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Tamoxifen for relapse of ovarian cancer (Review)

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[Intervention Review]

Tamoxifen for relapse of ovarian cancer

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ABSTRACT

Background

Tamoxifen is an important drug for treating breast cancer. Ovarian cancer cells are known to possess receptors for hormones and may thus also respond to tamoxifen.

Objectives

Tamoxifen is used to treat breast cancer in women whose tumours have oestrogen receptors. Since ovarian cancers also commonly have oestrogen receptors, it has been suggested that tamoxifen may be of some benefit. The objective of this review was to assess the effects of tamoxifen in women with relapsed ovarian cancer.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Issue 1, 2009. Cochrane Gynaecological Cancer Group Trials Register, MEDLINE from 2002 to April 2009, EMBASE from 2002 to April 2009. We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of review articles and contacted experts in the field, as well as drugs companies.

Selection criteria

Randomised and non-randomised studies of tamoxifen in women with ovarian cancer who have not responded to conventional chemotherapy. Only trials involving 10 or more patients were included.

Data collection and analysis

Two review authors independently assessed whether potentially relevant studies met the inclusion criteria. No trials were found and therefore no data were analysed.

Main results

The search strategy identified 1392 unique references of which 1360 were excluded on the basis of title and abstract. The remaining 32 articles were retrieved in full, but none satisfied the inclusion criteria. Only observational data from single arm studies of women treated with tamoxifen were reported.

Authors' conclusions

We are unable to make any evidence-based recommendations as we found no comparative studies assessing the effectiveness of tamoxifen in women with recurrent ovarian cancer. There is limited evidence on anti-tumour activity from phase 2 studies, but these contain no data on the effect of tamoxifen on symptom control, QOL or the prolongation of life.

PLAIN LANGUAGE SUMMARY

No evidence to suggest tamoxifen benefits patients with relapsed ovarian cancer

Ovarian cancer often spreads before symptoms show. Cytotoxic drugs are often only partly effective and cause severe side-effects. The main aims of treatment for relapsed disease are symptom control and prolongation of life. No data from RCTs or non-RCTs were found, so there was no evidence that tamoxifen was effective and safe as a treatment for relapsed ovarian cancer. Laboratory studies suggest tamoxifen may be effective as a treatment for women with ovarian cancer. Although, uncontrolled non-comparative trials on patients with relapsed ovarian cancer showed tamoxifen may shrink or stabilise tumours in a small number, there is a strong need for an RCT or good quality non-randomised comparative studies to determine the effectiveness and safety of tamoxifen in terms of overall survival, tumour response, symptom control, quality of life and adverse events.

BACKGROUND

Description of the condition

Ovarian cancer causes more deaths from cancer than the other types of gynaecological cancer and is the sixth most common cancer among women. A woman's cumulative risk of developing ovarian cancer by age 65 years is 0.5%: 0.4% in less developed countries and 0.7% in more developed countries. It is less common in women under the age of 35 years, and its incidence increases with age (GLOBOCAN 2002). In Europe, just over a third of women with ovarian cancer are alive five years after diagnosis (EUROCARE 2003), largely because most patients present with advanced disease that is widespread within the abdominal cavity (Jemal 2008). At present there is no effective screening method. The other key factor explaining the poor recurrence and death rate is the relative lack of effectiveness of drug therapy for advanced disease (AOCTG 1991). Despite the introduction of taxanes and other new cytotoxic agents most patients with advanced ovarian cancer still relapse and die. Because of this there has been the need for new treatments and for drugs that may be useful for arresting ovarian cancer that is no longer responsive to conventional drugs. In this situation treatments that lack significant side-effects are very desirable.

Ovarian cancer cells have been shown to possess surface receptors for oestrogen, progesterone and androgen and that in vitro responses to tamoxifen and other hormonal agents occur (Gronroos 1983). Tamoxifen is routinely used to treat breast cancer with response rates of 50 to 60% in those women whose tumours possess oestrogen receptors.

Description of the intervention

Tamoxifen is an oral agent that has been one of the most important drugs in the management of breast cancer over the past 40 years. It is given as a simple single tablet daily. It blocks the activity of oestrogen at oestrogen receptors in cancer cells and possesses weak oestrogenic activity of its own. It's most important adverse effect if the induction of hyperplasia of the endometrium of the womb, which in some patients may progress to invasive cancer. This is due to its weak agonistic action. However, many patients with ovarian cancer will have had a hysterectomy as part of their treatment. Tamoxifen also increases the risk of venous thrombosis. The risk from both these serious side effects is low (in the order of a few percent). Subjective side effects are usually not severe and most patients will tolerate long term use of tamoxifen. The current recommendation is for 5 years adjuvant therapy.

Why it is important to do this review

Since ovarian cancers commonly possess oestrogen receptors, trials have been carried out to see if tamoxifen is also active in this type of cancer. An effective drug that has few major side-effects would be very helpful, either as a treatment for advanced disease or as an adjuvant following surgery, with or without chemotherapy.

OBJECTIVES

The aim was to review all comparative studies of tamoxifen in women with advanced and recurrent ovarian carcinoma which has failed conventional cytotoxic drugs. The review was designed to find out if tamoxifen could cause useful regression of advanced ovarian cancer and through this have a palliative effect.

METHODS

Criteria for considering studies for this review

Types of studies

Tamoxifen as a palliative agent in ovarian cancer, phase two or phase three comparative trials, with or without randomisation. Only studies with 10 or more patients were included.

Types of participants

Women with ovarian cancers that:

i) were never responsive to cytotoxic drug therapy
ii) are no longer responsive to cytotoxic drug therapy
iii) have relapsed after chemotherapy

Types of interventions

Intervention:

- Oral tamoxifen as a palliative therapy.

Comparison:

- Tamoxifen versus placebo
- Tamoxifen versus best supportive care
- Chemotherapy versus the same chemotherapy plus tamoxifen

Types of outcome measures

Primary outcomes

1. Overall survival: survival until death from all causes.
2. Objective response rate (using clinical and imaging techniques)

Secondary outcomes

1. Duration of response
2. Quality of life (QoL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication
3. Symptom control
4. Adverse events were classified according to CTCAE 2006:
   a. **gastrointestinal** (nausea, anorexia);
   b. **skin** (allergy);
   c. **neurological** (visual loss);
   d. **menopausal symptoms** (e.g. hot flushes);
   e. **other** (Venous thrombosis, endometrial cancer).

Search methods for identification of studies

Papers in all languages were sought and translations carried out where necessary.

Electronic searches

See: Cochrane Gynaecological Cancer Group methods used in reviews.
The following electronic databases were searched:

- The Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register
- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE

- EMBASE
- CancerLit

The Medline search strategy was based on terms related to the review topic and is presented in Appendix 1:

Tamoxifen (different brand names of the drug used mainly in USA and Canada - e.g. Nolvadex*, Apo-Tamox, Gen-Tamoxifen, Novo-Tamoxifen, Tamofen, Tamone - were also used for MEDLINE search, but search results were identical with searches based on word Tamoxifen only)
Ovar* (covering ovary, ovarian)
Cancer* or carcinom* or neoplasm* (where appropriate)

For databases other than MEDLINE, the search strategy was adapted accordingly. EMBASE search strategy is listed in Appendix 2. The CENTRAL search strategy is listed in Appendix 3. Databases were searched from 2002 until April 2009.

We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of review articles and contacted experts in the field, as well as drugs companies.

All relevant articles found were identified on PubMed and using the 'related articles' feature, a further search was carried out for newly published articles.

Searching other resources

Metaregister (mRCT), Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials were searched for ongoing trials. The main investigators of any relevant ongoing trials were contacted for further information, as were any major co-operative trials groups active in this area.

Handsearching

Reports of conferences were handsearched in the following sources:

- British Journal of Cancer.
- British Cancer Research Meeting.
- Annual Meeting of the International Gynecologic Cancer Society.
- Annual Meeting of the British Gynaecological Cancer Society (BGCS).
- Annual Meeting of the American Society of Gynecologic Oncologist.
- Annual Meeting of European Society of Medical Oncology (ESMO).
- Annual Meeting of the American Society of Clinical Oncology (ASCO).

Reference lists and Correspondence

The citation lists of included studies were checked and experts in the field contacted to identify further reports of trials, particularly those that are as yet unpublished.

The AstraZeneca (producer of Tamoxifen) web page was also scanned for any relevant information. The company was approached and agreed to identify trials sponsored by or known to them.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to the reference management database Endnote, duplicates were removed and the remaining references were examined by two review authors (AB, CW) independently. Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers were assessed independently by two review authors (AB, CW). Disagreements were resolved by discussion between the three review authors. Reasons for exclusion are documented. We did not identify any studies suitable for inclusion in the review. Should such studies be identified for future updates of the review the following methods will be employed (see below).

Data extraction and management

For included studies, data will be abstracted as recommended in Chapter 7 of the Cochrane Handbook 2008 (Cochrane Handbook). This will include data on the following:

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population
  - Total number enrolled
  - Patient characteristics
  - Age
  - Co-morbidities
  - Previous treatment
- Ovarian cancer details at diagnosis
  - FIGO stage
  - Histological cell type
  - Tumour grade
  - Presence or absence of hormone receptors or status unknown
  - Extent of disease
  - Disease free interval
  - Number of recurrences
- Total number of intervention groups
- Intervention details
  - Details of Tamoxifen
    - ☐ Type
    - ☐ Dose
    - ☐ Cycle length
    - ☐ Combination
  - Details of comparison
- Risk of bias in study (see below)
- Duration of follow-up

- Outcomes: Overall survival, objective tumour response, duration of response, quality of life, symptom control and adverse events.
  * For each outcome: Outcome definition (with diagnostic criteria if relevant);
  * Unit of measurement (if relevant);
  * For scales: upper and lower limits, and whether high or low score is good
  * Results: Number of participants allocated to each intervention group;
  * For each outcome of interest: Sample size; Missing participants

Data on outcomes will be extracted as below

- For time to event (e.g. overall survival) data, we will extract the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these are not reported, we will attempt to estimate them from other reported statistics using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events, tumour response, symptom control or deaths if it was not possible to use a HR), we will extract the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a relative risk (RR).
- For continuous outcomes (e.g. QOL measures, tumour response, duration of response), we will extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and its standard error.

Both unadjusted and adjusted statistics will be extracted, if reported.

Where possible, all data extracted will be those relevant to an intention-to-treat analysis, in which participants are analysed in groups to which they were assigned.

The time points at which outcomes were collected and reported will be noted.

Data will be abstracted independently by two review authors (AB, CW) onto a data abstraction form specially designed for the review. Differences between review authors will be resolved by discussion or by appeal to a third review author if necessary.

Assessment of risk of bias in included studies

The risk of bias in included RCTs will be assessed using the following questions and criteria:

Sequence generation

Was the allocation sequence adequately generated?

- Yes: e.g. a computer-generated random sequence or a table of random numbers
- No: e.g. date of birth, clinic id-number or surname
- Unclear: e.g. not reported.

Allocation concealment

Was allocation adequately concealed?

- Yes: e.g. where the allocation sequence could not be foretold
- No: e.g. allocation sequence could be foretold by patients, investigators or treatment providers
- Unclear: e.g. not reported

Blinding

Blinding will be in terms of participants, healthcare providers and outcome assessors.

Was knowledge of the allocated interventions adequately prevented during the study?

- Yes
- No
- Unclear.

Incomplete reporting of outcome data

We will record the proportion of participants whose outcomes were not reported at the end of the study.

Were incomplete outcome data adequately addressed?

- Yes, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
- No, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms
- Unclear if loss to follow-up was not reported

Selective reporting of outcomes

Are reports of the study free of suggestion of selective outcome reporting?

- Yes e.g if review reports all outcomes specified in the protocol
- No
- Unclear

Other potential threats to validity

Was the study apparently free of other problems that could put it at a high risk of bias?

- Yes
- No
- Unclear

The risk of bias in non-randomised studies will be assessed in accordance with four additional criteria:

Cohort selection

1. Were relevant details of criteria for assignment of patients to treatments provided?
   a. Yes
   b. No
   c. Unclear

2. Was the group of women who received the experimental intervention (Tamoxifen for relapse of ovarian cancer) representative?
   a. Yes, if they were representative of women with recurrent ovarian cancer
   b. No, if group of patients was selected
   c. Unclear, if selection of group was not described
3. Was the group of women who received the comparison intervention (best supportive care or another invention other than Tamoxifen) representative?
   a. Yes, if drawn from the same population as the experimental cohort
   b. No, if drawn from a different source
   c. Unclear, if selection of group not described

Comparability of treatment groups

1. Were there no differences between the two groups or differences controlled for, in particular with reference to FIGO stage, disease free interval, presence or absence of hormone receptors, histological subtype, number of recurrences, previous response to chemotherapy?
   a. Yes, if at least three of these characteristics were reported and any reported differences were controlled for
   b. No, if the two groups differed and differences were not controlled for.
   c. Unclear, if fewer than three of these characteristics were reported even if there were no other differences between the groups, and other characteristics had been controlled for.

The risk of bias tool will be applied independently by two review authors (AB, CW) and differences resolved by discussion or by appeal to a third reviewer. Results will be presented in both a risk of bias graph and a risk of bias summary. Results of meta-analyses will be interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect

We will use the following measures of the effect of treatment:

- For time to event data, we will use the HR.
- For dichotomous outcomes, we will use the RR.
- For continuous outcomes, we will use the mean difference between treatment arms (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales).

Dealing with missing data

We will not impute missing outcome data for the primary outcome. If data are missing or only imputed data are reported we will contact trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity

Heterogeneity between studies will be assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001), and, if possible, by sub-group analyses Subgroup analysis and investigation of heterogeneity. If there is evidence of substantial heterogeneity, the possible reasons for this will be investigated and reported.

Assessment of reporting biases

Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects. When there is evidence of small-study effects, publication bias will be considered as only one of a number of possible explanations. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, sensitivity analyses will be performed using fixed effects models.

Data synthesis

If sufficient, clinically similar studies are available their results will be pooled in meta-analyses. Adjusted summary statistics will be used if available; otherwise unadjusted results will be used.

- For time-to-event data, HRs will be pooled using the generic inverse variance facility of RevMan 5.
- For dichotomous outcomes, the RR will be calculated for each study and these will then be pooled.
- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences will be pooled.

If any trials have multiple treatment groups, the 'shared' comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons.

Random effects models with inverse variance weighting will be used for all meta-analyses (DerSimonian 1986).

If possible, indirect comparisons, using the methods of Bucher 1997 will be used to compare competing interventions that have not been compared directly with each other.

Subgroup analysis and investigation of heterogeneity

Sub-group analyses will be performed, grouping the trials by:

- presence/absence of hormone receptors
- prior response to chemotherapy/no prior response
- resistant to chemotherapy/resistance yet to be shown

Factors such as age, stage, length of follow-up, adjusted/unadjusted analysis will be considered in interpretation of any heterogeneity.

Sensitivity analysis

Sensitivity analyses will be performed (i) excluding non-randomised studies if RCTs have been included (ii) excluding studies at high risk of bias and (iii) using unadjusted results.

RESULTS

Description of studies

Results of the search

The search strategy identified 211 references in Medline, 1324 in Embase, 11 in Central and 28 in the specialised register. When the search results were merged into Endnote and duplicates were removed there were 1392 unique references. The abstracts of these were read independently by two reviewers and articles which obviously did not meet the inclusion criteria were excluded at this stage. A total of 32 articles were retrieved in full. The full text screening of these references excluded all of the studies for the reasons described in the table Characteristics of excluded studies.

Two reviewers independently searched the grey literature; these searches did not identify any relevant studies.

Included studies

No studies met our inclusion criteria.

Excluded studies

The full text was obtained for 32 references, but all were excluded from the review for the reasons given in Characteristics of excluded studies.

Risk of bias in included studies

No trials were found and therefore the risk of bias tool was not applied.

Effects of interventions

No data were available.

DISCUSSION

Summary of main results

We did not identify any studies that evaluated the effectiveness and safety of tamoxifen in relapsed ovarian cancer. The majority of studies appear to have been designed as single arm studies aiming to assess whether tamoxifen can induce response in ovarian cancer and the study designs did not allow assessment of the effect of tamoxifen on symptom control, quality of life and prolongation of survival.

The following questions remain unanswered. 1) Whether hormone receptor status is useful in selecting patients for tamoxifen in recurrent ovarian cancer. 2) Are certain histological subtypes of ovarian cancer more likely to respond than others? Can tamoxifen improve survival, symptom control and quality of life?

Overall completeness and applicability of evidence

The studies identified provided no data to answer the key question posed by the review. This was whether tamoxifen provided useful palliation in this group of women with advanced ovarian cancer. Although phase 2 studies have shown a potential for tumour response, no definite judgement can be about this. There were no data from the studies to say whether women with ovarian cancer had measurable benefit. There are too few patients in multiple small studies, which makes it difficult to answer subsidiary questions, such as identifying who is most likely to benefit. Where such studies were done, definitions used varied across studies. Tamoxifen remains in clinical use; mainly when clinicians have exhausted all reasonable chemotherapy options and wish to consider a simple oral, relatively non toxic treatment. From the results of non-comparative single arm tamoxifen studies it is likely that some patients will respond, but it is not clear whether or not there will be any clinical benefit.

Quality of the evidence

No studies fulfilled the inclusion criteria, so no evidence was found. Limited data from non-comparative studies were available. The response rates seen vary greatly from study to study, possibly due to patient selection and varying assessment of response.

Potential biases in the review process

A comprehensive search was performed, including a thorough search of the grey literature and all studies were sifted and data extracted by two reviewers independently. We were not restrictive in our inclusion criteria with regards to types of studies as we planned to include non-randomised studies with concurrent comparisons groups as we suspected that we would not find any relevant RCTs. Therefore we attempted to ensure that we did not overlook any relevant evidence by searching a wide range of reasonable quality non-randomised study designs (case-control studies and case series of fewer than 10 patients were excluded).

The greatest threat to the validity of the review is likely to be publication bias i.e. studies that did not find the treatment to have been effective may not have been published. We were unable to assess this possibility as we did not find any studies that met the inclusion criteria.

Agreements and disagreements with other studies or reviews

See table of results: Table 1; Table 2 which show the crude objective response and stable disease rates in phase 2 studies.

The only data that could be examined in this review were the response rates in the various non-comparative studies. All presented objective responses (defined as complete and partial, presumably according to standard criteria - though this definition was usually not available). Some, in addition, reported the numbers of patients who had stable disease. In some studies the duration of stable disease, required to define this criteria was given (this varied), whilst in others this information was not presented.

Overall, 60 of 623 patients (9.6%) responded objectively, using the criteria in the various trials. In those studies recording stable disease (a minimal definition is no evidence of a greater than 25% increase or more than a 50% decrease in the cross sectional area of the cancer lasting for at least one month), 131 of 411 patients (31.9%) had stable disease, as defined in the trials. There was marked heterogeneity in the objective response rates (0 - 56%) and disease stabilisation rates (0 to 83%). This may reflect both different selection criteria for patients included in the trials and different criteria of response or application of these criteria. The measurement of response in ovarian carcinoma is notoriously difficult. The inclusion of stable disease may be helpful in this situation, stable disease in response to hormone therapy in breast cancer appears meaningful. However, the data on stable disease in this review may not be robust since assessment of response

is difficult and duration of stability may have been short. Most studies did not report CA 125 measurements (a protein associated with active ovarian cancer), which might have helped define stable disease more clearly. In addition, not all trials reported the stable disease rate (it is not a standard definition of response), leaving the possibility that there was a bias for trials with a high disease stabilisation rate to report this data and for those with low stabilisation rates not to report it. The duration of stable disease defined in some studies was as short as four weeks (Marth 1997) and lack of progression of more than 25% of the cross-sectional area of any cancer in one month may not represent true stable disease. Despite this, achievement of stable disease in this setting may be useful since a number of trials reported cases where stable disease lasted for a number of years. However, the significance of such results is unclear in small trials where there is no comparator and no independent assessment of response.

In the Marth trial (Marth 1997) it was reported that responses were seen significantly more often in endometrioid cancers and that no responses were seen in clear cell cancers. However, the numbers were small in each of these groups and it is not clear whether this was a pre-specified sub-group analysis. They also found that young age at presentation and lower initial FIGO (International Federation of Gynecology and Obstetrics) stage disease were independent prognostic variables and that these patients were more likely to respond, though once again it is not clear whether these were pre-specified analyses.

A number of trials (Landoni 1985; Holt 1979 ;Abu-Jawdeh 1996; Anderl 1988; Beecham 1988) reported on the prognostic significance of the presence of hormone receptors in the tumour. The results were heterogeneous and there was no consensus that hormone receptor status could be used as a predictor of response to subsequent tamoxifen therapy. The quality and small size of the trials was inadequate for a review to draw any useful conclusions on the prognostic significance of the presence of hormone receptors when using tamoxifen.

This review gives no evidence to support the use of tamoxifen in recurrent and refractory ovarian carcinoma as we did not find any studies that were relevant to our inclusion criteria. Even in the non-comparative studies there was no definitive information predicting which patients were likely to respond, although Marth (Marth 1997) found that endometrioid patients were significantly more likely to respond and that there were no responses in a small group with clear cell cancers. These analyses do not appear to have been pre-specified and are also unreliable as the study did not have a comparison group. Those trials that did include measurement of hormone receptors found no correlation with the presence of such receptors and response to tamoxifen. Although there was an anecdotal suggestion that trials likely to have the highest rates of chemotherapy refractory patients had the lowest response rates, there were no clear data to substantiate this. Of interest, however, is the high objective response rate in the group of previously untreated patients in one study (Gennatas 1996). In the absence of good quality comparative studies we can only speculate the efficacy of tamoxifen for relapsed ovarian cancer.

AUTHORS' CONCLUSIONS

Implications for practice

We are unable to make any evidence-based recommendations as we found no comparative studies assessing tamoxifen for women with recurrent ovarian cancer.

There were no data, from any of the sifted references, that help in selecting those most likely to respond, or on whether the presence of hormone receptors is a useful criteria to predict response. Although the data in phase 2 studies do not corroborate the hypothesis, tamoxifen may be active in those patients who are not yet truly refractory to a wide range of chemotherapeutic agents. Tamoxifen is generally well tolerated and is usually less toxic than the alternatives in patients who have failed routine chemotherapy, but there is no evidence about its effectiveness.

Implications for research

Ideally, a large randomised controlled trial is needed to compare tamoxifen and best supportive care or another medical intervention for women with recurrent ovarian cancer. However, if such a trial is not possible then it is important to conduct well designed non-randomised studies that use multivariate analysis to adjust for baseline imbalances.

In the absence of reliable data, it is unclear whether tamoxifen could be considered for the management of relapsed ovarian carcinoma. The inclusion criteria, dose and schedule and method of assessment of response in phase 2 studies has been very variable. In addition, the single arm studies failed to measure whether tamoxifen is a useful palliative agent. A new generation of trials is needed to try to define more clearly whether tamoxifen is a useful palliative therapy. It would seem appropriate to avoid trials that only accrue patients who are truly refractory to cytotoxic drugs. If such trials show that tamoxifen does possess useful activity in ovarian carcinoma, there might be a role for new RCTs testing the effect of using tamoxifen in conjunction with cytotoxic chemotherapy or as an adjuvant therapy.

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Abu-Jawdeh 1996	No comparison group
Ahlgren 1993	No comparison group
Ahlgren 1993a	Published later
Anderl 1988	No comparison group
Beecham 1988	Published later in a peer review journal - Hatch 1991
Belinson 1987	Tamoxifen in combination with megestrol acetate
Bruzzone 1995	Tamoxifen given in combination with triptorelin
Gennatas 1996	No comparison group
Hamerlynck 1985	No comparison group
Hamerlynck 1985 (a)	Duplicate publication - see Hamerlynck 1985
Harvey 1987	Overlap with patients in Osborne 1988
Hatch 1991	Probable major overlap of patients with later paper by Markman 1996
Holt 1979	No comparison group
Jaeger 1993	Published in peer review journal later
Jager 1995	More than one hormonal agent used
Jakobsen 1987	Tamoxifen in combination with medroxyprogesterone acetate
Landoni 1983	Probable overlap with Landoni 1985
Landoni 1985	No comparison group

Study	Reason for exclusion
Lopez 1996	Tamoxifen in combination with Leuprolide acetate
Losa 1993	172 patients randomised to three arms of different hormones
Markman 1996	No comparison group
Marth 1997	Excluded as 155 patients treated with tamoxifen, but only 65 evaluable for response. Median survival of 155 patients was 3.8 months (95% CI: 3.3- 5.4), 5-year survival rate was 2%.
Millward 1994	Tamoxifen in combination with etoposide.
Milward 1992	Combination - published in several sources
Osborne 1987(a)	Duplication of Osborne 1988
Osborne 1987(b)	Duplication of Osborne 1988
Osborne 1988	No comparison group
Schwartz 1989	RCT of chemotherapy (cisplatin/doxorubicin) with or without tamoxifen. No survival differences between the groups (49 with tamoxifen, 51 without). Hormone receptors did not correlate with outcome.
Schwarz 1980	No comparison group. There was evidence of correlation between the level of oestrogen receptors and stable disease.
Shirey 1985	No comparison group
Slevin 1986	No comparison group
Trippa 1993	Tamoxifen in combination with beta interferon
van der Vange 1995	Multiple different hormonal therapies
van der Velden 1995	No comparison group
Weiner 1987	No comparison group

ADDITIONAL TABLES

Table 1. Objective responses: complete plus partial response rates

Trial	no. CR + PR	no. treated
Ahlgren 1993	5	29
Gennatas 1996	28	50
Hamerlynck 1985	2	78
Jager 1995	0	33

Table 1. Objective responses: complete plus partial response rates *(Continued)*

Landoni 1985	0	41
Losa 1993	1	55
Markman 1996	13	102
Marth 1997	4	65
Osborne 1988	1	51
Schwarz 1980	1	13
Shirey 1985	0	23
Slevin 1986	0	22
van der Velden 1995	2	30
Weiner 1987	3	31

Table 2. Stable disease rates

Study	No. stable disease	No. treated
Hamerlynck 1985	7	78
Jager 1995	3	33
Landoni 1985	19	41
Losa 1993	22	55
Marth 1997	50	65
Osborne 1988	0	50
Schwarz 1980	4	13
Sherey 1985	19	23
Slevin 1986	1	22
Weiner 1987	6	31

APPENDICES

Appendix 1. MEDLINE search strategy

Medline Ovid 2002-April week1 2009

1. exp Ovarian Neoplasms/
2. (ovar* adj5 (cancer* or carcinom* or neoplasm* or malignan* or tumour* or tumor*)).mp.

3. 1 or 2
4. exp Tamoxifen/
5. tamoxifen.mp.
6. novaldex.mp.
7. apo-tamox.mp.
8. gen-tamoxifen.mp.
9. novo-tamoxifen.mp.
10. tamofen.mp.
11. tamone.mp.
12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 3 and 12
14. limit 13 to yr="2002 - 2009"
15. Animals/
16. Humans/
17. 15 not (15 and 16)
18. 14 not 17

key: mp=title, original title, abstract, name of substance word, subject heading word

Appendix 2. EMBASE search strategy

Embase Ovid 2009 week 15

1 exp Ovary Tumor/
2 (ovar* adj5 (cancer* or carcinom* or neoplasm* or malignan* or tumour* or tumor*)).mp.
3 1 or 2
4 exp Tamoxifen/
5 tamoxifen.mp.
6 novaldex.mp.
7 apo-tamox.mp.
8 gen-tamoxifen.mp.
9 novo-tamoxifen.mp.
10 tamofen.mp.
11 tamone.mp.
12 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 3 and 12
14 limit 13 to yr="2002 - 2009"
15 exp Animal/
16 Human/
17 15 not (15 and 16)
18 14 not 17

key: mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

Appendix 3. CENTRAL search strategy

CENTRAL Issue 1 2009

#1 MeSH descriptor Ovarian Neoplasms explode all trees
#2 ovar* near/5 (cancer* or carcinom* or neoplasm* or malignan* or tumour* or tumor*)
#3 (#1 OR #2)
#4 MeSH descriptor Tamoxifen explode all trees
#5 tamoxifen
#6 novaldex
#7 apo-tamox
#8 gen-tamoxifen
#9 novo-tamoxifen
#10 tamofen
#11 tamone
#12 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
#13 (#3 AND #12)

#14 (#13), from 2002 to 2009

WHAT'S NEW

Date	Event	Description
23 November 2020	Review declared as stable	This review is not currently being update as it will be superseded by a new ongoing review.

HISTORY

Protocol first published: Issue 1, 1998
Review first published: Issue 2, 1998

Date	Event	Description
3 September 2018	Amended	New contributors required to update and maintain this Cochrane Review.
25 April 2009	New citation required but conclusions have not changed	Searches updated to April 2009. No new studies were identified.

CONTRIBUTIONS OF AUTHORS

CW: critically assessed studies, sifted references and wrote text. IS: prepared and ran the Search Strategy for the updated review (Update 2002) AB: drafted the methodological sections of the review, sifted references and wrote text (Update 2010).

DECLARATIONS OF INTEREST

The author was part of a group that undertook two of the trials included in the review (Slevin 1986; Osborne 1988).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Medical Research Council, UK
- Department of Health, UK

  NHS Cochrane Collaboration programme Grant Scheme CPG-506

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents, Hormonal [*therapeutic use]; Neoplasm Recurrence, Local [*drug therapy]; Ovarian Neoplasms [*drug therapy]; Tamoxifen [*therapeutic use]

MeSH check words

Female; Humans