardiovascular disease

COVER SHEET

Title Trastuzumab containing regimens for early breast cancer

Authors	Moja L, Brambilla C, Compagnoni A, Pistotti V
Contribution of author(s)	Lorenzo Moja (LPM), Anna Compagnoni (AC) and Cinzia Brambilla (CB) conceived the study and participated in developing the protocol. LPM and AC developed the search strategies and the quality assessment for observational studies. Vanna Pistotti (VP) revised all the search strategies.
Issue protocol first published	2006/4
Date of most recent amendment	23 August 2006
Date of most recent SUBSTANTIVE amendment	20 August 2006
What's New	Information not supplied by author
Contact address	Dr Lorenzo Moja Centro Cochrane Italiano Istituto Mario Negri Via Eritrea, 62 Milano 20157 ITALY E-mail: moja@marionegri.it Tel: +39 02 39014 Fax: +39 02 3559048
DOI	10.1002/14651858.CD006243
Cochrane Library number	CD006243
Editorial group	Cochrane Breast Cancer Group
Editorial group code	HM-BREASTCA