Polychemotherapy for early breast cancer: an overview of the randomised trials
Early Breast Cancer Trialists' Collaborative Group

Authors' objectives
To present an updated overview of the results of the many randomised trials of adjuvant prolonged polychemotherapy among women with early breast cancer.

Searching
The authors state that a standard procedure for trial identification was used, which is reported elsewhere (see Other Publications of Related Interest). This included: discussion with trial investigators; scrutiny of review articles; scrutiny of lists of trials prepared by the UICC, NCI and UKCCCR; scrutiny of ASCO, AACR and UICC proceedings; a computer-aided literature search; discussions with drug manufacturers; and discussion with at least one member of each major trial organisation.

A secretariat and collaborative group of trial investigators (Early Breast Cancer Trialists' Collaborative Group) was established to identify the trials and 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) begun before 1990.

Specific interventions included in the review
Polychemotherapy compared either with no chemotherapy, another regimen, or the same regimen given for a different duration. Polychemotherapy included chemotherapy consisting of cyclophosphamide, methotrexate and fluorouracil (CMF) or consisting of any anthracycline-containing regimen.

Participants included in the review
Women with early breast cancer.

Outcomes assessed in the review
The outcomes of interest were local recurrence, breast cancer mortality, incidence of contralateral breast cancer, and mortality from other causes.

How were decisions on the relevance of primary studies made?
The relevance of the primary studies was established through communication with trial investigators.

Assessment of study quality
The authors state that standard procedures for data checking were used. These are reported elsewhere (see Other Publications of Related Interest). These included checks that might indicate improper exclusions after randomisation, undocumented changes in treatment allocation, and systematic differences in completeness of follow-up between the treatment and control groups.

The balance between the groups with respect to age, entry date, and menopausal, nodal, and oestrogen receptor status was also checked; as was the internal consistency of individual patient records. Attempts were made to rectify any anomalies by seeking further information from the trial investigators and national mortality records. Once the checking process was complete, a transcript of the corrected IPD was returned to the trialists who had collected it. They were afforded the opportunity to make corrections at this stage. The authors do not state explicitly how judgements of validity were made, in terms of who made the decisions or the criteria used.
Data extraction
Trial investigators provided IPD for their trial. A full list of the data categories requested is provided elsewhere (see Other Publications of Related Interest); this included identifiers, allocated treatments, the duration of follow-up, the incidence of contralateral breast cancer, and information on recurrence, mortality rates and all-cause death rates.

Methods of synthesis
How were the studies combined?
Studies were combined using a meta-analysis of IPD based on the intention to treat principle. Each trial was analysed separately, and then the resulting log-rank statistics (one per trial) were added together to give an overall estimate of the effect of chemotherapy. A 95% confidence interval was calculated for each point estimate. Two-sided significance testing was conducted for comparisons of adjuvant chemotherapy regimes and for chi-squared tests on one degree of freedom. One-sided significance testing was used for chi-squared tests on more than one degree of freedom.

The results were expressed as proportional benefits (percentage reduction or increase) or as absolute benefits (percentage).

A more comprehensive description of the statistical pooling methods used in the meta-analysis has been provided elsewhere (see Other Publications of Related Interest).

How were differences between studies investigated?
The trials were grouped according to the type and duration of chemotherapy administered: polychemotherapy compared with control therapy, polychemotherapy of more than 6 months' duration compared with polychemotherapy of less than 6 months' duration, and anthracycline-based polychemotherapy compared with CMF polychemotherapy.

The meta-analysis of local recurrence and mortality was also subdivided by age at randomisation, time since randomisation, menopausal status, nodal status, oestrogen receptor status and endocrine co-therapy.

A chi-squared test for statistical heterogeneity was applied to all meta-analyses.

Results of the review
IPD from 47 RCTs (n=17,723) were included. These included data on: 17,723 patients in 47 RCTs of polychemotherapy compared with no chemotherapy; 6,104 patients in 11 RCTs of longer polychemotherapy compared with shorter chemotherapy regimens; and 5,942 patients from 11 RCTs of anthracycline-containing polychemotherapy compared with no chemotherapy.

It is unclear from the report why data from ten reports were unavailable, or whether the unavailability of data referred to summary data or specifically to IPD.

For recurrence, polychemotherapy produced substantial and highly significant proportional reductions, both among women aged under 50 years at randomisation (35% reduction; 2p<0.00001) and among those aged 50 to 69 (20% reduction; 2p<0.00001).

For mortality, the reductions were also significant among women aged under 50 years (27% reduction; 2p<0.00001) and among those aged 50 to 69 (11% reduction; 2p=0.0001). The recurrence reductions emerged chiefly during the first 5 years of follow-up, whereas the difference in survival grew throughout the first 10 years.

After standardisation for age and time since randomisation, the proportional reductions in risk were similar for women with node-negative and node-positive disease.

Applying the proportional mortality reduction observed in all women aged under 50 years at randomisation would typically change a 10-year survival of 71% for those with node-negative disease to 78% (an absolute benefit of 7%). The survival would change from 42 to 53% (an absolute benefit of 11%) for those with node-positive disease. The smaller proportional mortality reduction observed in all women aged 50 to 69 years at randomisation would translate into smaller absolute benefits: the 10-year survival would change from 67 to 69% (an absolute gain of 2%) for those...
with node-negative disease, and from 46 to 49% (an absolute gain of 3%) for those with node-positive disease.

The age-specific benefits of polychemotherapy appeared to be largely irrespective of menopausal status at presentation, oestrogen receptor status of the primary tumour, and of whether adjuvant tamoxifen had been given.

There was a reduction of about one-fifth (2p=0.05) in contralateral breast cancer, which has already been included in the analyses of recurrence.

There was no apparent adverse effect on deaths from causes other than breast cancer (death rate ratio 0.89).

The directly randomised comparisons of longer versus shorter durations of polychemotherapy did not indicate any survival advantage with the use of more than about 3 to 6 months of polychemotherapy.

The directly randomised comparisons did suggest that, compared with CMF alone, the anthracycline-containing regimens produced somewhat greater effects on recurrence (2p=0.006) and mortality (69 versus 72% for 5-year survival; log-rank 2p=0.02). The authors state that (at the time of writing) ‘the results of several of the relevant trials are not yet available’.

Authors’ conclusions
Several months of adjuvant polychemotherapy (e.g., with CMF or an anthracycline-containing regimen) typically produce an absolute improvement in 10-year survival of about 7 to 11% for women aged under 50 at presentation with early breast cancer, and of about 2 to 3% for those aged 50 to 69 (unless their prognosis is likely to be extremely good even without such treatment).

CRD commentary
The review addressed a clear question in terms of the participants, intervention, outcomes and study design.

The strategy undertaken to identify trials was extensive, and a collaborative group of trial investigators was established to maximise retrieval of the IPD and to conduct the meta-analysis. The authors state how many trials were identified for which data could not be retrieved, and comment that the few missing data should not materially affect the meta-analysis of long-term mortality reported in the review. The strategy used to identify the studies was reported elsewhere (see Other Publications of Related Interest).

The validity of the eligible trials was assessed by checking and reanalysing the raw data from each trial, and attempting to resolve any problems encountered through communication with the trial investigators. No trials are reported to have failed the data checking procedures.

The data were analysed using appropriate techniques for this form of meta-analysis of IPD, and the rationale for the subgroup analysis was clear. Heterogeneity was assessed, and was presented graphically and discussed in the text.

The conclusions and implications for practice and future research appear to follow from the evidence presented. It is important to note that this report is part of an on-going series, and that the meta-analysis is due to be up-dated every five years.

Implications of the review for practice and research
Practice: The authors state that several months of adjuvant polychemotherapy typically produce an absolute improvement in 10-year survival for women aged under 70 years at presentation. Treatment decisions should consider not only the improvements in cancer recurrence and survival, but also the adverse side-effects of treatment. The report makes no recommendations as to who should or should not be treated.

Research: The authors state that too few women aged 70 years or over have, as yet, been studied for direct assessment of the effects of treatment amongst them.
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