EDITORIAL

Adjuvant therapy for operable breast cancer; more answers, new questions

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The first overview of systemic adjuvant treatment for early breast cancer by The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was published in 1990. It demonstrated, over a 5 year period, a significant improvement in mortality for women over the age of 50 when treated with tamoxifen and for women under the age of 50 when treated with chemotherapy.

The publication in 1992 of the second EBCTCG overview provides us with reliable data over 10 years of follow-up (Early Breast Cancer Trialists' Collaborative Group, 1992a,b). It has answered a number of important questions, provided some unexpected results and raised a series of new issues to be addressed by future research, particularly in terms of the potential benefits to be realised by combinations of systemic chemotherapy and hormonal therapies in women of all ages.

The 1992 overview has confirmed the efficacy of chemotherapy for women under the age of 50, and of tamoxifen for women over the age of 50. For women aged less than 50, the use of adjuvant combination chemotherapy reduces the annual odds of recurrence by 37% with a standard deviation of ±5% (SD5) and the annual odds of death by 27% (SD6). For women over the age of 50, the use of adjuvant tamoxifen reduces the annual odds of recurrence by 30% (SD2) and the annual odds of death by 19% (SD3).

Since the vast majority of women who develop recurrent breast cancer ultimately die from the disease, it is anticipated that, after sufficiently long periods of follow-up, the reduction seen in the annual odds of death will match that seen for recurrence. To convert these figures into numbers which are more easily understood, a reduction in the annual odds of death of about 30% equates to approximately 12 extra women alive at 10 years for every 100 women treated with stage II breast cancer, and approximately six extra women alive at 10 years for every 100 women treated with stage I breast cancer. Although these improvements do not appear large, they should be considered in the context of the millions of women treated worldwide each decade for operable breast cancer. Adjuvant treatment of just one million women could well prevent, or substantially delay, an additional 100 000 deaths.

The first overview (Early Breast Cancer Trialists' Collaborative Group, 1990) suggested a limited role for hormonal manipulation in women aged less than 50 with breast cancer. Data from trials of adjuvant tamoxifen suggested a significant reduction in the annual odds of recurrence, but no significant reduction in mortality. Data with respect to ovarian ablation were incomplete.

The 1992 overview has unexpectedly shown that ovarian ablation used as adjuvant therapy in this group of women results in a 30% (SD9) reduction in the annual odds of recurrence and a 28% (SD9) reduction in the annual odds of death. The magnitude of this effect shows no sign of diminishing even after 15 years of follow-up.

More detailed analyses of the tamoxifen trials in women aged less than 50 in the 1992 overview have also provided some surprises with respect to duration of tamoxifen administration. The previous interpretation of these analyses was misleading, since patients treated with both tamoxifen and chemotherapy had a shorter duration of tamoxifen administration (mean 1.6 years) than those treated with tamoxifen alone (mean 2.6 years). Thus, comparisons of tamoxifen duration between trials were likely to have been confounded by the use of chemotherapy. In the 1992 overview, unconfounded analyses of tamoxifen duration in 2216 women treated for a mean of 2.6 years have shown a reduction in the annual odds of recurrence of 27% (SD7) and in the annual odds of death of 17% (SD10), not dissimilar to the results achieved for women over the age of 50. Indeed, further breakdown of these data reveal that, when women aged less than 50 are treated with tamoxifen for 2 years or more, the reduction in the annual odds of recurrence is 43% (SD11), and in the annual odds of death is 27% (SD17) - very similar to those figures described earlier for chemotherapy in this age group. However, it should be noted that because of relatively small numbers in these analyses the confidence intervals are much wider than those in the chemotherapy analyses, implying a degree of statistical instability to the results.

The first overview also suggested a limited role for chemotherapy when given alone to women over the age of 50, for whom a significant reduction in the annual odds of recurrence was demonstrated, but this did not translate into a significant effect on mortality. The 1992 overview, however, clearly shows that chemotherapy does in fact have a significant effect in this age group, reducing the annual odds of recurrence by 22% (SD4), and the annual odds of death by 14% (SD5).

Thus, for women aged less than 50, there are three effective treatments, namely chemotherapy, ovarian ablation and tamoxifen. And for women over the age of 50 there are two effective treatments, namely tamoxifen and chemotherapy. What is not known with any accuracy at the present time is what happens when these treatments are combined and whether the benefits are additive. Data now available from the 1992 overview, shown in Table I, suggest that, for women aged less than 50, tamoxifen may be less effective when given in combination with chemotherapy, in that the additional reductions in the annual odds of recurrence and death from the addition of tamoxifen were only 7% (SD4) and 3% (SD5) respectively when compared with chemotherapy alone.

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Table 1 Estimates from the 1992 overview of reductions in the annual odds of recurrence and death in trials testing combinations of chemotherapy (CT), ovarian suppression (OS) or tamoxifen (Tam)

| Type of systemic therapy | Number of patients | Percentage reduction (s.d.) in annual odds of Recurrence or Death from any cause |
|--------------------------|--------------------|--------------------------------------------------------------------------------|
| Age < 50 years           |                    |                                                                                  |
| (a) CT vs CT + OS        | 939                | 21 (9) 19 (11)                                                                     |
| (b) CT vs CT + Tam (mean 1.6 years) | 6362            | 7 (4) 3 (5)                                                                          |
| (c) Tam vs Tam + CT      | 386                | 32 (16) 6 (23)                                                                       |
| Age 50 + years           |                    |                                                                                  |
| (d) Tam vs Tam + CT      | 3932               | 26 (5) 10 (7)                                                                        |
| (e) CT vs CT + Tam       | 8148               | 28 (3) 20 (4)                                                                        |

*Note that the indicated reductions in the annual odds of recurrence and death are in addition to those reductions already achieved by the therapy in the control arm alone.*
from overseas. As a result of successful recruitment a
definitive grant is now being sought through the UKCCCR
to support the further running of the trial over the next few
years.

The success of the ABC trial depends not only on
dedicated clinicians, but also on a steady supply of patients
who are prepared to give consent to be randomised into
the study. To this end the trial has been developed in colla-
gation with organisations representing the interests of patients,
including BACUP, Breast Cancer Care and the UK Breast
Care Nursing Society. It will also be important to widen
the public debate concerning participation of patients in clinical
trials. Currently patients are often taken aback when app-
roached concerning a clinical trial; ideally they, should expect
to be offered entry into clinical trials. By heightening public
awareness and broadening discussion of these items, the ABC
trial can make a contribution to achieving this aim.

The advisory group on health technologies has already
recognised the importance of well-designed randomised trials
to the research and development strategy of the National
Health Service. A trial such as the ABC trial has, on the
basis of previous research, identified a possible improvement
in the treatment of a major health problem, and sets out to
test this in a large number of patients. Issues such as quality
of life will be incorporated into the trial, as an additional and
voluntary module to be conducted in certain centres, as it is
clearly important to be able to determine whether the addi-
tional toxicities resulting from combined modality treatments
are worthwhile in terms of improved outcome for patients.

Of particular concern are the long-term toxicities that may
result from ovarian ablation in the younger premenopausal
women. In the shorter term, but nevertheless poten-
tially substantial, toxicities that may result from the addition
of chemotherapy to tamoxifen in post-menopausal women.
The results of the ABC trial will ultimately be analysed with
respect to their impact and cost, allowing calculation of
statistics such as number of women—years of life saved, the
added costs of treatment and cost savings of a cured patient.

A study of the size of the ABC trial will also facilitate the
development of parallel studies to investigate aspects of the
biology of breast cancer. Of particular interest is the further
investigation and refinement of markers that may predict for
chemotherapy or endocrine responsiveness. In premenopausal
women there is already a suggestion from a trial that com-
pared adjuvant combination chemotherapy with adjuvant
ovarian ablation that the benefits of ovarian ablation were
mainly seen in patients with hormone receptor-positive
tumours and the benefits of chemotherapy mainly in patients
with hormone receptor-negative tumours (Scottish Cancer
Trials Breast Group and ICRF Breast Unit. Guys Hospital,
London. 1994). Other trials have suggested that CMF-type
adjuvant chemotherapy may be most effective in patients
with tumours negative for the c-erbB-2 oncogene (Allred
et al. 1992; Gusterson et al., 1992), while a trial of dose inten-
sity incorporating adjuvant anthracycline based chemos-
therapy has suggested that dose-intensive anthracycline
chemotherapy has its main effect in patients with tumours
positive for the c-erbB-2 oncogene (Muss et al., 1994). How-
ever, all of these studies are relatively small or derived from
subgroups of larger studies and require confirmation. Well-
conducted biological studies run alongside a trial of the size
of the ABC study will be able to contribute significantly to
this research. Ultimately the goal must be to identify reliable
markers that will allow specific treatments, or combinations of
treatments, to be targeted to the individuals most likely to
benefit from them. If this can be achieved it will also be
possible to spare patients from receiving treatments they do
not require, as well as to identify patients not well served by
the current generation of adjuvant therapies who will become
candidates for experimental therapies. A side-effect of this
activity will be the generation of a sizeable well-documented
tumour bank which will be available for testing the
significance of new markers identified by ongoing fundamen-
tal molecular biological and genetic research.

Any clinician currently treating patients with operable
breast cancer who is not already entering patients into
clinical trials is urged to join the ABC trial. It is only
through participation in such studies as this that we will be
able to further define optimal treatments for individual
patients.

For further information and in order to discover who is
coordinating the ABC trial in your region contact Lindsay
Johnson by telephone, 0181 643 8901 extension 4188, or fax,
0181 770 7876.

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