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Purpose: To conduct a series of comprehensive systematic reviews of randomised trials addressing specific questions in the use of chemotherapy and endocrine therapy in advanced breast cancer.

Scope: The effectiveness of each treatment will be evaluated using survival, time to disease progression, quality of life and treatment toxicity when possible. A protocol is being developed for each review question which clearly states the methods of the review including data collection, inclusion criteria, critical appraisal and analysis. Every attempt is being made to identify and include the results of **all** randomised trials conducted in each question. The results of these reviews will enable patients and clinicians to make treatment decisions based on the best available evidence, and which balance the ability to achieve cancer control against factors such as treatment toxicity and quality of life. The reviews will also enable the researchers to identify areas in need of further research, as well as questions for which there are already clear answers and further research is unnecessary.

Major findings: This project is currently underway and results are not yet available for any of the reviews.

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FOREWORD

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INTRODUCTION

It is not possible for those involved in the management of women with advanced breast cancer to read even a small percentage of the thousands of journals that publish the findings of relevant clinical research. Review articles summarising current knowledge can therefore be a valuable information source. Unfortunately many traditional review articles are flawed as they are influenced by the interests and beliefs of the reviewer. The results of these reviews may therefore be incorrect and mislead those who rely on them for making their treatment decisions. A properly conducted systematic review follows a protocol, developed before the review commences, which clearly states the methods of the review including data collection, inclusion criteria, critical appraisal and analysis. Every attempt is then made to identify and include the results of all of the best evidence available that addresses the review question.

The main objective of this project is to conduct a series of systematic reviews addressing specific questions in the use of chemotherapy and endocrine therapy in advanced breast cancer. Work will focus on the identification and assimilation of the results of randomised clinical trials. The effectiveness of each treatment will be evaluated using survival, time to disease progression, quality of life and treatment toxicity when possible.

The results of these systematic reviews will enable patients and clinicians to make treatment decisions based on the best available evidence, and which balance the ability to achieve cancer control against factors such as treatment toxicity and quality of life. The reviews will also enable the researchers to identify areas in need of further research, as well as questions for which there are already clear answers and further research is unnecessary.

BODY

In the first year it was planned to:

1. Compile a summary of the available randomised evidence in the management of advanced breast cancer.
2. Compile an updateable database of randomised trials in advanced breast cancer.
3. The completion of protocols for *at least* each of the questions outlined in this proposal. At least 3 systematic reviews will be completed each year for the duration of the project.
4. Consultation with breast cancer consumers.

Note: Funding provided under the terms of this grant was received by the University of Sydney in September 1999. It was not possible to advertise for the positions to be paid for by the funds provided by this grant until that time. Although this has had some influence on initial progress, we anticipate being able to deliver the completed reviews according to schedule.

Details of each work item.

1. **A summary of the available randomised evidence in the management of advanced breast cancer, and**
2. **An updateable database of randomised trials in advanced breast cancer**

These two tasks are pivotal to the success of this project: the ability to identify trials in advanced breast cancer being fundamental to our ability to conduct reviews addressing each question. As of the 18th July a total of 1,226 references in advanced breast cancer using randomised evidence had been identified. These were found using a comprehensive search strategy that has been applied to a number of databases including Medline, The Cochrane Library, PDQ and other databases of published and unpublished literature. (See Appendix A for a copy of the search strategies).

The references have been imported into the bibliographic software package Reference Manager. This package automatically allocates a unique identification number to each publication. A Research Assistant has read and coded each abstract using a data collection form (see Appendix B). This form is then coded and the data entered into an Excel spreadsheet, including details of each treatment arm. This spreadsheet will be used to identify trials for each review question, and to identify additional research questions for future reviews. The search strategy is re-applied and the results used to update the Reference Manager database at the beginning of each month.

Question	Number of trials reports identified
Which is better, chemotherapy or endocrine therapy, in women with advanced breast cancer:	
• As initial treatment?	21
• After first-line endocrine treatment?	21
• After multiple endocrine treatments?	21
Given that chemotherapy is administered only until disease progresses, which is optimal?	
• a longer or a shorter duration of chemotherapy? (eg 3 vs 6 months of CMF)?	212
• continuous chemotherapy or intermittent chemotherapy?	212
What is the value of increasing the dose of a chemotherapy regimen? This would include:	
• A higher vs a lower total dose of the same drug?	100
• The same total dose given over a shorter vs longer time period?	136
• A more vs a less active regimen?	212
• The value of adding growth factors and marrow support?	181
• The value of adding drugs to a chemotherapy regimen which result in an increase in treatment-related toxicity?	177

Note: Coding has resulted in the identification of trials that are potentially relevant to more than one question. The total number of trial reports that apply to Table 1 is 533. A copy of the published paper is required for each potentially eligible trial. The published paper has been obtained for 402 of the 533

reports and 226 of these have been masked, in preparation for the review process. Masking involves removing the results section and other identifying features such as authors names.

The nature of the remaining trials on the database has been summarised in Table 2.

Table 2: Nature of questions of remaining trials on the database

Question	Number of trials identified
Addition of endocrine therapy to a chemotherapy regimen	37
Anthracycline vs non-anthracycline regimens	23
Calcium and bone metabolism	47
Cardioprotection	13
Combination chemotherapy vs combination chemotherapy	250
Chemotherapy vs chemoendocrine therapy	71
Endocrine therapy dose issues	84
Estrogenic recruitment	18
Endocrine therapy vs chemoendocrine therapy	52
One endocrine treatment vs another	166
Immunotherapy	41
Non-cytotoxic and supportive therapy	58
Psychological intervention questions	17
Radiation therapy questions	57
Single agent chemotherapy v combination chemotherapy	63
Single agent chemotherapy vs single agent chemotherapy	55

Note: The coding performed identified trials that are potentially relevant to questions. Some papers are assigned to more than one question, which means that the numbers will not add to the total number of papers.

3. **The completion of systematic reviews for *at least* each of the questions outlined in this proposal. At least 3 systematic reviews will be completed each year for the duration of the project.**

As discussed above, work has begun on each of the questions outlined in the proposal through the identification of potentially eligible studies. In addition, progress has been made on the 3 reviews in chemotherapy vs endocrine therapy, that is:

Which is better, chemotherapy or endocrine therapy, in women with advanced breast cancer:

- *As initial treatment?*
- *After first-line endocrine treatment?*
- *After multiple endocrine treatments?*

A protocol has been completed and submitted to the Cochrane Breast Cancer Group for peer review. (Appendix C) The comments of peer reviewers are expected to be received by July 21. The comments of the peer reviewers will be addressed by the reviewers, and it is anticipated that the protocol will be published in Issue 4, 2000 of the Cochrane Library (due to be released in October 2000). Work will begin on this review once the comments of peer reviewers have been addressed and the editorial committee of the Cochrane Breast Cancer Group gives its approval. It is expected that the review will be completed by December, 2000. The results would then be published in Issue 2, 2001 of the Cochrane Library.

Attention will next be given to the set of questions relating to the dose of chemotherapy, starting with:

The value of adding drugs to a chemotherapy regimen which result in an increase in treatment-related toxicity?

A protocol is in development and expected to be submitted for peer review by October, 2000.

Also in development is a protocol addressing the question:

Higher dose chemotherapy per week vs lower dose chemotherapy per week

In addition to the questions outlined in the original proposal, a review is currently underway addressing the question:

Bisphosphonates for bony metastases in advanced breast cancer

A protocol has been completed and submitted to the Cochrane Breast Cancer Group for peer review. (Appendix D) The comments of peer reviewers have been received and forwarded to the reviewers. It is anticipated that the protocol will be published in Issue 4, 2000 of the Cochrane Library (due to be released in October 2000).

As none of the reviews mentioned above has been completed, review results cannot be reported.

4. Consultation with breast cancer "consumers" to identify other questions of importance.

Efforts have been made to increase the involvement of women with breast cancer in the work of the Cochrane Breast Cancer Group through a number of activities including:

- Increasing the number of names on the Cochrane Breast Cancer Group's contact directory. This has been achieved (with varying degrees of success) through:
  - The conduct of a Workshop on the Cochrane Collaboration during the Eighth Annual Advocacy Training Conference of the National Breast Cancer Coalition Fund. A membership form was distributed to attendees to encourage involvement in the Cochrane Breast Cancer Group.
  - Making contact with regional breast cancer groups, such as the Alamo Breast Cancer Group (San Antonio, Texas)
- Increasing the number of consumers who are actively involved in the work of the Cochrane Breast Cancer Group. Particularly successful have been strategies to involve consumers in peer reviewing protocols and completed reviews, and handsearching journals to identify randomised trials.
- Formation of a consumer working party, co-convened by 2 consumers. Both have constituencies with whom they communicate (Christine Brunswick from the USA, and Sue Lockwood from Australia)
  - A teleconference meeting of the convenors (with the project coordinator for this grant) is planned for Wednesday 2nd August, 2000.
  - The convenors have suggested a number of individuals from various countries. These individuals will be invited to join the working party. The aim is to compile a list of questions consumers would like to see addressed in systematic reviews.
- A web site has been developed for the Cochrane Breast Cancer Group. The site provides information on the group, and includes a membership form should individuals be interested in making a contribution, as well as a mechanism for consumers to let us know the questions they would like to see addressed. The site will be launched on 21st July, and the value of using the web to obtain consumer input will be monitored.

KEY RESEARCH ACCOMPLISHMENTS

Key accomplishments to date:

- The identification of 1,226 references in advanced breast cancer reporting the results of randomised clinical trials.
- Establishment of an updateable database of randomised trials in advanced breast cancer.
- Completion of a protocol addressing the questions "Which is better, chemotherapy or endocrine therapy, in women with advanced breast cancer":
    - As initial treatment
    - After first-line endocrine treatment
    - After multiple endocrine treatments
- Development of a web site to facilitate consumer contributions.

REPORTABLE OUTCOMES

- 1,226 references in advanced breast cancer reporting the results of randomised clinical trials identified.
- A database of randomised trials in advanced breast cancer established.
- Web site established to facilitate consumer contributions.

CONCLUSIONS

To be reported in future annual reports.

REFERENCES

To be reported in future annual reports.

APPENDICES

Appendix A

Medline Search Strategy

1 | exp breast neoplasms/
2 | exp "neoplasms, ductal, lobular, and medullary (non mesh)"/
3 | exp fibrocystic disease of breast/
4 | or/1-3
5 | exp breast/
6 | breast.tw.
7 | 5 or 6
8 | (breast adj milk).ti,ab,sh.
9 | (breast adj tender$).ti,ab,sh.
10 | or/8-9
11 | 7 not 10
12 | exp neoplasms
13 | 11 and 12
14 | exp lymphedema/
15 | 14 and 11
16 | (breast adj25 neoplasm$).ti,ab,sh.
17 | (breast adj25 cancer$).ti,ab,sh.
18 | (breast adj25 tumour$).ti,ab,sh.
19 | (breast adj25 tumor$).ti,ab,sh.
20 | (breast adj25 carcinoma$).ti,ab,sh.
21 | (breast adj25 adenocarcinoma$).ti,ab,sh.
22 | (breast adj25 sarcoma$).ti,ab,sh.
23 | (breast adj50 dcis).ti,ab,sh.
24 | (breast adj25 ductal).ti,ab,sh.
25 | (breast adj25 infiltrating).ti,ab,sh.
26 | (breast adj25 intraductal).ti,ab,sh.
27 | (breast adj25 lobular).ti,ab,sh.
28 | (breast adj25 medullary).ti,ab,sh.
29 | or/16-28
30 | 4 or 13 or 15 or 29
31 | exp mastectomy/
32 | 30 or 31
33 | exp "analytical, diagnostic and therapeutic techniques"
34 | 33 and 11
35 | 34 or 32
36 | exp mammary neoplasms/
37 | (mammary adj25 neoplasm$).ti,ab,sh.
38 | (mammary adj25 cancer$).ti,ab,sh.
39 | (mammary adj25 tumour$).ti,ab,sh.
40 | (mammary adj25 tumor$).ti,ab,sh.
41 | (mammary adj25 carcinoma$).ti,ab,sh.
42 | (mammary adj25 adenocarcinoma$).ti,ab,sh.
43 | (mammary adj25 sarcoma$).ti,ab,sh.
44 | (mammary adj50 dcis).ti,ab,sh.
45 | (mammary adj25 ductal).ti,ab,sh.
46 | (mammary adj25 infiltrating).ti,ab,sh.
47 | (mammary adj25 intraductal).ti,ab,sh.
48 | (mammary adj25 lobular).ti,ab,sh.
49 | (mammary adj25 medullary).ti,ab,sh.
50 | or/36-49
51 | limit 50 to human
52 | 35 or 51
53 | exp breast self-examination/
54 | (breast adj25 self$).ti,ab,sh.
55 | (breast adj25 screen$).ti,ab,sh.
56 | exp mammography/
57 | or/52-56
58 | mammograph$.tw.
59 | 58 and 11
60 | 57 or 59
61 | limit 60 to randomized controlled trial
62 | limit 60 to controlled clinical trial
63 | limit 60 to meta analysis
64 | or/61-62
65 | randomized controlled trials.sh.
66 | random allocation.sh.
67 | double-blind method.sh.
68 | single-blind method.sh.
69 | or/65-68
70 | limit 69 to human
71 | 60 and 70
72 | 71 not 64

Cochrane Library Search Strategy

1. Breast-Neoplasms:ME
2. Cancer
3. Carcinoma
4. Neoplasm*
5. Malignant*
6. #2 or #3 or #4 or #5
7. Breast
8. #6 and #7
9. #1 or #8
10. RCT
11. #9 and #10
12. CCTR
13. #11 and #12
14. CCT
15. #9 and #14
16. #12 and #15

Other strategies

Embase: Currently developing a search strategy
Bibliography supplied by the Early Breast Cancer Trialists' Collaborative Group
National Research Register (NRR)
Physician Data Query (PDQ)
The CARE database (Australian Cancer Society)
The National Clinical Trials Registry: Cancer Trials (Australia)
UK CCCR Register/ Eurocode
Adjuvant Therapy for Primary Breast Cancer: Proceedings of the 6th International Conference. St Gallen, 1998.
Zeneca Breast Cancer Database (1987-1998)

Appendix B

Collaborative Review Group in Breast Cancer

Ref ID: _____

Advanced Breast Cancer: Data Collection Form

A separate form should be competed for each trial

1. For which systematic review questions could this trial be potentially suited?
eg. more vs less chemotherapy (per week, in total, other), addition of a drug to a regimen, addition of endocrine therapy to chemotherapy, immediate vs delayed therapy.

_____

_____

_____

_____

_____

_____

_____

_____

2. Describe the patient population. *eg. Stage, menopausal status, ER / PR status*

_____

_____

_____

_____

3. What outcomes are considered? *(tick all that are relevant)*

Overall Survival	☐	Psychosocial	☐	Other	☐
Disease Free Survival	☐	Toxicity	☐		
Response	☐	Unknown	☐		

Specify "other" outcomes: _____

_____

_____

4. Comments: _____

_____

_____

_____

Appendix C

Chemotherapy versus endocrine therapy for metastatic breast cancer

Background

Breast cancer is the commonest cause of cancer and cancer-death worldwide in women (1). It has been shown that both chemotherapy and endocrine therapy improve survival in early breast cancer (2, 3). Once breast cancer becomes metastatic, it is no longer curable, but is still treatable. Both chemotherapy and endocrine treatments have long been used in this setting. They have both been shown to produce tumour responses which may impact on the duration and quality of life (4,5). It is unclear, however, whether one mode of treatment is more effective than the other, either as initial or subsequent treatment. 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. Overall, there is considerable uncertainty about the differential impact of these treatments 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 the available evidence that compares the effects of chemotherapy and endocrine therapy on treatment-related outcomes in women with advanced breast cancer, when used as first line treatment, after first line endocrine treatment and after multiple endocrine treatments.

References

1. The International Agency for Research on Cancer, WHO, 1998.

2. Early Breast Cancer Trialists' Collaborative Group. Chemotherapy overview Lancet 1998

3. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen overview Lancet 1998

4. Stockler M, Wilcken N, Ghersi D, Simes J. The Management of Advanced Breast Cancer: Systematic Reviews of Randomised Controlled Trials Regarding the Use of Cytotoxic Chemotherapy and Endocrine Therapy. Australian NH&MRC National Breast Cancer Centre, 1996.

5. Stockler M, Wilcken N, Coates A. Chemotherapy For Metastatic Breast Cancer - When is Enough Enough? European Journal of Cancer 1997, 33(13), 2147-2148

Objectives

Primary Objective: To review the evidence and determine whether chemotherapy or endocrine therapy has the most beneficial effect on treatment outcomes (listed below) for metastatic breast cancer.
Secondary Objective: To determine whether a variety of factors influence the efficacy of chemotherapy or hormonal therapy in this setting. E.g. Age, menopausal status, hormone receptor status of the cancer, the predominant site of metastases and whether the treatment is given as first line treatment or later in the disease process.

Criteria for considering studies for this review

Types of studies

Properly randomised controlled trials
Any trial including
- only patients with metastatic breast cancer,
- or trials that stratified by stage of disease to allow patients with metastatic breast cancer to be separated out
- or trials where more than 85% of patients have metastatic breast cancer (ie a trial where less than 15% of patients had locally advanced breast cancer would be eligible)
-Trials must compare chemotherapy with endocrine therapy (as defined below)

Types of participants

Women diagnosed with metastatic breast cancer
Any metastatic site
Any age of patient
Any menopausal status
Any hormone receptor status (ER or PR)

Types of interventions

Conventional cytotoxic chemotherapy (with or without colony stimulating factors), excluding cytokines or monoclonal antibodies used alone, and 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

If appropriate, treatments will be classified according to proposed duration and proposed other therapies to be given at disease progression

Types of outcome measures

Primary Outcome:
-Overall survival
Secondary Outcomes:
-Time to treatment failure
-Time to disease progression
-Tumour response rates
-Quality of life
-Toxicity will be noted

Subgroup Analyses
Will be performed if there are sufficient data to justify them:
Any hormone receptor positive versus all receptors negative or receptor status unknown
Initial therapy for metastatic disease versus therapy as second-line or more
Age less than or equal to 50 versus age more than 50
Pre-menopausal versus post-menopausal
The proportion of patients with bone or visceral disease will be noted and if possible a qualitative analysis will be made of any differential impact this may have on treatment effect

Search strategy for identification of studies

The specialised register maintained by the Secretariat of the Cochrane Breast Cancer Group will be searched. 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 on the Cochrane Library. A copy of the full article for each reference reporting a potentially eligible trial will be obtained.

Methods of the review

Assessing trial for eligibility
The selection criteria will be applied to each trial
Any exclusions from a review of a potentially eligible trial will be justified in the final report
Trial publications will be used to assess the trial's eligibility with the results section (and any other area where the results may appear) masked
If a trial has not been published, information will be obtained from the trial protocol or next best available resource
Where necessary, additional information will be sought from the principal investigator of the trial concerned
Two reviewers will independently assess each potentially eligible trial for:
Inclusion in the review (according to the eligibility criteria)
Quality, based on the quality of the randomisation
A third reviewer will resolve any discrepancies regarding eligibility or quality

Analysis
The most complete dataset feasible will be assembled

Results of eligible studies will be statistically synthesised (meta-analysis) if appropriate and possible

All analyses will be by intention to treat

Time to event analyses will be conducted (if possible) for time to death (survival). They will be approximated by either:

Analysing for different follow-up periods

Calculating a weighted average of survival duration across studies

A decision regarding if and how to combine QoL outcomes will be made depending on if and how this information is collected in each trial

A fixed effects model will be used for the primary analyses wherever possible
Heterogeneity between trials will be tested where appropriate

If there are sufficient numbers of trials of adequate size, subgroup analyses will be conducted as listed above.

Sensitivity analyses will be performed if appropriate and possible

Appendix D

Bisphosphonates for bony metastases in advanced breast cancer

Background

Breast cancer is the commonest cause of cancer and cancer related mortality in women world wide (WHO 1998). Bone metastases are the most common site of metastatic disease associated with breast cancer, affecting more than half of women during the course of their disease (Scheid 1986). Bone metastases are a significant cause of cancer-related morbidity in these women due to pain, pathological fractures, hypercalcaemia and spinal cord compression, as well as contributing to mortality (Coleman 1985). Yet women with bone metastases alone tend to live longer (24- 28 months+) than those with visceral metastases (Coleman 1987). Breast cancer bone metastases are predominantly osteolytic (50%)and mixed osteolytic and osteoblastic (40%) with only a small proportion (~10%) being osteoblastic alone (Harvey 1997). The pathophysiology of bone metastases includes increased bone turnover, imbalance and uncoupling of the processes of resorption and remodelling (Kanis 1995). Ostoeclasts are primarily responsible for the bone resorption of lytic metastases, either through direct activation by tumour cells or via tumour secreted factors such as cytokines and parathyroid hormone related peptide (Mundy 1997). Up until now, management strategies for symptomatic bone disease have included analgesics, chemotherapy, hormone therapy, radiotherapy. (But in spite of these treatments progressive skeletal destruction often leads to ongoing symptoms and deterioration of quality of life (Mundy 1991).)

Bisphosphonates inhibit osteoclast bone resorption (Rogers 1997). They are effective in conditions characterized by osteoclast-mediated bone resorption such as Paget's disease and osteoporosis (Russell 1999). In malignancy they have become part of the standard treatment of tumour-induced hypercalcaemia (Body 1998). Randomized controlled trial evidence has shown that in multiple myeloma, bisphosphonates reduce bone pain, increase quality of life, and reduce the number of and time to skeletal events (Bloomfield 1998). Over the last decade there have also been several controlled clinical trials looking at the use of bisphosphonates in women with bone metastases from breast cancer (Body 1998, Bloomfield 1998). The reduction in skeletal events in advanced disease by bisphosphonate inhibition of osteoclast bone resorption suggests that bisphosphonates may have a role to play in preventing bone metastasis formation. As bone is the commonest site of first distant recurrence of breast cancer and the presence of micrometastatic cells in bone marrow of women with early stage breast cancer has been shown to increase relapse rate (Braun 2000), the use of bisphosphonates to prevent bone recurrence of breast cancer as an adjuvant treatment in women with high risk early breast cancer, has also been recently investigated.

The purpose of this review is to review the evidence for the use of bisphosphonates in advanced breast cancer and the evidence for the use of bisphosphonates as adjuvant treatment in women with early breast cancer.

Objectives

Specific primary objectives:

To assess the effect of bisphosphonates in women with metastatic breast cancer and in women with early breast cancer, with regards to skeletal events, bone pain, QoL and survival.

Criteria for considering studies for this review

Types of studies

(i) Randomised controlled trials comparing treatment with a bisphosphonate to the same treatment without a bisphosphonate in women with metastatic breast cancer and in women with early breast cancer.
(ii) Randomised controlled trials comparing treatment with a bisphosphonate, A, with treatment with a different bisphosphonate, B.

Studies must include at least one of the following outcomes to be considered for evaluation:

skeletal events (as defined below) or
QoL or
Bone pain or
Survival

Types of participants

Women with a history of breast cancer.

Types of interventions

The use of any bisphosphonates administered orally or intravenously in any dose and of any duration. Control will be placebo or open control.

Types of outcome measures

The following outcomes will be assessed in all studies included unless otherwise stated:

The primary outcome will be:

The number of skeletal complications/events (Defined as any one of the following):
- new bone metastases
- pathological fractures
- spinal cord compression
- irradiation of or surgery on bone
- the development or progression of bone pain

Secondary outcomes will be:

Time to first skeletal event.
Survival.
Quality of life.
Hypercalcaemia
Severe (WHO Grade III/IV) adverse drug related events.
Extra-skeletal recurrence/progression of breast cancer (adjuvant studies only).

Subgroup analysis will include comparisons by:

- age
- previous or concomitant chemotherapy
- previous or concurrent endocrine therapy
- menopausal status
- the presence of skeletal disease

In women receiving bisphosphonates as adjuvant therapy, in addition to the above factors, subgroup analysis will also include:

- nodal status
- oestrogen receptor status

Search strategy for identification of studies

See: Cochrane Collaboration Collaborative Review Group in Breast Cancer search strategy. The specialised register maintained by the Secretariat of the CRG in Breast Cancer will be searched. (Details of the search strategy applied to Medline for the Register is outlined in the group's module). These search strategies will also be applied to EMBASE and CANCERLIT. Bisphosphonate investigators will be contacted for additional studies, as will trialists identified in Clinical Trials Registries. Recent Oncology Meetings Proceedings and bibliographies of references and reviews will also be searched.

Methods of the review

Description of studies See below.

Methodological quality of included studies

All trials will be assessed for quality (mainly of randomisation), independently and in a blinded fashion (to authors, journal, drug,company, institutions and results) by two reviewers and disagreement resolved by consensus. Quality assessment (and description) will be based on the susceptibility to bias using the MERGE criteria
(Appendix 1: Liddle 1996, NSW Department of Health) for evaluating the quality of studies assessing the effect of interventions (Checklist 2). Specifically, concealment of treatment allocation, blinding of treatment, standard, validity and reliability of outcome measures, withdrawal rate, intention to treat analysis and homogeneity between centres will be assessed for each study. These criteria will be evaluated in a pilot sample of papers addressing the use of bisphosponates in multiple myeloma.

Statistical Analysis:

Presentation of statistical data (meta-analysis) will include the use of odds ratios, hazard ratios and the dichotomisation of data. Outcomes such as QoL or Pain scores will be presented as percent change. If data is not presented in the same format across studies, then standardise mean difference will be used. Data will be extracted for the outcomes listed in Types of Outcome measures. Authors may be contacted for information that is not in the published trial. Homogeneity of the data will be calculated using a Chi-square test on N-1degrees of freedom. Meta-analysis will be conducted according to a fixed effects model. If there is heterogeneity a random effects model will be used. Sensitivity analyses and funnel plots will also be performed. Where possible the analyses will be based on intention-to-treat data.

Acknowledgements

Cochrane Collaboration Collaborative Review Group in Breast Cancer, NHMRC Clinical Trials Centre.

Potential conflict of interest

Nil.

ADDITIONAL REFERENCES:

WHO 1998

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APPENDIX 1

MERGE: Method for Evaluating Research Guideline Evidence

The following is an extract from MERGE describing its function and development:

MERGE was developed by the Centre for Clinical Policy and Practice of the NSW Health Deartment, Australia,to help guideline developers comply with the principles outlined by the National Health and Medical Research Council Quality of Care and Health Outcomes Committee set out below:
Clinical practice guidelines should be based on the best available evidence.
The method used to synthesise the evidence should be the strongest applicable.
Guidelines should contain a statement concerning the strength of the recommendations.

MERGE was developed through consultation with other epidemiologists working in Australia, the Cochrane Collaboration and clinicians on the NSW Health Department Expert Panel on Diabetes Guidelines Working Group. Each provided information on areas of potential bias, checklists in use and content issues relating to guideline development. The literature was also reviewed. Early drafts were piloted in the clinical management of diabetes and the prevention, management and rehabilitation of fractured neck of femur.
An initial document was widely circulated for comment in 1995. Comments and results from inter-rater reliability of the draft checklists indicated areas which required further development, rewording or further exploration. This led to a combined checklist to assess randomised controlled trials and studies, non-randomised controlled studies, cohorts, case-controlled studies, before and after studies as well as a new checklist for interrupted time series studies. MERGE was further reviewed to incorporate work done by the Cochrane Collaboration on Effective Professional Practice and the University of York NHS Centre for Reviews and Dissemination.

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