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Tamoxifen beyond 5 years—patients' decisions regarding entry to the aTTom trial

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Abstract

The aim of this study was to assess among a population of women who had taken adjuvant tamoxifen for 5 years, how many were prepared to enter a randomised trial looking at the duration of tamoxifen treatment and what was the preference of those who declined trial entry. There is uncertainty as to the optimum duration of adjuvant tamoxifen and this is the subject of the aTTom (adjuvant Tamoxifen Treatment offer more?) trial in which patients are randomised to continue or stop tamoxifen after 5 years. Patients have been recruited to the aTTom trial in Dundee since 1996 and a record has been kept of all the patients with whom the trial was discussed. Patients who declined trial entry were allowed to choose whether to electively stop or continue tamoxifen. 306 patients were eligible for trial entry of whom 171 (56%) consented to randomisation (82 to continue and 89 to stop). Amongst the 135 (44%) who declined randomisation, 28 (21%) elected to stop tamoxifen treatment, 90 (67%) elected to continue and in 17 (13%) their decision was unclear. These results illustrate that patients eligible for the aTTom trial share our clinical equipoise. A majority (56%) of patients were agreeable to randomisation, but among those who declined, some (67%) preferred to continue, some (21%) to stop tamoxifen. This trial is unusual in that the patients have already experienced the treatment options, so the patients' preferences reflect a truly informed choice.

Keywords: aTTom; Patient and clinician equipoise; Tamoxifen

1. Introduction

Patient recruitment into a randomised clinical trial is ethical only if the clinician is in perfect equipoise about both of the two treatments under evaluation. In addition, the patient, having been fully informed about the trial should also express perfect equipoise. This is often difficult to appraise. Most patients at the time of randomisation have only a theoretical knowledge of any potential benefits and/or side-effects of the proposed treatments, hence the ideal of fully informed consent and true equipoise on the part of the clinician and the patient may not be achievable in practice [1].

We report here on the pattern of local recruitment to the aTTom trial—a randomised study to assess the risks and benefits of extending adjuvant tamoxifen treatment in early breast cancer beyond 5 years. We propose that in this study, because eligible women are already familiar with the treatment involved, the decision to enter the study and the choices made by those who decline trial entry give a truer indication of patient equipoise.

Tamoxifen, as an adjuvant treatment following surgery for oestrogen receptor-positive breast cancer, extends disease-free and overall survival [2,3]. The optimum duration of treatment remains undetermined. Both the Swedish Breast Cancer Co-operative Group [4] and the Cancer Research Campaign (CRC) 'over 50' study [5] demonstrated a significant reduction in event-free survival in women treated with tamoxifen for 5 versus 2 years [4,5]. The Swedish study also demonstrated a significant increase in overall survival at 10 years in the group treated for 5 years—with a similar trend to increased overall survival also seen in the CRC study.

Although continuing tamoxifen treatment to 5 years has been shown to be superior to stopping at 2 years, uncertainty remains regarding the optimum duration of therapy. Two large multicentre trials, aTTom (adjuvant

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Tamoxifen Treatment offer more?) and ATLAS (Adjuvant Tamoxifen-Longer versus Shorter), are currently recruiting patients to address this question [6]. Ninewells Hospital in Dundee is one of the centres recruiting patients to the aTTom study. Data has been collected prospectively on the characteristics of women who agree to be randomised within aTTom and those who decline trial entry. We also report here the decisions made regarding the continuation of tamoxifen or otherwise in women who decline randomisation.

2. Patients and methods

The aTTom trial was launched in 1996 and aims to recruit 20 000 women to determine whether any overall survival benefit is derived from extending the duration of adjuvant tamoxifen treatment beyond 5 years. In Dundee, the trial is discussed with patients in whom substantial uncertainty exists as to whether tamoxifen should be continued or stopped who are attending for follow-up after their primary therapy for breast cancer and who have been taking adjuvant tamoxifen for at least 5 years. Eligible women are invited to consider trial entry and given an information sheet that summarises the background to the trial (as above) and the factors in favour of continuing (e.g. reduction in osteoporosis, possible reduction in breast cancer recurrence) and those against continuing (e.g. increased risk of endometrial cancer, continuation of any side-effects). Those who consent are randomised either to stop tamoxifen or to continue taking tamoxifen for a further 5 years. Women who decline entry in to aTTom are given a free choice of either electively stopping or continuing tamoxifen. They have been informed of the advantages and disadvantages of continuing tamoxifen, aTTom is an ethical trial and neither arm is of proven superiority, hence it was felt ethical for the patient to make an informed choice as to their treatment if they declined trial entry. A register of all women eligible for aTTom since 1996 has been kept and the treatment decisions made by those who declined randomisation have also been recorded. No formal prospective record was kept of the reasons why patients declined trial entry.

3. Results

Fig. 1 summarises the decision tree of the 306 eligible patients with whom the trial was discussed from 1996 to 2001. A majority (56%) consented to randomisation within aTTom. Amongst the 44% of women who declined trial entry, 21% elected to stop taking tamoxifen at 5 years and 67% elected to continue treatment beyond 5 years. In 13%, it was difficult to ascertain whether tamoxifen would be stopped or continued.

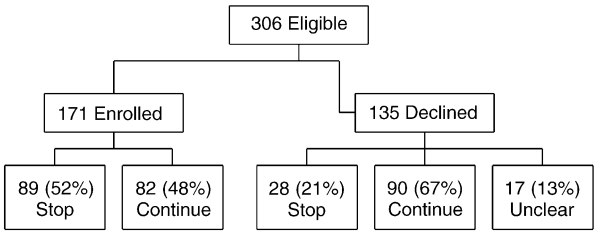

Fig. 1. aTTom—Tayside.

The oestrogen receptor status, lymph node status and menopausal status of the patients who were randomised within aTTom and those who preferred to make personal choices regarding tamoxifen treatment were examined. There was no statistically significant difference between the two groups (data not shown).

4. Discussion

These results illustrate that the majority of patients eligible for the aTTom trial share our clinical equipoise with 56% agreeing to trial entry and randomisation. We have also shown that there is no difference with respect to the oestrogen receptor status, lymph node status or menopausal status between those who agree to and those who decline trial entry. The latter is reassuring and supports the generalisability of the data from the trial.

For those who declined trial entry, no attempt was made to systematically record the women's reasons for preferring to stop or continue tamoxifen. Anecdotally, however, reasons given by some of the women who elected to continue taking tamoxifen included "feeling more secure" on tamoxifen and knowing that they would regret having stopped if they later relapsed with their breast cancer. Some women wanted to retain the beneficial effects of tamoxifen therapy with respect to protection against osteoporosis and ischaemic heart disease. Some of the reasons given by the women who elected to stop tamoxifen therapy included side-effects such as weight gain, flushing and hair loss. Four of the women stated the reported increase risk of endometrial cancer with prolonged tamoxifen therapy as their reason for choosing to stop treatment and refuse trial entry. The large number of women in our patient group who declined randomisation within aTTom and elected to continue taking tamoxifen reflects the experience of the CRC group in 1996 where patients were offered randomisation at 2 years to stop or continue tamoxifen to 5 years. In this study, 29% patients elected to continue tamoxifen, declining randomisation.

Conventional trials involving cancer patients report aversion to the randomisation procedure itself as the

major barrier to recruitment [7]. Other reasons commonly cited by patients for refusing entry in to randomised clinical trials include uncertainty about personal benefit and wanting the doctor to choose their treatment [8,9]. Altruism has been found to be one of the main reasons that cancer patients agree to take part in clinical trials [10]. Trials such as aTTom (and ATLAS) differ from most randomised clinical trials in that the patients have already been exposed to the treatment on offer. Eligible patients have first-hand experience of the likely side-effects and the agent under study is neither new nor experimental, resulting in a greater depth of informed consent. This contrasts with the more usual invitation of cancer patients to participate in randomised trials of newer agents or drug combinations to which they are clinically naïve. For this reason, it was felt reasonable to allow women who declined trial entry a free choice as to whether to stop or continue tamoxifen. They already know how tamoxifen affects them personally and having considered trial entry, are aware of the potential risks and benefits.

The importance of the ongoing large randomised trials to fully answer the question of whether an overall survival benefit is attained by extending the duration of adjuvant tamoxifen beyond 5 years is paramount. As previously stated by Hazel Thornton [11], however, many women wish to make an informed personal choice regarding their breast cancer treatment and the way forward is likely to come from sharing responsibilities and knowledge from both sides of the consultant's desk.

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