Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials

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CRD summary
This review of individual patient data concluded that in women with hormone-receptor-positive breast cancer, the addition of luteinising-hormone-releasing hormone (LHRH) agonists to tamoxifen, chemotherapy, or both, reduces the risk of recurrence and death after recurrence and that LHRH agonists are as effective as chemotherapy. This review had some methodological weaknesses that may undermine the reliability of the results.

Authors' objectives
To evaluate the efficacy of luteinising-hormone-releasing hormone (LHRH) agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer.

Searching
PubMed and SpringerLink were searched; the search terms were reported. The abstracts from breast cancer meetings, the database of the Oxford overview group, and references from published reports of known trials were checked, and investigators from known studies were contacted to identify additional studies. A steering committee was established to undertake the meta-analysis.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs). The median duration of follow-up ranged from 4.1 to 11.5 years.

Specific interventions included in the review
Studies evaluating an LHRH agonist alone or in combination with an adjuvant therapy for early breast cancer were eligible. Only studies in which an LHRH agonist was given to more than half of the patients were included. The included studies evaluated: LHRH agonist alone; LHRH agonist plus tamoxifen versus tamoxifen alone; LHRH agonist plus chemotherapy versus chemotherapy alone; and LHRH agonist plus chemotherapy plus tamoxifen versus chemotherapy plus tamoxifen. The LHRH agonists used were goserelin, triptorelin and leuprorelin, provided for 18 months up to 5 years. The type and regimens of chemotherapy differed across the studies and included most often a cyclophosphamide-methotrexate-fluorouracil based chemotherapy.

Participants included in the review
Studies of pre- or perimenopausal women with early breast cancer were eligible for inclusion. The review focused on women who were hormone-receptor-positive, defined as positive for oestrogen receptor and/or progesterone receptor. Patients with unknown receptor status were excluded.

Outcomes assessed in the review
The primary end points analysed were any recurrence and death after recurrence. The secondary outcomes were all deaths and the combined outcome of recurrence and death.

How were decisions on the relevance of primary studies made?
The authors did not state how many members of the steering group selected the studies, nor how any disagreements were resolved. It was not stated whether trial investigators were contacted to establish the relevance of the trials.
Assessment of study quality
The authors did not state how the validity of each trial was assessed. Results data were checked for internal consistency with published results and for outliers. If required, the data were updated or amended after contact with the trialists.

Data extraction
Investigators were contacted, if necessary, to obtain additional information and to verify the finalised data.

Methods of synthesis
How were the studies combined?
Comparisons between treatments were made on an intention-to-treat basis within the subgroups of hormone-receptor-positive and hormone-receptor-negative patients. Log hazard ratios (HRs) with 95% confidence intervals (CIs) were computed separately for each trial, and pooled estimates were calculated through the inverse variance-weighted fixed-effect method. In the text, the results were reported as the percentage relative change in HR.

How were differences between studies investigated?
Subgroup analysis was performed according to age (older than 40 years versus 40 years or younger), number of nodes (1 to 3, and 4 or more), tumour size (>2 cm) and basal metabolic index greater than 30 kg/m2.

Results of the review
IPD from 16 trials (including IPD for 11,906 women; 9,022 women were hormone-receptor positive) were included in the review. The authors stated that one other eligible trial was identified, but the investigator could not be contacted and the data were therefore not available.

Adjuvant treatments were provided without any blinding in all of the included studies.

Hormone-receptor-positive women. LHRH agonist alone (n=338).
There was no significant difference between LHRH agonists and no systemic adjuvant therapy for recurrence (% change in HR -28.4, 95% CI: -50.5, 3.5, p=0.08), death after recurrence (% change in HR -17.8, 95% CI: -52.8, 42.9, p=0.49) or any death (% change in HR -22.9, 95% CI: -44.1, 6.4, p=0.11), but they were associated with a significant reduction in the risk of the combined outcome of recurrence or death (% change in HR -25.2, 95% CI: -40.6, -3.8, p=0.01).

LHRH agonist plus tamoxifen and/or chemotherapy versus tamoxifen and/or chemotherapy (n=3,754). The addition of an LHRH agonist to tamoxifen, chemotherapy, or both significantly reduced the risk of recurrence (% change in HR -12.7, 95% CI: -21.9, -2.4, p=0.02), death after recurrence (% change in HR -15.1, 95% CI: -26.7, -1.8, p=0.03) and any death (% change in HR -13.6, 95% CI: -24.9, -0.6, p=0.04).

LHRH agonist versus chemotherapy. There was no significant difference between LHRH agonist and chemotherapy in the risk of recurrence (% change in HR 3.9, 95% CI: -7.7, 17.0, p=0.52), death after recurrence (% change in HR -6.7, 95% CI: -20.7, 9.6, p=0.40) and any death (% change in HR -14.9, 95% CI: -27.7, 0.1, p=0.05).

Details of other treatment comparisons were discussed in the text.

Women with negative, poor oestrogen-receptor or unknown status. In patients with negative or poor oestrogen-receptor status and either negative or unknown progesterone-receptor status (n=1,681), the addition of an LHRH agonist to any adjuvant treatment did not reduce the risk of recurrence or death after recurrence. Compared with chemotherapy alone, LHRH agonists were associated with a higher risk of recurrence (% change in HR 67.7, 95% CI: 22.2, 129.9, p=0.001), with similar rates for death after recurrence and all deaths.

Authors' conclusions
In women with hormone-receptor-positive breast cancer, the addition of LHRH agonists to tamoxifen, chemotherapy,
or both, reduces the risk of recurrence and death after recurrence. LHRH agonists do not appear to be effective in women with hormone-receptor-negative tumours.

**CRD commentary**
This meta-analysis of IPD addressed a well-defined question in terms of the participants, intervention, outcomes and study design. The authors searched two databases, although the precise timeframe of the bibliographic search was not stated. Publication bias was not assessed, but the authors did attempt to retrieve unpublished trials. The authors checked the internal consistency of the IPD, but it was unclear whether the adequacy of randomisation to study treatment and allocation concealment or the comparability of treatment groups were evaluated in each trial. The number of excluded studies, as well as the number of participants in trials for which data could not be retrieved, were specified. It was not stated how many members of the steering committee participated in the selection of the studies, or whether trial investigators were contacted to check each trial's eligibility for inclusion. No information was provided on how the data were acquired, or if any recoding or transformation of the data prior to the analysis was performed.

Statistical heterogeneity was not assessed, which leaves it unclear as to whether the authors' decision to pool the studies in a meta-analysis was appropriate. However, the influence of various factors on the results was explored. The authors' conclusions appear to reflect the evidence presented, but the incomplete reporting of review methods means it is not possible to assess their reliability.

**Implications of the review for practice and research**
Practice: The authors did not state any implication for practice.

Research: The authors stated that future trials should compare the combination of an LHRH agonist and tamoxifen against chemotherapy and tamoxifen. The efficacy of LHRH agonists should be better evaluated according to oestrogen and progesterone receptor status.

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