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Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

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Summary

Background

Quinquennial overviews (1985â€“2000) of the randomised trials in early breast cancer have assessed the 5 year and 10-year effects of various systemic adjuvant therapies on breast cancer recurrence and survival. Here, we report the 10-year and 15-year effects.

Methods

Collaborative meta-analyses were undertaken of 194 unconfounded randomised trials of

adjuvant chemotherapy or hormonal therapy that began by 1995. Many trials involved CMF (cyclophosphamide, methotrexate, fluorouracil), anthracycline-based combinations such as FAC (fluorouracil, doxorubicin, cyclophosphamide) or FEC (fluorouracil, epirubicin, cyclophosphamide), tamoxifen, or ovarian suppression: none involved taxanes, trastuzumab, raloxifene, or modern aromatase inhibitors.

Findings

Allocation to about 6 months of anthracycline-based polychemotherapy (eg, with FAC or FEC) reduces the annual breast cancer death rate by about 38% (SE 5) for women younger than 50 years of age when diagnosed and by about 20% (SE 4) for those of age 50â€“69 years when diagnosed, largely irrespective of the use of tamoxifen and of oestrogen receptor (ER) status, nodal status, or other tumour characteristics. Such regimens are significantly (2p=0Â·0001 for recurrence, 2p<0Â·00001 for breast cancer mortality) more effective than CMF chemotherapy. Few women of age 70 years or older entered these chemotherapy trials.

For ER-positive disease only, allocation to about 5 years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31% (SE 3), largely irrespective of the use of chemotherapy and of age (<50, 50â€“69, â‰¥70 years), progesterone receptor status, or other tumour characteristics. 5 years is significantly (2p<0Â·00001 for recurrence, 2p=0Â·01 for breast cancer mortality) more effective than just 1â€“2 years of tamoxifen. For ER-positive tumours, the annual breast cancer mortality rates are similar during years 0â€“4 and 5â€“14, as are the proportional reductions in them by 5 years of tamoxifen, so the cumulative reduction in mortality is more than twice as big at 15 years as at 5 years after diagnosis.

These results combine six meta-analyses: anthracycline-based versus no chemotherapy (8000 women); CMF-based versus no chemotherapy (14â€‚000); anthracycline-based versus CMF-based chemotherapy (14â€‚000); about 5 years of tamoxifen versus none (15â€‚000); about 1â€“2 years of tamoxifen versus none (33â€‚000); and about 5 years versus 1â€“2 years of tamoxifen (18â€‚000). Finally, allocation to ovarian ablation or suppression (8000 women) also significantly reduces breast cancer mortality, but appears to do so only in the absence of other systemic treatments.

For middle-aged women with ER-positive disease (the commonest type of breast cancer), the breast cancer mortality rate throughout the next 15 years would be approximately halved by 6 months of anthracycline-based chemotherapy (with a combination such as FAC or FEC) followed by 5 years of adjuvant tamoxifen. For, if

mortality reductions of 38% (age <50 years) and 20% (age 50â€“69 years) from such chemotherapy were followed by a further reduction of 31% from tamoxifen in the risks that remain, the final mortality reductions would be 57% and 45%, respectively (and, the trial results could well have been somewhat stronger if there had been full compliance with the allocated treatments). Overall survival would be comparably improved, since these treatments have relatively small effects on mortality from the aggregate of all other causes.

Interpretation

Some of the widely practicable adjuvant drug treatments that were being tested in the 1980s, which substantially reduced 5-year recurrence rates (but had somewhat less effect on 5-year mortality rates), also substantially reduce 15-year mortality rates. Further improvements in long-term survival could well be available from newer drugs, or better use of older drugs.

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