

Systemic adjuvant therapies for early breast cancer: 15-year results for recurrence and survival

There is clear evidence of long-term benefits

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2000 overview of adjuvant systemic treatment trials for early breast cancer has demonstrated clear evidence of substantial and significant reductions in both recurrence and mortality, with follow-up now to 15 years.¹ This is the fourth EBCTCG overview of adjuvant systemic therapies, conducted at 5-year intervals since 1985.²⁻⁶ The EBCTCG 2000 analysis, based on individual patient data from 145 000 women diagnosed with early breast cancer, involved 194 trials started by 1995 in which chemotherapy and hormonal therapy were evaluated alone and in combination for their effects on recurrence, breast cancer mortality and total mortality. This overview, with data from more trials than the earlier overviews, more patients and more years of follow-up, provided new and long-term information on adjuvant chemotherapy in women aged 50–69 years, tamoxifen duration, combined modality therapy, and cause-specific mortality (Box).

What were the benefits?

Chemotherapy regimens included single agents or polychemotherapy, either cyclophosphamide, methotrexate and fluorouracil (CMF), or anthracycline-containing regimens, mostly fluorouracil, adriamycin, and cyclophosphamide or substituting epirubicin for adriamycin. Anthracycline-containing regimens of about 6 months' duration reduced the annual breast cancer death rate by 38% in women younger than 50 years, and by 20% in women aged 50–69 years. Similar reductions in annual recurrence rates were seen. The benefits were largely independent of the use of tamoxifen, oestrogen receptor status, or nodal status. Anthracycline-containing regimens were significantly better than CMF regimens for recurrence ($2P = 0.0001$ [$2P$ is a two-sided P value]) and mortality ($2P = 0.00001$). There were insufficient trials involving women older than 69 years (< 5% of women) to reliably determine treatment effects.

Hormonal therapies studied were tamoxifen (in most trials), ovarian ablation or ovarian suppression. The 15-year follow-up provided an opportunity to evaluate both early and late effects on recurrence and breast cancer mortality for each modality, given alone or in combination with chemotherapy. With respect to mortality, in women with oestrogen-receptor-positive tumours, 5 years of tamoxifen use reduced the annual breast cancer death rate by 31% and the annual recurrence rate by 40%, independent of patient age, the use of chemotherapy, progesterone receptor status or tumour characteristics. However, there was no advantage for a higher dose of tamoxifen than 20 mg per day. Tamoxifen given for 5 years was significantly superior to 1–2 years of therapy, but the evidence for any effect of continuing tamoxifen for more than 5 years remained inconclusive. With respect to recurrence, a significant trend was seen with increasing reduction of annual recurrence rates with increasing age (40–49 years, 29%; ≥ 70 years, 51%; age trend $2P = 0.05$).

The overview did not include any trials in which tamoxifen and chemotherapy given concurrently were compared with one

modality followed by the other. However, as the benefits of tamoxifen and of chemotherapy were largely independent of whether treatment included the other modality, a mortality reduction of 57% for women younger than 50 years and 45% for women aged 50–69 years could be expected by using both modalities together.

Do benefits occur early or late?

Most of the benefit of polychemotherapy on recurrence was seen in the first 5 years (absolute reductions of recurrence of 12.5%, 12.4% and 12.4% at 5, 10 and 15 years follow-up, respectively, for women younger than 50 years), whereas the benefit for mortality continued to increase for 15 years (absolute reductions in breast cancer mortality of 4.7%, 7.9% and 10.0% at 5, 10 and 15 years, respectively). The early effect of chemotherapy on recurrence had been well established in the previous overview,⁶ but the continuing late mortality benefit has only now been established by the longer follow-up. The late mortality benefit was less apparent for chemotherapy in women aged 50–69 years.

The pattern of benefit from 5 years of tamoxifen was similar to that seen with chemotherapy for women aged less than 50 years, but was apparent in all age groups. Again, most of the effect on recurrence occurred in the first 5 years (absolute reductions for recurrence: 10.4%, 13.6% and 11.8% at 5, 10 and 15 years), whereas much of the benefit on breast cancer mortality occurred after the first 5 years (absolute reductions of 3.6%, 7.9% and 9.2% at 5, 10 and 15 years).

This extended mortality benefit, seen with both chemotherapy and tamoxifen, is striking and suggests that an important number of patients with residual disease after primary therapy are cured of their original tumour by adjuvant tamoxifen or chemotherapy, although they remain at continuing risk of new contralateral breast cancer in the long term. Given the similar pattern for clinical benefits observed for the two treatment modalities, the biological outcomes of their effects at the cellular level may have more in common than has previously been recognised.

Ovarian ablation or suppression also had a significant, beneficial effect on recurrence ($2P < 0.00001$) and mortality ($2P < 0.004$). The pattern of benefit — an early effect on recurrence and a later effect on mortality — was similar to tamoxifen. However, in contrast to tamoxifen, the effect of suppression or ablation was less in trials where all women also received chemotherapy, perhaps because the chemotherapy also suppressed ovarian function. This question is being addressed in current trials.

What were the harms?

There were minimal long-term effects of all of these agents on non-breast cancer mortality. Chemotherapy was associated with a small, non-significant increase in mortality from heart disease, leukaemia and lymphoma (0.2%); tamoxifen was associated with a small excess mortality from uterine cancer and pulmonary

Key findings of the Early Breast Cancer Trialists' Collaborative Group 2000 overview

- Overview of 194 randomised trials of systemic therapies for early breast cancer started by 1995, including data at 10 and 15 years follow-up.
- Anthracycline-containing regimens are superior to cyclophosphamide, methotrexate and fluorouracil (CMF).
- Anthracycline-based polychemotherapy reduced annual death rates by 38% (standard error [SE], 5) for women younger than 50 years, and by 20% (SE, 4) for women aged 50–69 years.
- Tamoxifen reduced annual mortality rates for oestrogen-receptor-positive tumours in all age groups (31%; SE, 3).
- Combination therapy with tamoxifen and chemotherapy may produce a larger mortality reduction (45%–57%).
- Effects on recurrence occur early; effects on mortality occur later.
- Long-term benefits maintained to 15 years.
- Long-term non-breast cancer deaths from treatment are a few per 10 000 per year, and are greatly outweighed by the reduction in breast cancer deaths.
- More rapid data dissemination from overviews is required. ♦

embolus (0.2%). However, the small increase in non-cancer deaths (a few per 10 000 patients per year) was very much less than the reduction in breast cancer deaths seen for each treatment modality.

What are the implications?

The data from the earlier EBCTCG overviews have already contributed to widespread changes in practice and a recent fall in breast cancer mortality of around 20% in several developed countries. The findings of the 2000 overview will encourage an even wider use of systemic therapies and should contribute to further reductions in mortality.⁷

Overall, the most important finding from the 2000 overview is that important practical and biological information is gained from long periods of follow-up. Not only has this overview produced definitive results relevant to breast cancer management but, importantly, it has clearly demonstrated two important biological principles. First, that an early reduction in recurrence rates is invariably followed by a reduction in mortality. Hence, recurrence rate reduction may be an acceptable basis on which to recommend changes in practice before survival data is obtainable. Second, despite the substantial benefits of 5 years of tamoxifen, 2% of patients continue to have a breast cancer recurrence each year from years 5 to 15 after diagnosis. This is a several-fold greater risk of new breast cancer events than was required for the “high risk” women to be eligible for the tamoxifen prevention trials.⁸ New strategies for ongoing management of these women should be considered. Further, other questions will need to be addressed by the overview process, including the value of tamoxifen or other endocrine therapies beyond 5 years and addition of a taxane to chemotherapy regimens.⁹

What are the limitations?

The current overview only encompassed therapies used up to 1995, which — although clearly effective — are not optimal for

all patients in 2005. The 2000 overview did not involve taxanes (there are now more than 10 000 patients in several trials) or aromatase inhibitors (about 30 000 patients in seven trials).^{10,11} Nor did it include trials with trastuzumab (Herceptin) for women with tumours expressing HER2.¹² However, answers to other specific questions such as the value of long-term aromatase inhibitors and of targeted therapies will likely be based on a smaller number of larger trials rather than an overview of many smaller trials. Many such trials, including the important “SOFT”, “TEXT”, and “PERCHE” trials of different combinations of chemotherapy, aromatase inhibitor and tamoxifen for younger women, as well as trials for older women, and trials of taxanes and of trastuzumab, are being conducted in Australia by the Australian New Zealand Breast Cancer Trials Group through international collaboration. These trials should be the subject of separate meta-analyses, conducted in a timely manner to facilitate rapid dissemination of the results. However, long-term follow-up is a particularly valuable feature of the EBCTCG overviews, and the EBCTCG investigators are pursuing strategies to ensure that data from the 2005 overview will be made available sooner and more widely.

John F Forbes

Professor of Surgical Oncology, University of Newcastle
Newcastle Mater Hospital, Newcastle, NSW
john.forbes@anzbctg.newcastle.edu.au

Jack Cuzick

John Snow Professor of Epidemiology
Centre for Epidemiology, Mathematics and Statistics
Wolfson Institute of Preventive Medicine, London, UK

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