Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials

Early Breast Cancer Trialists’ Collaborative Group

CRD summary
This review aimed to evaluate the effects of adjuvant polychemotherapy regimens in oestrogen-receptor-poor (ER-poor) breast cancer. It concluded that in women younger than 50 years or aged 50 to 69 years, polychemotherapy was safe and substantially reduced the 10-year risks of recurrence and death. This was a well-conducted meta-analysis of individual patient data and its conclusions are likely to be reliable.

Authors' objectives
To evaluate the effects of adjuvant polychemotherapy regimens in oestrogen-receptor-poor (ER-poor) breast cancer, and the extent to which these are modified by age or tamoxifen use.

Searching
The authors state that a standard procedure for trial identification was used, which is reported elsewhere (see Other Publications of Related Interest field and URL for Additional Data field). This procedure included: discussion with trial investigators; scrutiny of review articles; scrutiny of lists of trials prepared by the UICC (International Union Against Cancer), NCI (National Cancer Institute) and UKCCCR (United Kingdom Coordinating Committee on Cancer Research); scrutiny of ASCO (American Society of Clinical Oncology), AACR (American Association for Cancer Research) 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
Trials were eligible for inclusion in the analysis if they began before 2000, included women with ER-poor breast cancer, and evaluated polychemotherapy, tamoxifen or both. Included trials compared: polychemotherapy alone versus no adjuvant therapy; tamoxifen versus no adjuvant therapy; and combined polychemotherapy and tamoxifen versus one of these treatments alone. The techniques used to identify women with ER-poor status varied between the included studies.

Assessment of study quality
The authors stated that standard procedures for data checking were used. These are reported elsewhere (see Other Publications of Related Interest field) and 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. Errors and omissions were checked with, and where possible rectified by correspondence with the principal investigators. Final corrected data and summaries were supplied to trialists.

Data extraction
Trial investigators provided individual patient data (IPD), including treatment regimens allocated, numbers of women with ER-poor disease, duration of follow-up, and information on recurrence, breast cancer mortality and all-cause mortality rates.

Event rate ratios for recurrence, breast cancer mortality, all mortality and their confidence intervals (CIs) were calculated for the included comparisons.

Methods of synthesis
Logrank statistics were used to determine the effects on outcome, and to estimate event rate ratios and their confidence
intervals. For fine subdivisions (e.g. age at entry within comparison type), event rate ratios and 99% CIs were presented in forest plots. For subtotals and totals (e.g. comparison type), pooled event rate ratios with 95% CIs were calculated. The $\chi^2$ test was used to determine the statistical significance of observed trends in effects across subdivisions (e.g. age).

**Results of the review**
A total of 96 trials were included in the analysis: 46 trials of polychemotherapy versus not (n=6,029) and 50 trials of tamoxifen versus not (n=13,717).

In women younger than 50 years (n=1,907, 15% node-positive), 10 year risks with polychemotherapy versus not were: recurrence 33% versus 45% (event ratio 0.73, p<0.00001), breast cancer mortality 24% versus 32% (event ratio 0.73, p=0.0002), death from any cause 25% versus 33% (event ratio 0.75, p=0.0003).

In women aged 50 to 69 years (n=3,965, 58% node-positive), 10 year risks with polychemotherapy versus not were: recurrence 42% versus 52% (event ratio 0.82, p<0.00001), breast cancer mortality 36% versus 42% (event ratio 0.86, p=0.0004) and death from any cause 39% versus 45% (event ratio 0.87, p=0.0009).

Tamoxifen had little effect on recurrence or death in women classified as having ER-poor disease compared to no tamoxifen and did not significantly modify the effects of polychemotherapy.

**Authors' conclusions**
In women with ER-poor breast cancer, either younger than 50 years or aged 50 to 69 years, older adjuvant polychemotherapy regimens were safe and produced substantial reductions in the 10 year risks of recurrence and death. Current and future regimens could be more effective.

**CRD commentary**
This was a well-conducted meta-analysis of IPD from trials of polychemotherapy regimens in ER-poor breast cancer. The review addressed a clear question in terms of the participants, intervention, outcomes and study designs of interest. Attempts were made to identify all the relevant trials, with a collaborative group of trial investigators established to maximise retrieval of patient data. The validity of 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. The data were analysed using appropriate statistical techniques. The rationale for the subgroup analyses was clear. Heterogeneity among patient subgroups was assessed and was presented graphically in the text with discussion. Much of the methodological detail was not reported in the publication but is available from the project website (see URL for Additional Data field). The conclusions follow from the evidence presented and the results appear reliable. It should be noted that this report is part of an ongoing series and the meta-analysis is updated every five years.

**Implications of the review for practice and research**
The authors did not state any implications for practice or research.

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