Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women

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Authors' objectives
To assess the effectiveness of medical treatment for metastatic breast cancer.

Searching
The authors searched the electronic databases of MEDLINE and EMBASE (January 1, 1975 to December 31, 1997) using a search strategy that is reported in a table in the review. The authors also searched references from retrieved original and review articles as well as lists from recent meetings on related topics.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) in which different approaches to CHT and ET were compared, independently of the length of follow-up study.

Specific interventions included in the review
There were 12 specific interventions included in the review:

1. Polychemotherapy (PCHT) agents versus single agent.
2. PCHT regimens with antracycline versus PCHT without anthracycline.
3. Other PCHT versus cyclophosphamide, methotrexate, andfluourouracil (CMF).
4. Chemotherapy (CHT) with epirubicin versus CHT with doxorubicin.
5. CHT versus same CHT delivered with less intensive schedules.
6. Other endocrine therapy (OET) versus tamoxifen.
7. OET plus tamoxifen versus tamoxifen alone.
8. OET versus medroxyprogesterone.
9. OET versus aromatase inhibitors.
10. OET versus megestrol.
11. Endocrine therapy (ET) versus same ET at lower doses.
12. CHT plus ET versus CHT.

Participants included in the review
Patients undergoing treatment for breast cancer.

Outcomes assessed in the review
Tumour response rates, mortality hazards ratio (HR) (survival) and frequency of severe side effects (toxicity) were the outcome measures.

How were decisions on the relevance of primary studies made?
Two people independently reviewed the trials to determine whether they met the inclusion criteria and discussed disagreements about rejection between themselves. When disagreements could not be resolved, a third independent reviewer's opinion was sought.

**Assessment of study quality**
The authors used only the criteria that a study was of acceptable quality if it was an RCT design. There was no formal assessment of the methodology of the RCTs.

**Data extraction**
Two of the authors read the papers to extract the data. Agreement between the two authors was assessed comparing 246 time points from 19 randomly selected different survival curves, which were read by both the investigators. The mean difference between measurements by the two readers was 0.83 percentage points (95% CI: 0.69, 0.96).

Data extracted included: year of publication; time period of patient accrual, number of eligible patients randomised, median age of patients; menopausal status; state of estrogen receptors; clinical patterns of relapse; prior palliative therapies; full description of treatment regimens used; presence of any health-related quality-of-life assessment, and outcome measures.

**Methods of synthesis**
How were the studies combined?
A fixed-effect model was used to pool the studies using the Peto method for response rates and adverse effects, and the log HRs were combined across trials using an inverse variance weighting.

How were differences between studies investigated?
Predefined subsets of studies were formed and summarised and the chi-square statistic was used to test for heterogeneity between the trials.

**Results of the review**
A total of 189 trials met the inclusion criteria with 31,150 participants.

Heterogeneity was not found for comparisons 1, 3, 4, 5, 6, 7, 8, 10, 11 and 12; but was found for interventions 2 and 9. Statistically significant differences for response emerged for comparisons 1, 2, 3, 5, 7, 8, 11, and 12. All but intervention 8 (OET versus medroxyprogesterone) favoured the first term of the comparison.

Overall survival analysis showed better results of:

a. PCHT versus single-agent CHT (HR = 0.82, 95% CI: 0.75, 0.90).

b. CHT with doxorubicin versus CHT with epirubicin (HR = 1.13, 95% CI: 1.00, 1.27).

c. CHT versus the same CHT delivered with less intensive schedules (HR = 0.90, 95% CI: 0.83, 0.97).

d. ET versus the same ET at lower doses (HR = 0.86, 95% CI: 0.77, 0.97).

Quality of life was measured in only 2,995 of 31,510 patients (9.5%).

**Authors' conclusions**
Despite some evidence of effectiveness of specific regimes, the relevance of these findings is limited by the modest survival benefit and the lack of evaluation of the quality-of-life impact of these treatments.

The analysis of different types of medical treatments used in metastatic breast cancer showed, at best, a relatively
modest benefit as regards survival (a survival gain of 9% at the 1-year comparison number 1), more pronounced differences in response rate and very difference toxicity profiles.

**CRD commentary**

This review has a clearly stated research question and has listed inclusion and exclusion criteria. The literature search is reported in detail and the search strategy and its terms are given in a table in the review. It is probable that all relevant published studies have been included in the review.

The authors have reported who selected the included studies, but have limited their quality assessment of the individual studies to only including RCT study designs. This would not exclude poorly executed studies. The authors also do not report how the data extraction was performed. The data from individual studies and the statistical results are reported in detail in the graphics and text of the review.

The statistical pooling is appropriate and the authors have tested for heterogeneity, although in cases where heterogeneity was found, the authors have proceeded with the pooling of that data without discussion.

The conclusions of the review follow from the results reported, but should be viewed with caution, particularly where heterogeneity exists.

**Implications of the review for practice and research**

**Practice:** The authors state that the results of this overview provide oncologists with a few clinical guidelines:

1. CHT schemes with lower toxicity (e.g. standard CMF) should be preferred.

2. Further evidence of the real value and feasibility of cytostatic treatments at high doses (even with bone marrow or colony-stimulating factor support) should accumulate before their widespread use becomes routine practice.

3. Hormonal therapy should be chosen with a view to the best risk/benefit ratio, i.e. with the side effect profile appropriate to the individual patient.

**Research:** The authors state that the results of this review can help in planning new phase III clinical trials.

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