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Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer (Review)

Wilcken N, Hornbuckle J, Ghersi D

Wilcken N, Hornbuckle J, Ghersi D.
Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer.
Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD002747.
DOI: 10.1002/14651858.CD002747.

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[Intervention Review]

Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer

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Editorial group: Cochrane Breast Cancer Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 2, 2021.

Citation: Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. *Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD002747. DOI: 10.1002/14651858.CD002747.

ABSTRACT

Background

Both chemotherapy and endocrine therapy can be used as treatments for metastatic breast cancer.

Objectives

To review the evidence and determine whether starting treatment with chemotherapy or starting treatment with endocrine therapy has the more beneficial effect on outcomes (survival, response rate, toxicity and quality of life).

Search methods

The Cochrane Breast Cancer Group Specialised Register was searched (31 August 2006) using the codes for "advanced breast cancer", "chemotherapy" and "endocrine therapy". Details of the search strategy applied by the Group to create the register, and the procedure used to code references, are described in the Group's module in *The Cochrane Library*. Handsearching the proceedings of the annual meetings of the American Society of Clinical Oncology (2005 to 2006) and the San Antonio Breast Cancer Symposium (2005) were also conducted. A further search was carried out in the Specialised Register (until 2008), MEDLINE (2008 to 24 September 2010), EMBASE (2008 to 30 September 2010) and the WHO International Clinical Trials Registry Platform search portal (23 July 2010).

Selection criteria

Randomised trials comparing the effects of chemotherapy alone with endocrine therapy alone on pre-specified endpoints in women with metastatic breast cancer.

Data collection and analysis

Data were collected from published trials. Hazard ratios were derived for survival analysis and a fixed-effect model was used for meta-analysis. Response rates were analysed as dichotomous variables. Toxicity and quality of life data were extracted, where present.

Main results

The primary analysis of overall effect using hazard ratios derived from published survival curves involved six trials (692 women). No significant difference was seen (hazard ratio 0.94, 95% CI 0.79 to 1.12, P = 0.5). A test for heterogeneity gave a P value of 0.1.

A pooled estimate of reported response rates in eight trials involving 817 women showed a significant advantage for chemotherapy over endocrine therapy with a relative risk of 1.25 (95% CI 1.01 to 1.54, P = 0.04). However the point estimates for the two largest trials were in opposite directions, and an overall test for heterogeneity gave a P value of 0.0009.

There was little information available on toxicity and quality of life. Six of the seven fully published trials commented on increased toxicity with chemotherapy, mentioning nausea, vomiting and alopecia. Three of the seven trials mentioned aspects of quality of life, with differing results. Only one trial formally measured quality of life, concluding that it was better with chemotherapy.

Authors' conclusions

In women with metastatic breast cancer and where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease.

PLAIN LANGUAGE SUMMARY

Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer

Breast cancer is the most common cancer in women. If the cancer has spread beyond the breast (metastatic disease), treatments include chemotherapy (anti-cancer drugs) and endocrine therapy (also known as hormonal treatment). Endocrine therapy is mainly given to women whose cancer is determined to be hormone-responsive, that is, where hormone receptors (oestrogen or progesterone receptors) are expressed in the tumour cells. The aim of this review was to see if starting treatment with chemotherapy or starting treatment with endocrine therapy provides more benefit in terms of survival, response to treatment, toxicity from treatment and quality of life. Ten eligible studies were identified, eight of which provided information on response to treatment (in 817 patients) and six on overall survival (in 692 patients). Trials were generally old (published between 1963 and 1995) and small in size (median of 70 women, range 50 to 226 women in each trial) and were of modest quality. The types of chemotherapy used were reasonably conventional by today's standards; the endocrine therapies varied considerably.

This review found that while initial treatment with chemotherapy rather than endocrine therapy may be associated with a higher response rate, the two initial treatments had a similar effect on overall survival. No single group of patients who might benefit from or be harmed by one treatment over the other were identified, although there was little information to address this question. Six of the seven fully published trials commented on increased toxicity associated with chemotherapy including nausea, vomiting and alopecia. Three of the seven trials mentioned aspects of quality of life but their findings provided differing results. Only one trial formally measured quality of life (QOL), concluding that QOL was better with chemotherapy. Based on these trials, no conclusions can be made as to the QOL achieved with either treatment.

Accurate information about hormone receptor status is now routinely available for many women with metastatic breast cancer, and hormonal treatments have improved in their effectiveness in the last 10 years. In women with metastatic breast cancer where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy appears to be better, on the basis of the trials and outcomes in this review, except in the presence of rapidly progressive disease.

BACKGROUND

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (*The Cochrane Library* Issue 1, 2007). Breast cancer is the most common type of cancer in women and the most common cause of cancer-death for women. In 2005, an estimated 500,000 women died of this disease worldwide (WHO 2006). The stage of breast cancer at the time of diagnosis is an important indicator of prognosis. Metastatic breast cancer is an incurable yet treatable disease and, as survival can be several years, it can be viewed as a chronic relapsing and remitting disease (Stockler 2000).

Although there is no randomised evidence comparing chemotherapy with observation in women with metastatic breast cancer, it is widely accepted that women with metastatic disease should receive some form of systemic therapy at some time during the course of their disease. Chemotherapy is considered by many to be the appropriate first treatment option for women with multiple sites of recurrence or where visceral disease is not easily treated by local modalities. Chemotherapy is also considered to be useful in women whose cancer is either hormone refractory or is expected to be hormone resistant. Endocrine therapy is effective only where hormone receptors (oestrogen or progesterone receptors) are expressed in tumour cells (Hortobagyi 1998).

It has been shown that both chemotherapy and endocrine therapy improve survival in early breast cancer (EBCTCG 2005). It is unclear, however, whether one mode of treatment is more effective than the other, either as initial or subsequent treatment, in women with metastatic breast cancer. The popular view is that chemotherapy may be better than endocrine therapy in patients with predominantly visceral disease or with rapidly progressive disease. On the other hand, endocrine therapy may be better for predominantly bony disease (Hortobagyi 1998). Both chemotherapy and endocrine therapy have been shown to produce tumour responses in women with metastatic breast cancer (Stockler 1997a; Stockler 1997b) but uncertainty remains regarding the differential impact these treatments may have on outcomes such as overall survival and quality of life and, in particular, whether the (presumed) greater toxicity of chemotherapy is reflected in better treatment outcomes.

The aim of this review is to systematically identify and assess all of the available evidence from randomised trials that compared the effects of chemotherapy alone versus endocrine therapy alone on treatment-related outcomes for women with metastatic breast cancer. The treatment could be used either as first-line treatment or subsequent to initial chemotherapy or endocrine treatments.

OBJECTIVES

Primary objective: to review the evidence and determine whether chemotherapy alone or endocrine therapy alone has the most beneficial effect on treatment outcomes (listed below) for women with metastatic breast cancer.

Secondary objective: to determine whether any of a variety of factors influence the efficacy of chemotherapy or hormonal therapy in this setting; in particular age, menopausal status, the predominant site of metastases and whether the treatment is given as first-line treatment or later in the disease process.

METHODS

Criteria for considering studies for this review

Types of studies

Properly randomised controlled trials that compared chemotherapy versus endocrine therapy (as defined below).

Types of participants

Women diagnosed with metastatic breast cancer (excluding those with local recurrence disease alone). Trials in 'advanced' breast cancer often include women with 'locally advanced', non-metastatic disease. Such trials were eligible as long as women with truly metastatic disease could be identified separately or they comprised at least 85% of the total participants randomised. No restrictions were placed on age, menopausal status, hormone receptor status or sites of disease.

Types of interventions

Conventional cytotoxic chemotherapy (with or without colony stimulating factors but excluding cytokines or monoclonal antibodies) used alone, as well as high-dose chemotherapy requiring stem-cell support, versus endocrine manoeuvres including anti-oestrogens, oestrogens, androgens, aromatase inhibitors, progestogens and ablations (ovarian, adrenal), but excluding corticosteroids, used alone.

It was planned to classify treatments according to proposed duration and other therapies to be given at disease progression, if appropriate. This was not done due to the limited number of studies available.

Types of outcome measures

Primary outcome

- Overall survival

Secondary outcomes

- Tumour response rates
- Quality of life and treatment toxicity

Time to treatment failure or disease progression was also a planned outcome but was not reported in a sufficiently consistent way to be analysed.

For the purpose of this review, the following outcome definitions apply.
1. Response rate: the proportion of patients with a complete or partial response.
2. Time to progression (TTP): time from date randomised to date of progression or death (any cause); which may also be referred to as progression-free survival.
3. Time to treatment failure (TTF): time from date randomised to date of progression, death (any cause), withdrawal due to an adverse event, patient refusal or further anti-cancer therapy for documented progression.
4. Overall survival (OS): time from date randomised to date of death (any cause).

Subgroup analyses

The following subgroup analyses were prospectively planned but were not possible because of insufficient data.

- Hormone receptor positive versus negative or unknown receptor status.
- Trials of initial therapy for metastatic disease versus second-line or greater.
- Age less than or equal to 50 years versus more than 50 years.
- Premenopausal versus postmenopausal women.
- First-line or more than first-line.

Search methods for identification of studies

For the first full version of this review (Wilcken 2003), the Specialised Register maintained by the editorial base of the Cochrane Breast Cancer Group was searched (16 September 2002) using the codes for "advanced breast cancer", "chemotherapy" and "endocrine therapy". This search was repeated (31 August 2006) for this update. Furthermore, handsearches were done of the proceedings of the annual meetings of the American Society of Clinical Oncology (2005 to 2006) and the San Antonio Breast Cancer Symposium (2005). Details of the search strategy applied by the Cochrane Breast Cancer Group to create the register, and the procedure used to code references, are described in the Group's module in *The Cochrane Library*.

A further search was carried out in the Specialised Register (until 2008), MEDLINE (2008 to 24 September 2010) (Appendix 1), EMBASE (2008 to 30 September 2010) (Appendix 2) and the WHO International Clinical Trials Registry Platform search portal (23 July 2010) (Appendix 3).

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

Data collection and analysis

Study selection

Study selection was undertaken independently by two of the authors (JH and NW), both of whom are content experts. The above selection criteria were applied to each trial, initially based on title. The subsequently agreed pool of potentially eligible trials were screened with the results section and any other area where the results appeared masked. For unpublished trials, available information from conference proceedings was screened.

Assessment of trial quality

A quality score was applied to describe the adequacy of allocation concealment:
A. low risk of bias in the randomisation process (e.g. randomisation by telephone call to central office);
B. moderate risk of bias (e.g. sealed envelopes);
C. high risk of bias;
D. trials where there was insufficient information to score allocation concealment.

Quality assessment was repeated by the third author (DG).

Data extraction

Initial data were extracted independently by two of the authors (JH and NW). This included baseline characteristics of the patients, the interventions being tested, tumour response rates, median survival, information about toxicity and quality of life and the proportion of patients with bone or visceral disease. Subsequent information about survival was independently extracted by one author (NW) and Elizabeth Weir. This involved extracting survival times at three-monthly intervals from the published survival curves in order to derive hazard ratios and confidence intervals (Parmar 1998).

Analysis

The most complete dataset that was feasible was assembled and results of eligible studies were statistically synthesised in a meta-analysis. Response rates were analysed as dichotomous variables and a pooled relative risk was derived. A pooled weighted ratio of median survival was also derived (data not shown).

The hazard ratio (HR) is the most appropriate statistic for time-to-event outcomes. When possible, the HR was extracted directly from the trial publication(s). If not reported, it was obtained indirectly through the methods described by Parmar et al using either other available summary statistics or from data extracted from published Kaplan-Meier curves (Parmar 1998). A pooled HR was obtained by combining the observed (O) minus the expected (E) number of events and the variance obtained for each trial using the fixed-effect model (Yusuf 1985). A weighted average of survival duration across studies was then calculated. A fixed-effect model was used for the primary analyses (see the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005)). Chi^2 tests for heterogeneity were used to test for statistical heterogeneity between trials. There were insufficient numbers of trials that were of adequate size to justify the planned subgroup analyses. Quality of life and toxicity data were not formally analysed.

RESULTS

Description of studies

When the Specialised Register of the Cochrane Breast Cancer Group was searched in September 2002, it contained 5380 references pertaining to clinical trials in breast cancer. A total of 1111 of these were coded as "advanced breast cancer", of which 71 were coded as "chemotherapy" and "endocrine therapy". Based on information in the abstracts it was possible to exclude 47 references that clearly did not relate to eligible trials (most did not compare chemotherapy with endocrine therapy and others were not metastatic breast cancer or were clearly not randomised trials). The full papers were retrieved for the remaining 24 references resulting in the exclusion of five further references (not metastatic breast cancer or did not compare chemotherapy with endocrine therapy). The 19 remaining references reported the results of 13 potentially eligible trials, of which three were excluded: one randomised by date of birth (Cole 1973), one was reported as a comparative study but its randomisation status could not be ascertained (Newsome 1963), and more than 30% of patients who were randomised in the third study had locally advanced but not metastatic breast cancer (Villalon 1993).

At the time of the new search in August 2006, the Register contained 6081 references pertaining to clinical trials in breast cancer. Of

these, 1789 were coded as "advanced breast cancer", of which 99 were coded as "chemotherapy" and "endocrine therapy". For the 2010 update, a repeat search was carried out in the Specialised Register, MEDLINE, EMBASE and WHO International Clinical Trials Registry Platform search portal but no extra eligible studies were identified.

Of the 10 eligible studies identified, eight provided information on response (817 patients) and six on overall survival (692 patients). The trials were generally old (published between 1963 and 1995) and small (median 70 participants, range 50 to 226 women). The chemotherapy regimens used were reasonably conventional, although taxanes were not included. Endocrine therapies were less conventional (see the Characteristics of included studies).

Two studies included over 100 patients. One study (ANZBCTG 1986) randomised 226 postmenopausal women with metastatic breast cancer to doxorubicin and cyclophosphamide (AC) chemotherapy, to be followed on failure by tamoxifen (TAM); or TAM, followed on failure by AC (a third group were allocated the combination of AC plus TAM). Receptor status was mostly unknown and over 50% of the patients had visceral metastases. The other study (Taylor 1986) randomised 181 women who were over the age of 65 years with metastatic breast cancer to cyclophosphamide, methotrexate and fluorouracil (CMF) or tamoxifen, with crossover planned following disease progression. The majority of the women were either hormone receptor positive or of unknown status and over 50% had visceral metastases.

Risk of bias in included studies

It was not possible to accurately assess the quality of most studies (including the quality of the randomisation process) due to lack of information in the published articles. The quality of two trials were graded as A (Abe 1995; Taylor 1986) with an additional two being graded as B (ANZBCTG 1986; Priestman 1978) (see table of Characteristics of included studies). The remaining studies were all graded as D, including one study that has only been reported in abstract form (Rosner 1974). Two potentially eligible studies were excluded from the review due to the inadequacy of the randomisation process: one allocated women to treatment based on date of birth (Cole 1973) and the other was described simply as a "comparative study" (Newsome 1963).

Effects of interventions

Ratios of treatment effects are reported so that relative risks (RRs), hazard ratios (HRs) and odds ratios (ORs) less than 1.0 favour endocrine therapy and values greater than 1.0 favour chemotherapy.

Overall survival

The primary analysis of overall effect using hazard ratios derived from published survival curves included six trials (692 women). There was no significant difference (HR 0.94, 95% CI 0.79 to 1.12, P = 0.5). A test for heterogeneity gave P = 0.1 (discussed below).

In one trial (Priestman 1978) it was not possible to ascertain the proportion of women who had definite metastatic disease. If this trial was excluded from the survival analysis the estimated HR changed (HR 0.84, 95% CI 0.70 to 1.02, P = 0.08).

Other measures of survival were consistent with the above findings. There was no significant difference seen in survival at 12 months (OR 1.03, 95% CI 0.74 to 1.43) or 24 months (OR 0.92, 95% CI 0.68 to 1.25). A pooled, weighted average of median survival ratios involving seven trials (742 women) was similar (HR 0.98, 95% CI 0.72 to 1.34).

Subset analyses

There were insufficient data to justify any quantitative analysis of prospectively identified subsets. There were no obvious trends apparent to suggest an effect of age, menopausal status or pattern of metastatic disease on the efficacy of either treatment modality. The majority of women in these trials had tumours of unknown hormone receptor status. Results were similar whether treatment was first line or subsequent to other chemotherapy or endocrine therapy.

The commonly held view that endocrine therapy is less effective where there are visceral metastases was not supported by subset analyses carried out in the largest trial (ANZBCTG 1986) nor by the fact that over 50% of the women in all the trials (combined) had visceral disease. Post hoc analysis restricted to the higher quality studies suggested that a significant survival benefit in favour of chemotherapy is unlikely.

Tumour response rates

A pooled estimate of reported response rates in eight trials involving 817 women showed a significant advantage for chemotherapy over endocrine therapy (RR 1.25, 95% CI 1.01 to 1.54, P = 0.04). However, the point estimates for the two largest trials (ANZBCTG 1986; Taylor 1986) were in opposite directions,and an overall test for heterogeneity gave P = 0.0009 (discussed below).

Toxicity and quality of life

There was little information available from the included trials on toxicity and quality of life. Six of the seven fully published trials commented on increased toxicity (nausea, vomiting and alopecia) with chemotherapy. Three of the seven trials commented on aspects of quality of life. In one trial (Dixon 1992) it was noted that an equal improvement in performance status (a measure of physical functioning) was seen with chemotherapy and endocrine therapy. In another trial (Clavel 1982) quality of life was said to be better in the endocrine therapy arm. In a third trial (Priestman 1978) quality of life was formally measured with linear analogue scales and was better with chemotherapy.

DISCUSSION

With the increasing advent of more and more sophisticated and expensive cytotoxic drugs for the treatment of breast cancer, it is important not to lose sight of the benefits of endocrine therapy. In incurable, metastatic disease it is generally considered reasonable to begin treatment with endocrine therapy where the tumour is hormone receptor positive. However, the evidence base for this recommendation has been modest. Only one systematic review (Stockler 2000) with two identified randomised trials had been carried out before the present review. There is also an accepted wisdom that women with visceral metastases tend to respond better to chemotherapy, and endocrine therapy may be avoided for such women.

The trials identified in our review are relatively small and of modest quality. However, the sum of the identifiable evidence is that in women with metastatic breast cancer a policy of treating first with endocrine therapy rather than chemotherapy (where hormone receptors are present) is associated with an inferior tumour response rate but similar overall survival, less toxicity and an uncertain effect on quality of life. The fact that many of the women treated in these trials did not have endocrine responsive tumours means that the survival data may be underestimating the effect of endocrine therapy. This strengthens the notion that there is no disadvantage in using endocrine therapy before chemotherapy.

This review did not identify any subset of patients who might preferentially benefit from (or be harmed by) one treatment modality over the other, but information on this question was very sparse. Indirect comparisons of phase two trials might be a better source of information in this instance. Meanwhile, it would seem prudent to introduce chemotherapy first where there is rapidly progressive disease.

Evidence of statistical heterogeneity among trials was identified for tumour response rate and might be present in the survival analysis as well. Funnel plots did not strongly suggest publication bias, and the reasons for the heterogeneity must remain speculative. It is possible that there were significant differences in the proportion of patients who were truly hormone receptor positive in the different trials. This would be expected to affect the relative effects of chemotherapy and endocrine therapy and may explain the heterogeneity.

How should the results of this review be seen in the light of treatments not available at the time these trials were performed? First, accurate information about hormone receptor status is now routinely available for many women with metastatic breast cancer. This should increase the ability to identify women for whom endocrine treatment would be an appropriate first choice. Second, endocrine therapy may now be more effective than in previous decades. Aromatase inhibitors as treatment for postmenopausal women are probably slightly more effective than tamoxifen, as well as being slightly less toxic (for a review see Henderson 2002), while combined endocrine treatment for premenopausal women is superior to tamoxifen or ovarian suppression (Klijn 2001). Thus, this review may underestimate the effects of endocrine therapy on survival for women with hormone receptor disease. Conversely, new cytotoxic agents such as taxanes may also be more effective than some older chemotherapy agents (Ghersi 2005). Certainly some new agents are less toxic. Supportive treatments such as 5-hydroxytryptamine (5HT3) antagonists are also more effective in alleviating chemotherapy side-effects. Thus, this review may be overestimating the toxicity of chemotherapy.

In summary, however, these considerations would not be predicted to alter our main conclusions following this review.

AUTHORS' CONCLUSIONS

Implications for practice

In women with metastatic breast cancer and where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease.

Implications for research

Further trials using modern endocrine and cytotoxic agents and quality of life endpoints are justified. However a pragmatic policy of initiating endocrine treatment and crossing over to cytotoxic treatment following failure is valid and may mitigate the need for further trials. This may be reflected in the fact that in the seven years since this review was first published (Wilcken 2003) we have not found any further, eligible trials.

ACKNOWLEDGEMENTS

The authors would like to thank the following: Mike Clarke and the UK Cochrane Centre for assistance with the review update and the Cochrane Breast Cancer Group, NHMRC Clinical Trials Centre for editorial assistance. We would also like to acknowledge Libby Weir (Cochrane Breast Cancer Group) who duplicated data extraction from survival curves and Martin Stockler who calculated pooled weighted averages for median survivals.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abe 1995

Study characteristics	
Methods	RCT
Participants	Pre, peri and postmenopausal women with advanced or recurrent breast cancer with measurable or evaluable disease (proportion metastatic unclear)
Interventions	CAF (cyclophosphamide, adriamycin, 5-fluorouracil) versus medroxyprogesterone acetate
Outcomes	response rate

Abe 1995 *(Continued)*

	median survival overall survival toxicity
Notes	Multi-centre, national trial Randomisation achieved over phone to central office who randomly assigned patients to treatment (method unclear) Mean age 50.7 (chemo) and 53.9 years (endo) Opened to accrual February 1990, closed July 1991 Included first-line and second-line for metastatic breast cancer

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

ANZBCTG 1986

Study characteristics

Methods	RCT
Participants	Postmenopausal women with metastatic breast cancer
Interventions	AC (adriamycin + cyclophosphamide) versus tamoxifen
Outcomes	response rate median survival overall survival progression-free survival toxicity
Notes	Multi-centre, international trial Randomisation achieved by opaque sealed envelopes derived from computer-generated random number list. Unclear who opened envelope. Age: up to 70 years Opened to accrual July 1978, closed June 1981 All patients randomised included in analysis Included first-line for metastatic breast cancer

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Clavel 1982

Study characteristics

Clavel 1982 *(Continued)*

Methods	RCT
Participants	Postmenopausal women with breast cancer
Interventions	CMF (cyclophosphamide + methotrexate + 5-fluorouracil) versus tamoxifen + androgen
Outcomes	response rate median survival overall survival toxicity
Notes	Centres not assessable Randomisation method not assessable Age: over 65 years Accrual dates not known. Published 1982. Included first-line for metastatic breast cancer

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Dixon 1992

Study characteristics

Methods	RCT
Participants	Postmenopausal women with advanced breast cancer (88% metastatic) relapsing within 6 months of starting chemotherapy
Interventions	Mitoxantrone versus medroxyprogesterone acetate
Outcomes	response rate median survival overall survival progression-free survival toxicity
Notes	Centres not assessable Randomisation method not assessable Median age 64 (43-78) years in medroxyprogesterone acetate group and 61 (42-75) years in mitoxantrone group Dates opened and closed to accrual unclear. Published in 1992. Included second-line for metastatic breast cancer

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Edinburgh 1979

Study characteristics	
Methods	RCT
Participants	Women with local or systemic advanced breast cancer considered to be beyond control by local treatment alone
Interventions	Cyclical chemotherapy with CAF (cyclophosphamide, adriamycin, 5-fluorouracil) repeated every 21 days for 11 cycles followed by CMF (cyclophosphamide, methotrexate, 5-fluorouracil) versus medroxyprogesterone acetate
Outcomes	no outcome information available
Notes	69 patients were randomised

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Goldenberg 1975

Study characteristics	
Methods	RCT
Participants	Women with progressive metastatic breast cancer
Interventions	5-fluorouracil versus androgen
Outcomes	response
Notes	Randomisation and centres not assessable Published 1975 Mean age 60 (31-81) years

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Priestman 1978

Study characteristics	
Methods	RCT

Priestman 1978 *(Continued)*

Participants	Pre, peri and postmenopausal women with locally recurrent (40%) or metastatic (60%) breast cancer
Interventions	FACV (5-fluorouracil + adriamycin + cyclophosphamide + vincristine) versus various
Outcomes	response rate median survival overall survival toxicity
Notes	Centres not assessable Randomisation achieved by sequentially numbered, sealed envelopes. Unclear who opened envelope. Age: not assessable Unknown date opened to accrual, closed December 1976. 92/100 available for assessment Included first-line for metastatic breast cancer

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rosner 1974

Study characteristics

Methods	RCT
Participants	Women with metastatic breast cancer
Interventions	A/FCP (adriamycin/5-fluorouracil + cyclophosphamide + prednisone) versus adrenal
Outcomes	response rate toxicity
Notes	Centres not assessable Randomisation method not assessable Age: not assessable Date opened and closed to accrual not assessable. Abstract published 1974 Included first-line and second-line for metastatic breast cancer

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Tashiro 1990

Study characteristics

Methods	RCT

Tashiro 1990 *(Continued)*

Participants	Pre, peri and postmenopausal women with metastatic breast cancer
Interventions	FAC (5-fluorouracil + adriamycin + cyclophosphamide) versus adrenal/oophorectomy
Outcomes	response rate median survival overall survival
Notes	Centres not assessable Randomisation method not assessable Mean/median age 49.5 years (endocrine group) and 53.8 years (chemotherapy group) Opened to accrual September 1979, closed December 1983 Included first-line and second-line for metastatic breast cancer

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Taylor 1986

Study characteristics

Methods	RCT
Participants	Elderly women with metastatic breast cancer
Interventions	CMF (cyclophosphamide + methotrexate + 5-fluorouracil) versus tamoxifen
Outcomes	response rate median survival overall survival time to treatment failure
Notes	Multi-centre, international trial Randomisation achieved for most patients by phone call to central office. 41 (23%) randomised by sealed envelope. Age: over 65 years Opened to accrual March 1978, closed December 1981 Included first-line for metastatic breast cancer

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Auperin 1995a	Comparisons are confounded.
Cole 1973	Allocation to treatment was by date of birth.
Newsome 1963	Described simply as a "comparative" study. Randomisation status uncertain.
Villalon 1993	Over 30% of patients had locally advanced breast cancer.

DATA AND ANALYSES

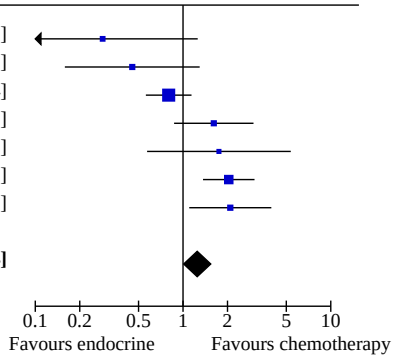
Comparison 1. Endocrine therapy versus chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Tumour response rate	7	767	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.01, 1.54]
1.2 Mortality at 12 months	6	679	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.74, 1.43]
1.3 Mortality at 24 months	6	679	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.68, 1.25]
1.4 Hazard ratio for overall mortality	6	692	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.94 [0.79, 1.12]
1.5 Hazard ratio for overall mortality without Priestman	5	600	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.84 [0.70, 1.02]
1.6 Tumour response rate (with Rosner)	9	874	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [1.06, 1.90]
1.7 Overall mortality by quality	6	692	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.94 [0.79, 1.12]
1.7.1 Quality A	1	194	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.84 [0.61, 1.16]
1.7.2 Quality B	2	318	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.02 [0.81, 1.29]
1.7.3 Quality D	3	180	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.89 [0.59, 1.34]

Analysis 1.1. Comparison 1: Endocrine therapy versus chemotherapy, Outcome 1: Tumour response rate

Study or Subgroup	endocrine therapy Events	Total	chemotherapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldenberg 1975	2	35	8	40	7.0%	0.29 [0.06 , 1.26]
Clavel 1982	4	30	10	34	8.8%	0.45 [0.16 , 1.30]
Taylor 1986	33	95	43	99	39.3%	0.80 [0.56 , 1.14]
Tashiro 1990	14	26	10	30	8.7%	1.62 [0.87 , 3.00]
Dixon 1992	7	30	4	30	3.7%	1.75 [0.57 , 5.36]
ANZBCTG 1986	51	113	25	113	23.4%	2.04 [1.37 , 3.05]
Priestman 1978	20	45	10	47	9.1%	2.09 [1.10 , 3.96]
Total (95% CI)		**374**		**393**	**100.0%**	**1.25 [1.01 , 1.54]**
Total events:	131		110			

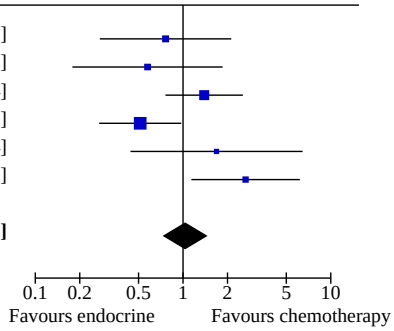
Heterogeneity: Chi² = 22.66, df = 6 (P = 0.0009); I² = 74%
Test for overall effect: Z = 2.06 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Endocrine therapy versus chemotherapy, Outcome 2: Mortality at 12 months

Study or Subgroup	endocrine therapy Events	Total	chemotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dixon 1992	12	30	14	30	12.0%	0.76 [0.27 , 2.12]
Tashiro 1990	7	30	9	26	10.6%	0.57 [0.18 , 1.85]
ANZBCTG 1986	32	113	25	113	25.6%	1.39 [0.76 , 2.54]
Taylor 1986	23	95	33	86	37.5%	0.51 [0.27 , 0.97]
Clavel 1982	7	34	4	30	4.8%	1.69 [0.44 , 6.44]
Priestman 1978	31	47	19	45	9.4%	2.65 [1.14 , 6.17]
Total (95% CI)		**349**		**330**	**100.0%**	**1.03 [0.74 , 1.43]**
Total events:	112		104			

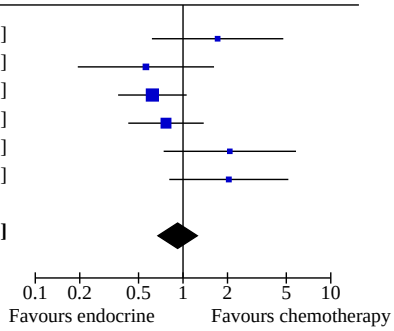
Heterogeneity: Chi² = 12.12, df = 5 (P = 0.03); I² = 59%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Endocrine therapy versus chemotherapy, Outcome 3: Mortality at 24 months

Study or Subgroup	endocrine therapy Events	Total	chemotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dixon 1992	18	30	14	30	6.5%	1.71 [0.62 , 4.77]
Tashiro 1990	13	30	15	26	10.6%	0.56 [0.19 , 1.62]
ANZBCTG 1986	60	113	73	113	39.9%	0.62 [0.36 , 1.06]
Taylor 1986	49	95	50	86	29.6%	0.77 [0.43 , 1.38]
Clavel 1982	16	34	9	30	5.9%	2.07 [0.74 , 5.82]
Priestman 1978	37	47	29	45	7.4%	2.04 [0.81 , 5.16]
Total (95% CI)		**349**		**330**	**100.0%**	**0.92 [0.68 , 1.25]**
Total events:	193		190			

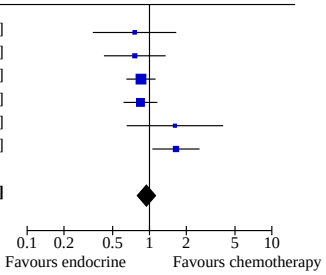
Heterogeneity: Chi² = 9.94, df = 5 (P = 0.08); I² = 50%
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Endocrine therapy versus chemotherapy, Outcome 4: Hazard ratio for overall mortality

Study or Subgroup	endocrine therapy Events	Total	chemotherapy Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Dixon 1992	18	30	14	30	-1.75	6.23	4.8%	0.76 [0.34 , 1.66]
Tashiro 1990	23	30	24	26	-3.15	11.39	8.7%	0.76 [0.42 , 1.36]
ANZBCTG 1986	95	113	100	113	-8.16	50.98	39.1%	0.85 [0.65 , 1.12]
Taylor 1986	68	99	69	95	-6.43	37.79	29.0%	0.84 [0.61 , 1.16]
Clavel 1982	17	34	16	30	2.23	4.66	3.6%	1.61 [0.65 , 4.00]
Priestman 1978	40	47	33	45	9.69	19.44	14.9%	1.65 [1.06 , 2.57]
Total (95% CI)		**353**		**339**			**100.0%**	**0.94 [0.79 , 1.12]**
Total events:	261		256					

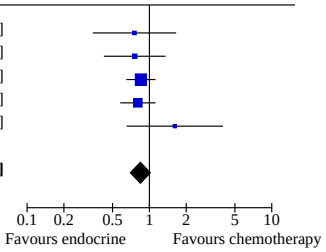
Heterogeneity: Chi² = 9.22, df = 5 (P = 0.10); I² = 46%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Endocrine therapy versus chemotherapy, Outcome 5: Hazard ratio for overall mortality without Priestman

Study or Subgroup	Endocrine therapy Events	Total	Chemotherapy Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Dixon 1992	18	30	14	30	-1.75	6.23	5.8%	0.76 [0.34 , 1.66]
Tashiro 1990	23	30	24	26	-3.15	11.39	10.5%	0.76 [0.42 , 1.36]
ANZBCTG 1986	95	113	100	113	-8.16	50.98	47.1%	0.85 [0.65 , 1.12]
Taylor 1986	68	99	69	95	-7.6	34.98	32.3%	0.80 [0.58 , 1.12]
Clavel 1982	17	34	16	30	2.23	4.66	4.3%	1.61 [0.65 , 4.00]
Total (95% CI)		**306**		**294**			**100.0%**	**0.84 [0.70 , 1.02]**
Total events:	221		223					

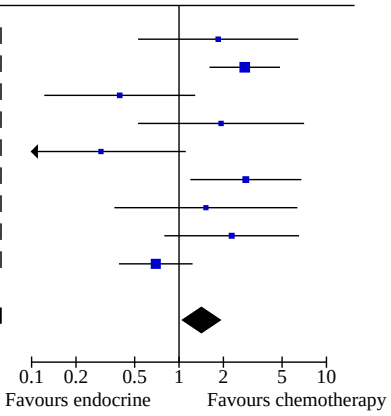
Heterogeneity: Chi² = 2.25, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



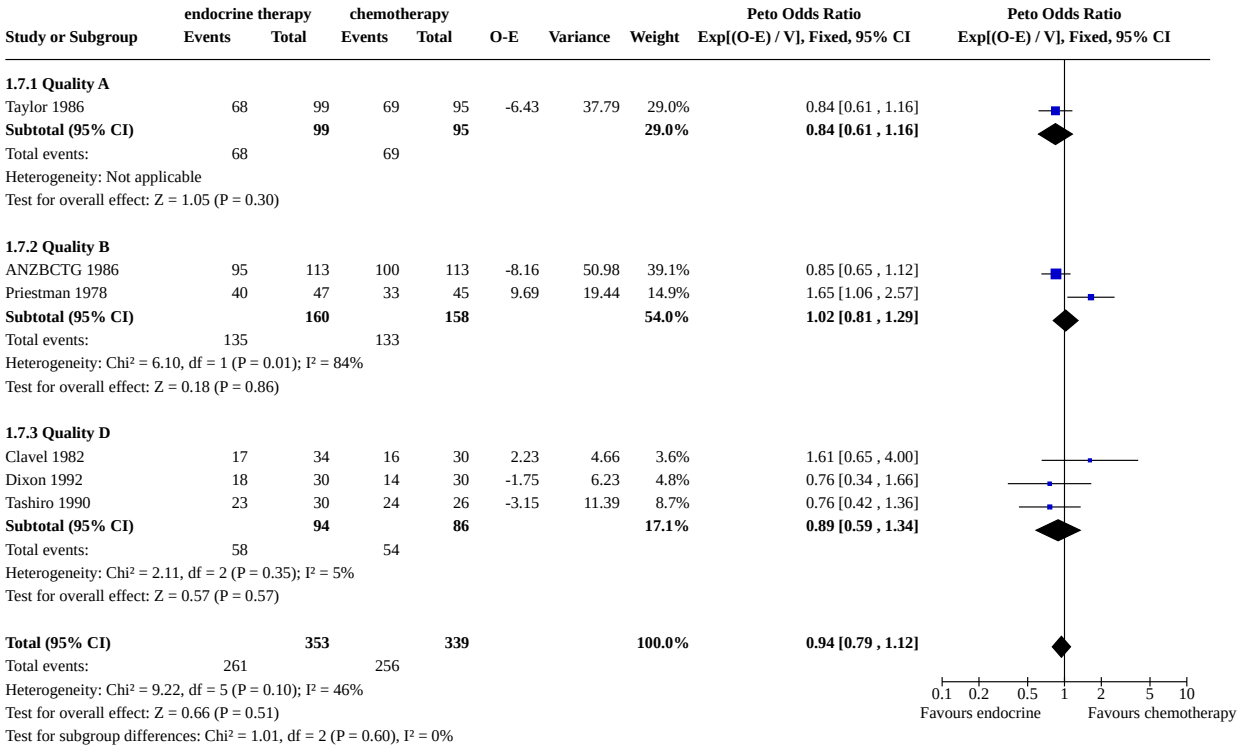
Analysis 1.6. Comparison 1: Endocrine therapy versus chemotherapy, Outcome 6: Tumour response rate (with Rosner)

Study or Subgroup	endocrine therapy Events	Total	chemotherapy Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Abe 1995	8	25	5	25	5.5%	1.84 [0.53 , 6.44]
ANZBCTG 1986	51	113	25	113	28.5%	2.79 [1.61 , 4.84]
Clavel 1982	4	30	10	34	6.2%	0.40 [0.12 , 1.29]
Dixon 1992	7	30	4	30	5.1%	1.93 [0.53 , 7.05]
Goldenberg 1975	2	35	8	40	4.9%	0.30 [0.08 , 1.11]
Priestman 1978	20	45	10	47	11.5%	2.84 [1.19 , 6.75]
Rosner 1974	21	48	3	9	4.2%	1.52 [0.36 , 6.35]
Tashiro 1990	14	26	10	30	7.8%	2.28 [0.80 , 6.52]
Taylor 1986	33	95	43	99	26.1%	0.70 [0.39 , 1.24]
Total (95% CI)		**447**		**427**	**100.0%**	**1.42 [1.06 , 1.90]**
Total events:	160		118			

Heterogeneity: Chi² = 25.21, df = 8 (P = 0.001); I² = 68%
Test for overall effect: Z = 2.33 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Endocrine therapy versus chemotherapy, Outcome 7: Overall mortality by quality



Study or Subgroup	endocrine therapy Events	Total	chemotherapy Events	Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 95% CI
1.7.1 Quality A								
Taylor 1986	68	99	69	95	-6.43	37.79	29.0%	0.84 [0.61 , 1.16]
Subtotal (95% CI)		**99**		**95**			**29.0%**	**0.84 [0.61 , 1.16]**
Total events:	68		69					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.05 (P = 0.30)								
1.7.2 Quality B								
ANZBCTG 1986	95	113	100	113	-8.16	50.98	39.1%	0.85 [0.65 , 1.12]
Priestman 1978	40	47	33	45	9.69	19.44	14.9%	1.65 [1.06 , 2.57]
Subtotal (95% CI)		**160**		**158**			**54.0%**	**1.02 [0.81 , 1.29]**
Total events:	135		133					
Heterogeneity: Chi² = 6.10, df = 1 (P = 0.01); I² = 84%								
Test for overall effect: Z = 0.18 (P = 0.86)								
1.7.3 Quality D								
Clavel 1982	17	34	16	30	2.23	4.66	3.6%	1.61 [0.65 , 4.00]
Dixon 1992	18	30	14	30	-1.75	6.23	4.8%	0.76 [0.34 , 1.66]
Tashiro 1990	23	30	24	26	-3.15	11.39	8.7%	0.76 [0.42 , 1.36]
Subtotal (95% CI)		**94**		**86**			**17.1%**	**0.89 [0.59 , 1.34]**
Total events:	58		54					
Heterogeneity: Chi² = 2.11, df = 2 (P = 0.35); I² = 5%								
Test for overall effect: Z = 0.57 (P = 0.57)								
Total (95% CI)		**353**		**339**			**100.0%**	**0.94 [0.79 , 1.12]**
Total events:	261		256					
Heterogeneity: Chi² = 9.22, df = 5 (P = 0.10); I² = 46%								
Test for overall effect: Z = 0.66 (P = 0.51)								
Test for subgroup differences: Chi² = 1.01, df = 2 (P = 0.60), I² = 0%								

APPENDICES

Appendix 1. MEDLINE search strategy

1. randomised controlled trial.pt.
2. randomized controlled trial.pt.
3. controlled clinical trial.pt.
4. randomized.ab.
5. randomised.ab
6. placebo.ab.
7. randomly.ab.
8. trial.ab.
9. groups.ab.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. (advance* adj6 breast adj6 cancer$).mp.
12. (advance* adj6 breast adj6 neoplasm$).mp.
13. (advance* adj6 breast adj6 carcinoma$).mp.
14. (advance* adj6 breast adj6 tumour$).mp.
15. (advance* adj6 breast adj6 tumor$).mp.
16. (metasta* adj6 breast adj6 cancer$).mp.
17. (metasta* adj6 breast adj6 neoplasm$).mp.
18. (metasta* adj6 breast adj6 carcinoma$).mp.
19. (metasta* adj6 breast adj6 tumour$).mp.
20. (metasta* adj6 breast adj6 tumor$).mp.
21. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22. exp Drug Therapy/
23. chemotherap*.mp.
24. (chemotherap* adj6 alone).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25. endocrine therap*.mp.
26. chemotherapy alone versus endocrine therapy.mp.
27. 22 or 23 or 24 or 25 or 26

28. 10 and 21 and 27
29. limit 38 to (humans and yr="2008-Current")

Appendix 2. EMBASE search strategy

#30
#29 AND [humans]/lim AND [embase]/lim AND [2008-2011]/py
#29
#8 AND #19 AND #28
#28
#23 AND #26 AND #27
#27
'chemotherapy'/exp AND alone AND versus AND endocrine AND 'therapy'/exp
#26
#24 OR #25
#25
endocrine AND therap*
#24
endocrine AND 'therapy'/exp
#23
#20 OR #21 OR #22
#22
chemotherap* NEAR/6 alone
#21
chemotherap*
#20
'chemotherapy'/exp
#19
#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#18
metastatic NEAR/6 breast AND tumor*
#17
metastatic NEAR/6 breast AND tumour*

(Continued)

#16
metastatic NEAR/6 breast AND carcinoma*
#15
metastatic NEAR/6 breast AND neoplasm*
#14
metastatic NEAR/6 breast AND cancer*
#13
advance* NEAR/6 breast AND tumor*
#12
advance* NEAR/6 breast AND tumour*
#11
advance* NEAR/6 breast AND carcinoma*
#10
advance* NEAR/6 breast AND neoplasm*
#9
advance* NEAR/6 breast AND cancer*
#8
#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#7
groups:ab
#6
trial:ab
#5
randomly:ab
#4
placebo:ab
#3
randomi*ed:ab
#2
controlled AND clinical AND trial
#1

(Continued)
randomised AND controlled AND trial

Appendix 3. WHO International Clinical Trials Registry Platform (ICTRP) search

Basic search:
1. advance breast cancer AND chemotherapy AND endotherapy
2. advance breast cancer AND chemotherapy AND endocrine therapy
3. metastatic breast cancer AND chemotherapy AND endotherapy
4. metastatic breast cancer AND chemotherapy AND endocrine therapy

Advanced search:
1. Condition: advance* breast cancer* OR advance* breast carcinoma* OR advance* breast neoplasm* OR metastatic breast cancer* OR metastatic breast carcinoma * OR metastatic breast neoplasm *
Intervention: chemotherapy AND endotherapy

2. Condition: advance* breast cancer* OR advance* breast carcinoma* OR advance* breast neoplasm* OR metastatic breast cancer* OR metastatic breast carcinoma * OR metastatic breast neoplasm *
Intervention: chemotherapy AND endocrine therap*

3. Condition: advance* breast cancer* OR advance* breast carcinoma* OR advance* breast neoplasm* OR metastatic breast cancer* OR metastatic breast carcinoma * OR metastatic breast neoplasm *
Intervention: chemotherapy OR endotherapy

4. Condition: advance* breast cancer* OR advance* breast carcinoma* OR advance* breast neoplasm* OR metastatic breast cancer* OR metastatic breast carcinoma * OR metastatic breast neoplasm *
Intervention: chemotherapy OR endocrine therap*

WHAT'S NEW

Date	Event	Description
6 February 2018	Review declared as stable	As breast cancer practice has changed, it is now thought to be unlikely that any clinical trials will be conducted comparing endocrine therapy alone versus chemotherapy alone for patients with metastatic breast cancer. The authors therefore do not expect to update this review.

HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 2, 2003

Date	Event	Description
24 September 2010	New search has been performed	Performed search for new studies on the 24th September 2010. No new studies included.

CONTRIBUTIONS OF AUTHORS

NW designed the review; developed the protocol; identified, selected and critically appraised the studies to be included in the review; applied eligibility criteria; extracted and entered data; analysed the data, wrote the first draft of the manuscript and updated the review. JH critically appraised the studies to be included in the review, applied eligibility criteria, extracted data and reviewed the draft and final versions of the manuscript.

DG collaborated in the design of the review and the development of the protocol, double checked eligibility and quality, and reviewed the draft and final versions of the manuscript.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- NHMRC Clinical Trials Centre, The University of Sydney, Australia
- Westmead Hospital, Sydney, Australia

External sources

- US Army Medical Research Acquisition Activity (DAMD17-99-1-9392), USA
- National Collaborating Centre for Cancer, UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Nil

NOTES

Both the Specialised Register search and the conference proceeding search were repeated in August 2006. No additional eligible studies were found. The text of the review was updated slightly to reflect this and to use more recent information, where appropriate. The review was also copyedited 29/09/2006 and 15/05/2011.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents, Hormonal [*therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [*therapeutic use]; Breast Neoplasms [*drug therapy]; Randomized Controlled Trials as Topic; Tamoxifen [therapeutic use]

MeSH check words

Female; Humans