Tamoxifen for early breast cancer: Better late than never

"There are many thousands of previously untreated women, with hormone-sensitive disease, who could still be offered tamoxifen, and for whom there would still be worthwhile benefit."

Worldwide each decade, about eight million women are diagnosed with breast cancer, and about half of these women will die from their disease [1]. Since breast cancer is so common, the reliable demonstration that practicable and widely available treatments can produce even a moderate improvement in long-term survival should lead to some hundreds of thousands of women being treated accordingly and the avoidance or delay of many thousands of deaths world-wide each year. The overviews, by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), of the worldwide randomised evidence on the treatment of breast cancer, have established reliably that, for women with potentially hormone-sensitive – i.e., oestrogen receptor (ER)-positive-disease, tamoxifen produces definite reductions in recurrence and breast cancer death [2]. In almost all of the studies reviewed, tamoxifen treatment started soon after surgery. The report by Delozier et al. in this issue of Annals of Oncology [3] is therefore important in that it demonstrates that, even if tamoxifen was omitted after surgery, the later introduction of tamoxifen produces survival benefits that appear to be comparable in size with those that can be achieved with earlier treatment.

This finding is of considerable practical importance because the most recent review of randomised trials of tamoxifen [2] shows that tamoxifen is of value to a broader group of women than originally thought, with the corollary that many women who could benefit from such treatment have not been receiving it. For example, the latest overview found that age and nodal status appeared to have little or no effect on the expected benefit from tamoxifen. Yet, an international survey of prescribing practice has shown that age and nodal status are often used as the main factors influencing use of tamoxifen (unpublished). Further, there was added benefit when tamoxifen was given in addition to chemotherapy compared with if chemotherapy was given alone. Again, however, because of theoretical concerns that tamoxifen might be less effective if given concurrently with chemotherapy, many women receiving chemotherapy have not also been offered tamoxifen. So, there are many thousands of previously untreated women, with hormone-sensitive disease, who could still be offered tamoxifen, and for whom there would still be worthwhile benefit. It is important that all clinicians treating breast cancer are aware of this because the late introduction of tamoxifen, up to 10 years after surgery, in younger women and women with node negative disease, who have not so far been treated, could avoid many thousands of deaths per year world-wide.

Where do we now stand with tamoxifen? The EBCTCG reviewed individual patient data on 37,000 women in 55 trials of tamoxifen versus no tamoxifen, with an average of about 10 years follow-up. There was no clear benefit for women with oestrogen receptor (ER)-negative tumours but, for women with potentially hormone-sensitive disease, tamoxifen produced definite reductions in recurrence and breast cancer death throughout the first decade after surgery. Five years of tamoxifen was of greater benefit than just one or two years in terms of recurrence prevention and survival. For every 100 women treated with 5 years of tamoxifen, about 16 relapses and 8 deaths are prevented (Figure 1).

In the trials in the overview, half of the women did not receive any tamoxifen initially. When these women relapsed, however, most of them would then have been prescribed tamoxifen. These 'control' women were compared with those who had received adjuvant tamoxifen from the time of surgery. In terms of time to recurrence, these trials compare tamoxifen vs. no tamoxifen. But in terms of survival, the randomised comparison is not of tamoxifen vs. no tamoxifen, but rather of immediate vs. delayed tamoxifen, as tamoxifen provides benefit not only amongst those who received tamoxifen initially, but also amongst those who received it when they relapsed. This explains why the 10-year difference between the two groups is only half as big for survival as for recurrence.

Five years of tamoxifen: Survival benefits thirty times greater than the risks

The overview now has reliable information on the adverse as well as the beneficial effects of 5 years tamoxifen on cause specific 10-year survival. Tamoxifen does increase the risk of endometrial cancer about threefold but few of these cancers are fatal and so the absolute risk is small. There is also a small increase in the risk of pulmonary embolism. However, the reduction in breast cancer deaths with tamoxifen greatly outweighs these risks (Table 1).

How long should tamoxifen treatment continue?

The conclusions in the overview, that five years of tamoxifen was superior to one or two years treatment,
Tamoxifen because the trials of this question that have already closed (NSABP B-14 [7], the ECOG studies [8], and the Scottish trial [9] of five years versus longer) were not large enough to look at this reliably, even with longer follow-up. So, even the next Overview in September 2000 will leave substantial uncertainty as to whether treatment should routinely continue beyond the fifth year. Until trials such as ATLAS and aTTom that are currently randomising five years versus longer hormonal therapy have entered and followed very large numbers of women, this question will remain unanswered [10].

### ATLAS and aTTom: Longer against shorter hormonal treatment

Newer hormonal agents are currently being tested such as aromatase inhibitors, newer anti-oestrogens, or luteinising hormone releasing hormone (LHRH) analogues. These may have a place in future adjuvant hormonal therapy either alone or in combination with tamoxifen or other adjuvants. But, even if tamoxifen is eventually superseded by some new (and currently unproven) hormonal agent, the question of duration will persist and concerns hormonal therapy as a category of adjuvant therapy. As such, the results of ATLAS and aTTom would also be relevant to other hormonal agents, and not just to tamoxifen. If, as seems likely to be the case by the end of the year 2000, there emerges a general consensus that 5 years of adjuvant hormonal treatment is definitely better than just 2 years, then the question of whether 10 years is superior to 5 years will become even more pertinent, and will have to be answered.

### Important questions about best use of tamoxifen remain unresolved

The EBCTCG overview analyses provide the most comprehensive and reliable source of information on the size of benefits to be expected, for different types of women, from tamoxifen and other adjuvant therapies for early breast cancer. All clinicians treating breast cancer should be familiar with them. Widespread adoption of the more effective therapies has already led to substantial falls in breast cancer mortality over the last decade or so in the UK and USA, with similar trends in other countries (Figure 2) [11]. The most recent overview results show that tamoxifen is of value to a broader group of women...
than originally thought. At the same time, the EBCTCG analyses have also highlighted the inadequacy of small-scale evidence and identified many important questions about everyday use of tamoxifen that remain unresolved. In particular, previous studies of five years of tamoxifen versus longer, have been too small to answer this important question reliably [12]. Much larger-scale evidence is needed and, to achieve this, an invitation to participate in a relevant clinical trial should become part of the standard management for most women with breast cancer. Better late than never!

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References
