PERGAMON

European Journal of Cancer 38 (2002) 1984–1986

European Journal of Cancer

www.ejconline.com

The ATAC (Arimidex™, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal patients: factors influencing the success of patient recruitment

Mike Baum*,[1]

The Portland Hospital, First Floor, 212–214 Great Portland Street, London W1W 5QN, UK

Received 1 February 2002; received in revised form 14 March 2002; accepted 10 May 2002

Abstract

The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial is a randomised, double-blind, double-dummy trial, evaluating anastrozole alone or in combination with tamoxifen compared with tamoxifen alone, as a 5-year adjuvant treatment for postmenopausal patients with early breast cancer. The rapid rate of recruitment into this trial was a major achievement, as frequently encountered differences between projected and actual recruitment rates can threaten the successful completion of clinical trials. A questionnaire designed in order to highlight possible factors influencing the success of patient recruitment was completed by 62% of the ATAC trialists. This included 11 statements rated for their level of importance on a three-point scale. The top three motives for recruiting patients were: (1) the attractive scientific rationale of the trial (84%); (2) a design that was easy to explain to patients (79%); and (3) a pragmatic trial design in line with standard practice (76%). A new questionnaire will solicit opinion from the participating patients.

Keywords: Anastrozole; Aromatase inhibitor; Early breast cancer; Trial recruitment

1. Introduction

The oestrogen antagonist, tamoxifen, has long been considered the 'gold standard' for the treatment of early breast cancer in women with tumours that are oestrogen receptor (ER)- and/or progesterone receptor (PR)-positive. Recently, the aromatase inhibitor, anastrozole ('Arimidex'), has been shown to be superior to tamoxifen for the first-line treatment of postmenopausal patients with advanced breast cancer with hormone-sensitive tumours [1]. The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial evaluates, in a randomised, double-blind design, anastrozole alone or in combination with tamoxifen compared with tamoxifen alone, as a 5-year adjuvant treatment for postmenopausal patients with early operable breast cancer. The trial was designed and powered to determine if anastrozole was equivalent to tamoxifen for the primary endpoint of disease-free survival, and also to determine if the combination of anastrozole plus tamoxifen was superior to tamoxifen alone. If equivalence was observed for anastrozole compared with tamoxifen, then this comparison was to be further assessed to determine whether anastrozole alone was superior to tamoxifen. To date, this trial is the largest adjuvant trial ever conducted in postmenopausal patients with early breast cancer. In approximately 45 months, the trial recruited over 9366 patients from 381 centres in 21 countries. The efficacy and tolerability results of this trial were reported in December 2001 [2].

Recruitment of patients in randomised controlled trials involves detailed screening, in order to determine eligibility, and enrolling a predetermined number of subjects within a planned time. Differences between projected and actual recruitment rates are not uncommon and, when large, pose a serious threat to the successful completion of the trial. Therefore, the rapid rate of recruitment into the ATAC trial was a major achievement. To identify possible reasons for this, and with a view to building on this success and providing ideas for future good practice to other clinical trial

* Corresponding author. Tel.: +44-207-390-8447; fax: +44-207-390-8448.

E-mail address: m.baum@ctc.ucl.ac.uk (M. Baum).

[1] On behalf of the ATAC Trialists' Group.

0959-8049/02/$ - see front matter
PII: S0959-8049(02)00154-5

organisations, several factors potentially influencing the success of patient recruitment into this trial were highlighted in a questionnaire. This was then distributed to all investigators while the trial was still ongoing. The results of this questionnaire are presented here.

2. Patients and methods

The questionnaire was designed by Professor Lesley Fallowfield at the University of Sussex (a member of the ATAC Steering Committee), to be completed by the clinicians who participated in the ATAC trial. The Steering Committee is comprised of the principal investigator, other trial investigators, the independent statistician and representatives from the various collaborative groups and AstraZeneca. Following completion of trial recruitment, the questionnaires were sent from the ATAC Steering Committee to all trial investigators worldwide and were returned to the ATAC Steering Committee anonymously. The questionnaire included 11 statements regarding recruitment to the ATAC trial (Table 1). Investigators were asked to rate each statement on a three-point scale of level of importance (very important, somewhat important, not important).

A further question asked for any other reasons that may have encouraged the investigators to recruit into the study. The final question requested the clinician to highlight a single statement from the 11 that they considered the most important reason for recruiting patients into the trial. The results are presented descriptively as percentages.

3. Results

Of the 381 questionnaires sent out, a total of 238 (62%) completed questionnaires were returned by the investigators. Table 1 shows the results of the questionnaire.

The top six incentives for the trialists to recruit patients were:

1. The scientific rationale of the trial was attractive (84%)
2. The design was easy to explain to patients (79%)
3. The trial was pragmatically designed in line with standard practice (76%)
4. Infrastructure was well organised (70%)
5. Endocrine treatments were oral and relatively non-toxic (69%)
6. This was a logical extension of earlier endocrine trials (67%)

Of these, the top three statements rated to be the single most important reason to enter patients into the trial were, that the scientific rationale was attractive (30%) and pragmatically designed in line with standard practice (17%), and that the trial was a logical extension of earlier endocrine trials (12%) (Table 1). The two incentives

Table 1
Results of the questionnaire

	Very important (%)	Somewhat important (%)	Not important (%)	Single most important reason (%)
I found the scientific rationale of the trial attractive	84	15	1	30
I found the design of the trial easy to explain to patients	79	18	3	8
The pragmatic design of the trial, which was in line with standard clinical practice and which allowed me to select appropriate primary therapy and chemotherapy prior to randomisation, made the ATAC trial attractive	76	21	3	17
The infrastructure of the trial was well organised and this made randomising patients easy	70	26	4	4
Accepting that proposed treatment arms were appropriate for evaluation in this large early breast cancer trial, the fact that the treatments themselves were oral and relatively non-toxic encouraged me to enter	69	28	3	6
This trial was a logical extension of earlier trials of endocrine therapy that had helped establish tamoxifen as a standard hormonal treatment in early breast cancer	67	29	4	12
The provision of trial medication free of charge from the sponsors encouraged me to join the trial	47	33	20	2
At the time, there was no other trial of adjuvant endocrine therapy open for recruitment	36	36	28	5
The international nature of the trial encouraged my participation	30	40	30	4
The level of financial support provided	29	45	26	10
Endorsement by Consumers Advisory Group for clinical trials encouraged me to put patients into the trial (UK only)	6	28	66	0

UK, United Kingdom.

for the trialists to recruit patients into the trial which scored the lowest (Table 1) were the endorsement by a consumers' advisory group (6%) and the level of financial support (29%). Other key reasons that encouraged investigators to recruit to recruitpatients into the study included, the timely initiation of the study (patients were asking for alternative treatments to tamoxifen); previously good co-operation by the clinical researchers and AstraZeneca; patients are keen to try new, modern pills; this trial was addressing the question of whether two drugs are more effective than one; there are many publications in this field and this study was a logical progression of the 1998 Early Breast Cancer Trialists' Collaborative Group [3]; and trials of this size always provide interesting additional results to the primary and secondary endpoints. Many reasons listed by the investigators reflected the meaning of the statements already included in the questionnaire (e.g. 'Simple design', 'Excellent scientific questions').

4. Discussion

The results of the questionnaire highlighted many reasons why the investigators were impressed with the trial. Approximately two-thirds of the clinicians returned the questionnaire (62%), which is likely to indicate enthusiasm on behalf of the investigators for the ATAC trial. Contributing reasons for their participation in the trial and subsequent rapid recruitment were the scientific rationale of the trial, pragmatism of the study design (reflecting standard clinical practice as closely as possible), and the relative safety of the treatments involved.

Incentives that were considered less important for recruitment into the trial included financial support and the endorsement of the trial by a consumers' advisory group. However, with respect to the latter factor, it should be emphasised that this is the opinion of the clinicians and it will be of interest to see if the results of a planned companion questionnaire to survey a sample of the patients from the trial shows the same profile.

The investigators were impressed by this trial as it was considered to be scientifically robust, well organised, and the design made the trial easy to implement in busy clinics. These reasons are very likely to have influenced the rapid recruitment into the ATAC trial, and they are in contrast to the Cancer Research Campaign breast conservation trial, which was designed to compare mastectomy with wide local excision, with the sample target of 1200 patients. This trial was aborted after recruiting only 150 patients over 3 years [4,5]. In the future, studies (either in the field of oncology or in other therapeutic areas) that consider the factors outlined in this paper in the trial design may maximise the potential recruitment rate.

Finally it could be argued that the respondents were less than honest in their replies in the name of 'social desirability' or 'faking good', by minimising the importance of the cash incentive for recruitment. This is of course a possibility, but has been minimised by the anonymous nature of the questionnaire and lack of face-to-face contact between the researcher and investigator which are proven techniques in improving the validity of responses in these kind of studies [6].

References

1. Bonneterre J, Buzdar A, Nabholtz JMA, *et al*. Anastrozole ('Arimidex') is superior to tamoxifen as first-line therapy in hormone receptor-positive advanced breast cancer: results of two randomized trials designed for combined analysis. *Cancer* 2001, **92**, 2248–2258.
2. Baum M, on behalf of the ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet*, 2002, **359**, 2131–2139.
3. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998, **351**, 1451–1467.
4. Peckham MJ, Chairman. Protocol for a Collaborative Trial to Evaluate the Need for Mastectomy in the Management of Early Breast Cancer. London, Cancer Research Campaign Clinical Trials Centre, 1982.
5. Fallowfield LJ, Baum M, Maguire GP. Effects of breast conservation on psychological morbidity associated with the diagnosis and treatment of early breast cancer. *Br Med J* 1986, **293**, 1331–1334.
6. Streiner DL, Norman GR. *Health Measurement Scales: A Practical Guide to Their Development and Use*. Oxford, Oxford University Press, 1989 54–66.