Primary systemic therapy in operable breast cancer
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Authors' objectives
To address several questions that must be considered before adopting primary systemic therapy (PST) as a standard approach.
What is the response rate of primary therapy?
Will more patients be treated with breast-conservation therapy?
Will primary therapy improve the disease-free survival (DFS) and overall survival (OS) of patients with breast cancer?
Can response to primary therapy be correlated with outcome?
Are there clinical or biologic predictors of outcome?
Potential limitations of primary chemotherapy must also be considered.
Could an initially resectable tumour progress to an inoperable state?
How many patients will be overtreated?
Does the use of primary chemotherapy result in the loss of standard prognostic factors (e.g. tumour size, nodal involvement and hormone receptor status) that are normally used to guide the decision-making process for patients treated with standard post-operative adjuvant therapy?

Searching
MEDLINE was searched from 1976 to 1999 for publications in the English language, using the keywords and synonyms for 'breast neoplasms', 'neoadjuvant therapy', 'combined-modality therapy' and 'clinical trials'. References in the published literature (including book chapters) were checked for other articles of interest. Abstracts published in meeting proceedings, and articles describing laboratory correlate studies conducted in conjunction with some of these trials, were also reviewed.

Study selection
Study designs of evaluations included in the review
Prospective, randomised clinical trials (RCTs) were included.

Specific interventions included in the review
The use of PST. Different schedules and types of chemotherapy were used in each of the included trials, in combination with surgery and/or radiotherapy and/or endocrine therapy.

Participants included in the review
Patients with operable breast cancer. The patients’ stage of disease and menopausal status varied between the studies.

Outcomes assessed in the review
The primary outcomes assessed appear to have been OS and DFS. Other outcomes included the response rates, recurrence rates, and the increase in the use of breast-conservation treatment.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following characteristics were extracted, where available: the number of patients; the patients' stage of disease; mean age and menopausal status; treatment plan; response rate of primary therapy; the percentage initial breast conservation; recurrence rates; the percentage DFS; and the percentage OS.

Methods of synthesis
How were the studies combined?
A qualitative narrative synthesis was undertaken. Publication bias was not assessed.

How were differences between studies investigated?
Heterogeneity was not assessed.

Results of the review
Six RCTs were included in the review.

The 6 included RCTs of PST for palpable operable breast cancer were reported since 1991. Data from these trials clearly showed a small but significant (less than 10%) absolute increase in the use of breast-conservation treatment, with similar rates of local control. Although one study showed better DFS and another showed better OS, most of the studies did not show any survival advantage of primary versus adjuvant systemic therapy.

Pathologic complete response seemed to be the best predictor of survival, but clinical response assessment correlated poorly with pathologic response. Pilot studies demonstrated the feasibility of procuring tissue at diagnosis and after treatment, for assays of potential intermediate biomarkers. The initial data suggested a potential correlation between markers of proliferation and apoptosis and in vivo chemotherapy sensitivity.

Authors' conclusions
RCTs of PST versus standard adjuvant therapy have not shown any clear benefit for DFS or OS in early breast cancer.

CRD commentary
The authors stated the review question and the inclusion criteria clearly, but the review question was rather non-specific. The literature search was restricted to English language articles and one database (MEDLINE), although references in the published literature were also checked for other articles. The authors did not attempt to identify unpublished or grey literature. This narrow search strategy may have missed relevant studies, thus allowing the introduction of publication bias. No analyses were conducted to assess publication bias. The validity of the individual studies was not assessed, and neither was the heterogeneity between them.

Details relating to the decision-making processes for study selection and data extraction were not reported, such as how many of the reviewers were involved, whether the studies were examined independently, and whether the reviewers were blinded to the source.

The authors' conclusions should be interpreted with caution owing to the limitations highlighted in relation to the review methodology, potential for selection bias and lack of a validity assessment.
Implications of the review for practice and research

Practice: The authors state that although PST results in a small increase in the rate of breast-conservation treatment, with similar rates of local control, current PST strategies should not replace standard adjuvant approaches. Rather, they represent an acceptable alternative to women with palpable, operable tumours.

Research: The authors state that ongoing trials should determine whether specific subsets of patients at risk would benefit from additional systemic therapy, and the potential role of intermediate biomarkers in identifying such women. They also state that PST strategies represent an excellent arena for clinical trials.

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