Scottish Adjuvant Tamoxifen Trial: a Randomized Study Updated to 15 Years

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Background and Methods: The Scottish Adjuvant Tamoxifen Trial (main trial) was initiated in April 1978 to assess the effect of tamoxifen given to patients with breast cancer immediately after mastectomy (or mastectomy plus radiation therapy) (adjuvant arm) or only after the patients had had a relapse (control arm); 1323 patients were randomly assigned (667 to the adjuvant arm and 656 to the control arm). Results have been reported for the follow-up period from 2.5 through 8 years. In this article, we report updated results after a median follow-up of 15 years. If agreeable and eligible, patients who were disease free at 5 years in the adjuvant arm of the main trial were entered into a duration trial and randomly assigned either to stop taking tamoxifen (169 patients) or to continue taking it indefinitely until relapse or death (173 patients). For this update, we analyzed information on death, recurrence, survival, and other malignancies for all but 21 of the 560 living patients from the original and duration trials to determine the probabilities of total survival, systemic relapse of disease, and death from breast cancer. All statistical tests are two-sided. Results: The beneficial effect of adjuvant tamoxifen given for 5 years on the probability of total survival (\( P = .006 \)), systemic relapse (\( P = .007 \)), and death from breast cancer (\( P = .002 \)) has been maintained through 15 years. No additional benefit was observed in those randomly assigned to continue taking tamoxifen beyond 5 years. Conclusion: Information from this study suggests that, if adjuvant tamoxifen is given to women with operable breast cancer, it need not be for more than 5 years. [J Natl Canc Inst 2001;93:456–62]

The Scottish Adjuvant Tamoxifen Trial was initiated in April 1978. From then through September 1984, a total of 1322 patients with primary breast cancer who were aged 27–79 years agreed to participate. Each patient had received a mastectomy and had axillary lymph node clearance (levels I–III) or a lower axillary lymph node sample by which three or four lymph nodes were removed for histologic examination. If sampling indicated involved lymph nodes, patients also had received radiotherapy to the chest wall and to the regional lymph node sites. Participants were randomly assigned either to receive tamoxifen (20 mg daily) immediately as adjuvant therapy for 5 years or to delay receiving tamoxifen until indicated by recurrent disease. The majority of patients (1079 patients) were postmenopausal; only premenopausal patients without proven disease in the axilla were eligible for the trial. Estrogen receptor concentrations in the primary tumors were determined for 57% of the participants by the dextran-coated charcoal exchange assay in university laboratories in Edinburgh and Glasgow, Scotland, as described previously (1); the estrogen receptor status of the remaining 43% was not determined.

Details of this trial, with a follow-up of 2.5–8 years, have been reported previously (1), and a survival advantage and a reduction in disease recurrence were reported for those receiving tamoxifen immediately compared with those receiving delayed tamoxifen therapy.

From February 1985 through September 1989, after completion of the 5-year period of adjuvant therapy, 342 consenting, disease-free patients were accepted into the duration trial after a second randomization (Fig. 1), conducted by using sealed envelopes prepared 6 months before their fifth anniversary in the study. The options were either to stop tamoxifen or to continue taking the drug for an indefinite period. The method of determining eligibility for inclusion in this second trial and the method of randomization were provided in more detail in the report of the 6-year follow-up results (2). No additional advantage in survival or freedom from recurrence was identified in those continuing to take adjuvant tamoxifen beyond the initial 5-year period (2).

Both parts of the Scottish trial have now been updated to a median follow-up period of 15 years (maximum = 19.3 years) for patients alive at the date of the last record.

Subjects and Methods

For this update, from February 1996 through January 1998, we were able to trace all but 21 of the living patients who entered the main trial and to record their disease state. As of February 1996, many living patients had been discharged from regular hospital follow-up; thus, this review involved personal contact with general practitioners, their practice secretaries, data managers in oncology units, and staff of the Scottish Cancer Therapy Network. Available hospital records were scrutinized for patients who had died in the hospital from alleged causes other than breast cancer. In April 1978, when the main trial was started, verbal consent to randomly allocated treatment was considered to be adequate and was included in the protocol as a requirement for all patients. Obtaining this verbal consent and also the approval for the protocol from the hospital ethics committees was the responsibility of the participating clinicians.

Death

Breast cancer was accepted as a cause of death if systemic breast cancer had been recorded in hospital notes or if the death certificate indicated breast cancer as the primary cause of death. The need to determine the cause of death from death certificates occurred rarely. For survival analyses, all contralateral breast cancers were regarded as systemic disease.

Disease Recurrence

Information on recurrent disease was largely available from hospital notes. In this article, we present only the results pertaining to systemic recurrences (i.e.,...
excluding recurrences involving the ipsilateral chest wall or regional lymph nodes). In addition to being counted as systemic recurrence for survival analyses, contralateral breast cancers arising more than 1 year after the initial mastectomy were recorded as new primary tumors, provided patients remained free of systemic disease at other sites and also free of ipsilateral locoregional disease for another year. Contralateral noninvasive cancer was accepted as a new primary disease irrespective of its time of onset and subsequent findings. New primary cancers that occurred in sites other than the contralateral breast were not counted as breast cancer-related events.

The duration of tamoxifen therapy was calculated in months from data in the hospital notes or, if necessary, in general-practice prescribing records. Reasons for stopping tamoxifen were also ascertained.

Survival

Analyses of survival times have been carried out according to the randomly assigned option (intention to treat). For this article, patients originally randomly assigned to delayed tamoxifen (tamoxifen on first relapse) are referred to as control patients; all others belong to the adjuvant arm within which those secondarily randomly assigned to stop adjuvant tamoxifen after 5 years are termed the “stopped” group and those randomly assigned to continue tamoxifen as the “continued” group. The results are presented in two sections, one for the main trial (a median follow-up of 15 years, with all but five patients followed for 10 years) and one for the duration trial (a median follow-up of 10 years from the date of re-randomization). A supplementary analysis of outcome was performed.
according to treatment actually given. For this analysis, 89 additional patients were available who, although not having recurrent disease and having had 5 years of adjuvant tamoxifen in the main trial, were not suitable for inclusion in the duration trial (Fig. 1).

Other Malignancies

The number of patients in each arm of the main trial who developed other malignancies (including primary contralateral breast cancers as defined above) was ascertained.

Statistical Methods

Kaplan–Meier survival curves were prepared for each outcome variable, and a two-tailed log-rank test was applied to determine the statistical significance. The 95% confidence intervals for the hazard ratio of the two treatments were estimated from Cox proportional hazards models. All statistical tests are two-sided.

RESULTS

Main Trial

Six hundred sixty-seven patients were randomly assigned to the adjuvant arm (to receive tamoxifen immediately), and 656 patients were randomly assigned to the control arm (to receive tamoxifen only after disease relapse) (Fig. 1). Of the 11 patients excluded from the 1987 analyses because of protocol violations, 10 have been included in the present analyses according to the advised practice of disallowing any withdrawals (3). The one patient still excluded had a lymphoma of the breast.

There were few violations of protocol therapy. Only 22 patients randomly assigned for adjuvant tamoxifen did not receive this therapy, and adjuvant therapy was given to only eight control patients. In the control arm, tamoxifen was correctly prescribed at relapse for 316 (92%) of the 344 patients with recurrent or contralateral disease (Table 1). Total exposure to tamoxifen for the 982 patients who received immediate or delayed tamoxifen is given in Fig. 2, which indicates that, in the adjuvant arm, most patients (449 patients) took tamoxifen for 4.5 years or more. Of the 203 patients who did not (including eight who started tamoxifen only on relapse), only 15 stopped taking tamoxifen because of toxicity. Other reasons for early stoppage included relapse of disease (121 patients), death without relapse (23 patients), stopping tamoxifen in error or on suspicion of relapse (35 patients), and protocol violations (nine patients). The peak duration, centered at 5 years, represents the 203 patients in the adjuvant arm who stopped tamoxifen at that time because they chose to, had to (from relapse or death), or did so because they accepted randomization in the duration trial to stop at 5 years (Fig. 1). It is of interest that eight of 155 patients taking tamoxifen for more than 12 years were in the control arm, despite having started tamoxifen because of disease relapse.

The number of patients whose disease has relapsed and the number of patients who have died in each arm of the trial are given in Table 1. It is of interest that 230 patients have died from other causes without relapse of disease. Cumulative survival curves are given in Fig. 3. Survival was increased statistically significantly; hazards of death from all causes, from death caused by breast cancer, and from the combined end point of systemic disease or death from any cause were statistically significantly reduced in those given tamoxifen immediately compared with those given delayed tamoxifen after the first disease relapse.

Table 1. Main trial: numbers of patients with and without relapse of disease and whether known to have died or not

<table>
<thead>
<tr>
<th></th>
<th>Adjuvant arm (n = 666)</th>
<th>Control arm (n = 656)</th>
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<tr>
<td></td>
<td>Total</td>
<td>Adjuvant tamoxifen</td>
</tr>
<tr>
<td>Relapsed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>242</td>
<td>232</td>
</tr>
<tr>
<td>Alive</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>No relapse</td>
<td>123</td>
<td>120</td>
</tr>
<tr>
<td>Alive</td>
<td>265</td>
<td>258</td>
</tr>
<tr>
<td>Total</td>
<td>666</td>
<td>644</td>
</tr>
</tbody>
</table>
Fig. 3. Main trial. A) Total survival, with numbers of patients at risk (deaths from all causes included). B) Survival, with numbers of patients at risk (only breast cancer deaths included). C) Survival free of systemic (including contra-lateral) disease. HR = hazard ratio; CI = 95% confidence interval; p = probability by two-tailed log-rank testing.
recurrence. In Fig. 3, A and C, there is a suggestion of non-proportionality, with the curves coming together at the end of the follow-up period. In contrast, the survival curves, based on breast cancer deaths (Fig. 3, B), do not show any appreciable convergence.

**Duration Trial**

Only patients entering the main trial after March 1, 1980, who were free of disease at 5 years were eligible for inclusion in the duration trial. Thirty-two patients otherwise suitable for randomization who entered the main trial before March 1, 1980, were thereby lost to the duration trial. Three hundred forty-two of the remaining 399 eligible patients agreed to the second randomization to stop tamoxifen or to continue the drug for as long as they remained disease free. Fifteen of the 169 patients who were randomly assigned to stop and two of the 173 patients who were randomly assigned to continue adjuvant tamoxifen refused to comply with their randomly assigned option (Fig. 1). These 17 noncomplying patients have been included in the analyses as randomly assigned. The median duration of adjuvant tamoxifen, from first randomization until this update, was 60 months (range = 56–205 months) for the 169 patients randomly assigned to stop tamoxifen at 5 years and 163 months (range = 58–205 months) for the 173 patients allocated to the continue arm. Although 49 patients of this latter group remain on the drug, 52 stopped taking it while still disease free. The remaining 72 patients either had a relapse (49 patients) or died without relapse (23 patients) while still taking tamoxifen.

The current status of patients included in the duration trial is given in Table 2, and the cumulative survival curves are shown in Fig. 4. These data show no disadvantage for patients who were randomly assigned to stop tamoxifen at 5 years compared with those who were randomly assigned to continue. The supplementary analysis based on treatment actually received beyond 5 years (183 patients stopped versus 248 patients continued; Fig. 1) also did not indicate any advantage from continuing adjuvant therapy (data not shown). Fig. 5 is presented to complete the information available according to subgroupings of the patient population. Because of the small numbers in each subgroup, Fig. 5 cannot be interpreted reliably but may be of value for merging with similar data from other trials.

**Other Malignancies**

Table 3 gives the numbers of patients within each arm of the main trial who have developed other primary malignancies. There are weak trends suggesting that tamoxifen has protected against contralateral breast cancer and has increased the risk of endometrial cancer, but these data do not approach statistical significance. There is also a small statistically insignificant increase in cancers affecting the gastrointestinal tract. In addition, among the 295 patients who received tamoxifen for more than 66 months, there were seven cases of endometrial cancer and nine cases of colorectal cancer, suggesting that these increased risks could be related to duration of usage.

**DISCUSSION**

This update of the main Scottish Adjuvant Tamoxifen Trial indicates that the beneficial effect of adjuvant tamoxifen, when prescribed for 5 years to patients with operable breast cancer, persists for 15 years.

In updating the status of those patients who were last recorded as alive prior to 1996, variations in the method of data collection for this analysis have been unavoidable. With increasing age (seven patients in the trial are now older than 85 years), cessation of regular hospital review, changes of name and address, and an inevitable increase in unrelated illnesses, follow-up becomes more difficult. Despite these problems, with invaluable cooperation from general practitioners, only 21 patients could not be traced. Ten of these patients were known to have left Scotland. The remaining 11 patients had a median follow-up of 12 years.

In accordance with our previous practice (4), contralateral breast cancers have been handled as systemic disease in the survival analyses, while still being recorded as new primary tumors (Table 3). To date, only nine of the 48 patients have died without other evidence of recurrence. Consequently, the effects on Fig. 3, B, are minimal. If these contralateral tumors had not been treated as systemic recurrences, the effect on Fig. 3, C, would be to produce a slight narrowing of the difference between the two curves that would not affect the statistical significance of the conclusion.

This update also confirms our earlier finding that no additional benefit from tamoxifen accrues from continuation of the drug beyond 5 years. Indeed, the direction of the (statistically nonsignificant) difference in survival suggests a benefit from stopping tamoxifen at 5 years. The absence of a benefit from continuing beyond 5 years is in keeping with the report of the larger National Surgical Adjuvant Breast and Bowel Project trial in which the period of follow-up was shorter (5). Several other ongoing multicenter trials may determine optimal duration more precisely. However, the results of the Swedish trial, which reported that a 5-year treatment with tamoxifen gave better disease control than a 2-year treatment (6), would suggest that prescribing adjuvant tamoxifen for 5 years is reasonable in the meantime. This view is also supported by the results of the overview of tamoxifen trials (7). As indicated in other reports (7,8), for patients receiving tamoxifen, the number developing independent cancers in the contralateral breast decreased and the number developing endometrial cancer increased.

The results of this update indicate that, as a result of prescribing adjuvant tamoxifen, 48 fewer patients (242 patients versus 290 patients) have died from breast cancer over a median period of 15 years—a relative reduction in the proportion of deaths of 17.8%. However, when deaths from all causes were considered, the proportionate reduction (352 in the tamoxifen arm versus 397 in the control arm) was less (12.8%).

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**Table 2. Duration trial: numbers of patients with and without relapse of disease and whether known to have died or not**

<table>
<thead>
<tr>
<th></th>
<th>“Stopped” group (n = 169)</th>
<th>“Continued” group (n = 173)</th>
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<tr>
<td></td>
<td>Total</td>
<td>Agreed</td>
</tr>
<tr>
<td><strong>Relapsed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Alive</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td><strong>No relapse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Alive</td>
<td>103</td>
<td>95</td>
</tr>
<tr>
<td>Total</td>
<td>169</td>
<td>154</td>
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Fig. 4. Duration trial. A) Total survival, with numbers of patients at risk (deaths from all causes included). B) Survival, with numbers of patients at risk (only breast cancer deaths included). C) Survival free of systemic (including contralateral) disease. HR = hazard ratio; CI = 95% confidence interval; p = probability by two-tailed log-rank testing.
REFERENCES


NOTES

Sources of funding, for administration only, included the Cancer Research Campaign, the Medical Research Council, ICI Ltd., and the Hartwell Trust Fund (University of Edinburgh).

We are grateful to Linda Lockerbie and Ruby Wood for statistical and secretarial assistance and to all those assisting with the provision of data.

H. J. Stewart was the Director, Scottish Cancer Trials Office (Medical Research Council) until it closed in 1997.

Manuscript received August 17, 2000; revised January 4, 2001; accepted January 12, 2001.