Editorial

The Optimal Duration of Adjuvant Tamoxifen Treatment for Breast Cancer Remains Uncertain: Randomize into aTTom

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INTRODUCTION

We are pleased to have the opportunity to contribute this timely editorial on duration of adjuvant tamoxifen treatment in early breast cancer; we remain convinced that the optimal duration of treatment is as yet unknown, and that as many women as possible should continue to be randomized into trials of tamoxifen duration.

The UK Co-ordinating Committee on Cancer Research (UKCCCR) aTTom trial (adjuvant Tamoxifen Treatment offer more?), and its international counterpart, ATLAS, have been set up to provide an answer to the optimal duration of tamoxifen question. The unique and pragmatic study design can accommodate the changes in clinical opinion that have already occurred since the study first started in 1994. This flexible design means that every woman with breast cancer who is recurrence-free and is still taking tamoxifen after a few years should be considered for the study at some stage. The aTTom trial recruits women when both the clinician and the patient are uncertain whether or not to continue tamoxifen treatment. Women are then randomized to stop or to continue tamoxifen for a further 5 years.

TWO- VERSUS 5-YEAR COMPARISONS

At the start of the aTTom trial, it was already known from the Early Breast Cancer Trialists’ Collaborative Group overview [1] that women benefited from continuing tamoxifen for at least 2 years. Indirect comparisons between studies using different durations of treatment suggested that more than 2 years might be even better. There is now increasingly convincing evidence from direct randomized comparisons of 2 versus 5 years of tamoxifen, which are discussed below, that 5 years’ treatment provides an advantage for women in both progression-free and overall survival.

The Swedish Breast Cancer Co-operative Group reported their trial of 2 versus 5 years in the Journal of the National Cancer Institute [2]: 3887 postmenopausal women who had axillary node-negative or -positive disease, and had either oestrogen receptor (ER)-positive or -negative tumours, were randomized at diagnosis to tamoxifen administration for 2 or 5 years (20 mg or 40 mg); 3545 (91%) were relapse-free at 2 years. The Group then proceeded with the randomization choice to stop or continue tamoxifen. The median follow-up from randomization was 5 years. There was a significant improvement in relapse-free ($P = 0.009$) and overall survival ($P = 0.03$) for patients allocated to 5 years of tamoxifen. Overall survival was 80% for those receiving tamoxifen for 5 years, compared with 74% in patients allocated to stop tamoxifen at 2 years. Both node-negative and node-positive women benefited from prolonging treatment. The benefit is most apparent for patients with ER-positive cancers and is most pronounced during years six to eight of follow-up.

The Cancer Research Campaign Breast Cancer Group’s 2 versus 5 years ‘over 50s’ trial was also reported recently in the Journal of the National Cancer Institute [3]. This group registered women over the age of 50 years at diagnosis, and, if disease-free at 2 years, randomized them to stop tamoxifen or to continue for a further 3 years; 2664 randomized patients, followed up for a median of 7.7 years, showed an event-free survival benefit in favour of continuing tamoxifen for 5 years, which was just statistically significant ($P = 0.03$). However in this trial there was only a non-significant trend ($P = 0.3$) towards better survival for longer treatment.

It is likely that the publication of these two studies will do much to persuade oncologists to use tamoxifen for about 5 years routinely in the adjuvant setting, rather than a lesser duration, at least for women with ER-positive breast cancer.

FIVE YEARS VERSUS LONGER

There are fewer randomized trials on the 5 years versus longer question. In our view, the clinical announcement from the National Cancer Institute (NCI) in November 1995 [4], recommending only 5 years’ treatment in routine clinical practice, prejudged the issue. It was based on the National Surgical
Adjuvant Breast and Bowel Project (NSABP)-B14 trial, which was closed by the data monitoring committee because of an apparent detrimental effect for women who continued tamoxifen after 5 years. The NCI cited data from the NSABP-B14 trial and a smaller Scottish study; at the time, both were unpublished. Since then, these studies have been published in full. In the NSABP-B14 trial [5], 1166 node-negative, ER-positive women were randomized at 5 years to take either tamoxifen or a placebo. At a median of 4 years after the second randomization, 92% of the group who received only 5 years of tamoxifen were alive and disease-free, compared with 86% in the group scheduled to receive 10 years of tamoxifen. However, only a small number of events were seen among these low risk women, and no differences were statistically significant. Despite this, the study was stopped at that stage and the NCI announcement made [4].

In the Scottish Tamoxifen Study [6], even fewer patients were randomized at the 5-year point (173 to continue tamoxifen for a further 5 years, and 169 to stop). The median follow-up on this study after the second randomization was 6.2 years, and at the time of reporting 70% of the patients randomized to stop tamoxifen are alive and disease-free compared with 62% of the group who continued treatment beyond 5 years. Again, this difference is not statistically significant.

In contrast to these two studies, an Eastern Cooperative Oncology Group trial [7], which compared 5 with 10 years' tamoxifen, reported better disease-free and overall survival with 10 years' tamoxifen when compared with 5 years, but again this was based on only a few dozen events. These mutually inconsistent findings from three studies are probably explained by the small numbers of events seen, and indicate the need for larger scale, and hence much more reliable, evidence on this question.

**TAMOXIFEN BENEFITS AND SIDE EFFECTS**

Besides its undoubted effects in prolonging disease-free and overall survival for women with breast cancer, tamoxifen also reduces the number of contralateral breast cancers by one-third [8,9], with the biggest reduction seen in studies assessing 5 years’ adjuvant treatment. Tamoxifen also has beneficial pro-oestrogenic activity in terms of a reduction in postmenopausal bone loss, a reduction in serum low density lipoproteins, and, in some trials, a reduction in the frequency of fatal cardiovascular events [10]. There is now more information on its toxicities, which include menopausal symptoms [9], an increased risk of endometrial cancer [11–15], an increased risk of thromboembolic events [16], and, very rarely, a reversible retinopathy [17]. The risk of endometrial cancer appears greater in studies of 5-years of administration of tamoxifen, and hence this is the biggest concern during long term treatment. Endometrial cancer, however, is relatively rare. Its annual incidence in the normal UK population is only 3 cases per 10000 women, which increases to about 6–9 per 10000 for women on tamoxifen, and so the risks, in absolute terms, remain small. Contrary to an early report, endometrial cancers among women on tamoxifen have been found to have equivalent grade and stage to those seen in the general population [13]. Another concern has been expressed over the possible general genotoxic effects of tamoxifen, with the IARC recently classifying tamoxifen as a carcinogen [18]. These concerns stem from the undoubted effect of tamoxifen as a genotoxic agent in the rat model, with DNA adduct formation and a high incidence of induced primary liver cancers [19–21]. However, in women and in other species studied, there has been no similar worrying excess of liver DNA adducts [22], and no reported excess of primary liver tumours [23]. This suggests that the induction of rat liver cancers may be due to the known differences in metabolism of tamoxifen between humans and other species; the metabolite alpha-hydroxytamoxifen is 40-fold more common in rats than in humans, and is several hundred-fold more likely to cause DNA adducts than the parent compound or other metabolites [24]. There is at present little evidence that tamoxifen is carcinogenic to humans at sites other than the endometrium. Although the Scandinavian group has reported an excess of gastrointestinal tract cancers, with a relative risk of 1.9 for those on tamoxifen [25], this is not supported by data from the American trials [14]. It seems likely that the increased risk of endometrial cancer is due to a promotional pro-oestrogenic effect of tamoxifen on the endometrium, rather than a genotoxic effect. In a recent paper, Carmichael et al. [26] have demonstrated a lack of any genotoxic effect either of tamoxifen on the endometrial cells in vitro or in DNA in endometrial biopsies, both obtained from patients on long term tamoxifen therapy.

**THE aTTom TRIAL**

The first generation of tamoxifen duration trials has narrowed the range of uncertainty about the optimal treatment duration but has failed to answer the key question of when, if at all, the balance of benefits and risks no longer favours continued treatment. There are reasons to be optimistic that further survival benefits can be achieved by prolonging tamoxifen treatment beyond 5 years, but this simple question is surprisingly difficult to answer for two main reasons. First, the likely benefit from longer treatment is an improvement in long term survival of 'only' a few per cent. This would be clinically important given that, each year, half a million women develop breast cancer around the world, but studies evaluating such moderate treatment benefits have to be much larger than is generally recognized. Secondly, tamoxifen has a substantial 'carry-over' benefit with less recurrences seen for a few years after the end of the treatment period. This means that trials comparing longer versus shorter regimens may show little or no apparent extra benefit for the first few years of additional treatment but that, later on, worthwhile benefit may emerge. Thus, much larger scale randomized evidence and
longer follow-up are needed to determine the important question of precisely how long tamoxifen treatment should continue.

In response to this need, the UKCCCR is organizing the 'aTTom' study. To facilitate large scale recruitment, entry to the study is uniquely pragmatic in that any prior duration of tamoxifen treatment is allowable, with randomization occurring at the point when uncertainty arises about whether or not to continue treatment. Thereafter, absolutely minimal follow-up information is requested, making it practicable for even the busiest clinicians to enter their patients. Long term follow-up is through national records of dates and causes of death; second cancers are monitored through the cancer registries.

The aim of aTTom, and its international counterpart, ATLAS, is to randomize the 20000 women needed to generate appropriately reliable evidence on the balance of benefits and risks of long term tamoxifen treatment. Information from these studies will help to guide the treatment of many hundreds of thousands of future women with breast cancer. It is, literally, vital for these women that ongoing tamoxifen duration studies should be supported.

If you would like more information about the aTTom trial, then please contact Dr K. Milligan (Tel: 0121 414 3796), or Dr L. Padmore (Tel: 0121 414 3793), fax the aTTom study office on 0121 414 3700, or e-mail: aTTom @bham.ac.uk Freephone randomization number: 0800 371969.

References


