Switching to an Aromatase Inhibitor Provides Mortality Benefit in Early Breast Carcinoma

Pooled Analysis of 2 Consecutive Trials

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RESULTS. In all, 828 postmenopausal women, mostly with estrogen receptor (ER)-positive and node-positive tumors who had been monitored for a median time of 78 months (range, 6–141 months) were analyzed. Of these women, 415 were randomly selected to continue tamoxifen and 413 switched to aminoglutethimide or anastrozole. All-cause mortality and breast cancer-specific mortality were significantly improved by the switch: all-cause mortality: hazard ratio (HR) = 0.61 (0.42–0.88) \( P = .007; \) breast cancer-specific mortality: HR = 0.61 (0.39–0.94) \( P = .025. \) No increase was recorded in breast cancer-unrelated mortality in women after switching. Multivariate analysis showed that patient age, tumor size, allocated treatment, and nodal status, in that order, were independent mortality predictors.

CONCLUSIONS. Switching to an aromatase inhibitor after 2 or 3 years of tamoxifen therapy significantly improves survival compared with continuing 2 or 3 years of additional tamoxifen treatment. *Cancer* 2007;109:1060–7.

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For many years tamoxifen has represented the gold standard adjuvant treatment for endocrine-responsive early breast cancer.\(^1\)\(^2\) A recent article on the effect of hormonal therapy on recurrence and 15-year survival of early breast cancer has confirmed that, for estrogen receptor (ER)-positive women, about 5 years of adjuvant tamoxifen therapy maintains a strong effect on the risk of tumor recurrence and reduces the annual breast cancer death rate by 31%.\(^3\) However, even though there was a comparable effect on all-cause mortality, resulting in an advantage in women who had received tamoxifen vs those who had not, there was also evidence that the prolonged use of this drug might increase the death rate due to other causes, such as vascular-related strokes or thromboembolic diseases, and other tumors other than breast cancer.\(^3\)

Several trials have shown that new generation aromatase inhibitors can further decrease the risk of recurrence in women with ER-positive breast cancer\(^4\)\(^–\)\(^10\) either when used upfront, instead of tamoxifen, or when given in sequence after 2 or 3 years of tamoxifen therapy or at the end of adjuvant treatment with 5 years of this antiestrogen. These trials, however, are not comparable to each other due to the fact that they differ in design, trial size, patient selection, aromatase inhibitor type and schedule, follow-up duration, and result maturity.

Nevertheless, a benefit of an additional 20% to 40% decrease in the recurrence risk has been reported for women receiving upfront, sequential, or extended treatment with an aromatase inhibitor compared with those given or continued with tamoxifen. However, no evidence of a comparable clinical benefit in mortality reduction has emerged so far from the 2 extensive studies that have demonstrated the superiority of 5-year upfront treatment with either anastrozole\(^4\) or letrozole.\(^5\) In contrast to upfront studies, a small but significant mortality benefit arises from the most recent analysis of 2 of the 4 switching trials, including a large multinational trial with exemestane.\(^11\)\(^12\) A mortality benefit, especially in node-positive women, also arises from the most recent analysis of the MA-17 trial, although it appears to be limited to the women in the placebo group who, after unblinding, choose to be switched to letrozole.\(^13\)

Since 1992 our group has been involved in developing a switching approach, as we presumed that this strategy would be superior to the standard approach of using only tamoxifen therapy. The benefit in mortality, favoring the switching strategy, was demonstrated by the first mature analysis of the former of the 2 studies performed by us in this framework.\(^14\) The latter trial adopted the same design with anastrozole (ANA), a more potent aromatase inhibitor, in place of aminoglutethimide (AG). The preliminary analysis of this study showed a significant difference between groups in relation to both event-free and recurrence-free survival in favor of the women who switched to ANA. However, no statistically significant mortality benefit was shown by this analysis.\(^6\)

The purpose of this present study was to further and fully investigate the effect of switching on patient mortality by way of a pooled analysis of our 2 trials.

MATERIALS AND METHODS

Trial Designs

The GROCTA 4B trial was conducted on 380 patients who were enrolled between September 1992 and January 1998. The details of this trial, including the reasons for interrupting patient recruitment and the results at a median follow-up time of 61 months, have been previously published.\(^14\) The results were updated...
when the median follow-up time was 104 months (range, 6–141 months) and mortality data utilized for the present analysis. In summary, women on tamoxifen treatment for an average of 3 years were centrally randomized to continue tamoxifen (TAM) at the same dose as previously for a further 2 years or to receive alternative treatment with AG at a daily dose of 250 mg for a comparable period of time.

The ITA trial, conducted between March 1998 and December 2002, enrolled 448 women according to an identical design with ANA instead of AG at a daily dose of 1 mg. The details of this latter trial have also been previously published.6 The patient mortality data utilized for the present analysis are that of the most recent analysis (median follow-up time, 64 months; range, 12–93 months) which forms the subject of a separate publication.15

The pooled analysis of the 2 trials was prospectively planned at the time the ITA trial was designed.6

Patient Population
Postmenopausal women, including those who had become irreversibly amenorrheic as a consequence of previous chemotherapy, were entered into both trials, provided they had ER-positive tumors. The patients selected also had a node-positive disease (even though a small proportion of 'high risk' node-negative women were allowed to be recruited into the GROCTA 4B trial) but no major contraindications in receiving alternative treatment with AG or ANA. In addition, they had to be able to guarantee an adequate compliance to the follow-up plan. Details can be found in the previous publications.6,14

Ethical Aspects
All patients were informed about the experimental nature of the respective trials and were asked to give their written consent. Both trials were approved by the local Ethics Committee at each participating center.

Study Endpoints
Mortality, irrespective of the cause, was the primary endpoint of the present analysis. Information about the vital status of patients was obtained by way of consulting flow charts of the women being monitored. Visits were scheduled every 3 months for the first 3 years after the randomized selection, every 6 months from year 3 to year 5, and thereafter on an annual basis. The vital status of women failing to attend the clinic for more than 1 year, or who had, for some reason, not been followed up, was checked directly by phone and/or by consulting local tumor registries if available, or the registry office of the location of residence.

For the purpose of the present analysis, deaths occurring after documented disease recurrence were arbitrarily defined as “breast cancer-related,” whereas those occurring before disease recurrence could be appropriately documented were defined arbitrarily as “breast cancer-unrelated.” The causes of death were recorded whenever possible.

Statistical Methods
Mortality curves were constructed using the Kaplan-Meier method and the groups compared by way of the log-rank test.17 To evaluate the role of the main prognostic factors, Cox proportional hazard models were fitted to all-cancer mortality, breast cancer-related mortality, and breast cancer-unrelated mortality.18

Assigned treatment, tumor size (≤2 cm vs >2 cm), tumor grade (G1-G2 vs G3 vs Gx: undetermined or missing information), number of involved nodes (zero vs 1–3 vs >3), treatment of primary (mastectomy vs mastectomy plus irradiation of the chest wall vs QUAD/tumorectomy plus axillary dissection and irradiation of the residual breast), prior adjuvant chemotherapy (no vs yes), and age (<65 years vs ≥65 years) were the covariates included in all models. All statistical tests were 2-sided. In addition, survival plots were generated in order to analyze data on both an individual trial basis and both trial basis. SPSS software (v. 10.0 for Windows, Chicago, IL) was used for all statistical analyses.

RESULTS
The present analysis includes a total of 122 deaths in 828 women monitored for a median time of 78 months (range, 6–141 months). Four hundred and fifteen of these women had been randomly selected for the continuation of tamoxifen and 413 switched to either AG or ANA. As shown in Table 1, treatment groups were well-balanced with respect to age at randomization, tumor size and grade, nodal status, local treatment, prior treatment with adjuvant chemotherapy, and median time on tamoxifen at randomization.

There were 74 deaths recorded in the women allocated to continue tamoxifen, 51 of which were breast cancer-related (according to the previous definition) and 48 deaths in the women who had switched to either AG or ANA, 33 of which were breast cancer-related. Causes of death are detailed in Table 2. Mortality curves and mortality hazard reductions are reported in Figures 1A–C and 2.

All-cause mortality (HR = 0.61 [0.42–0.88] P = .007) and breast cancer-related mortality (HR = 0.61 [0.39–0.94] P = .025) was significantly improved in women who switched to AG or ANA. On the contrary, even
though more women in the tamoxifen group appeared to have died in the absence of obvious disease recurrence, there was no significant difference between groups in breast cancer-unrelated mortality.

The probability of death increased over time both for the women who died after breast cancer recurrence and for those who died before disease recurrence. However, the average time before death was about double for women in the latter group compared with those in the former group (average time before death being 96 and 54 months, respectively).

Multivariate analysis (Table 3) shows that patient age, tumor size, allocated treatment, and nodal status, in that order, were independent predictors of the risk of dying for all the patients monitored. Tumor size, nodal status, and allocated treatment maintained their predictive value also with respect to breast cancer mortality, whereas age at randomiza-
tion was the only statistically significant predictor of breast cancer-unrelated mortality.

DISCUSSION
This pooled analysis has several strengths. It was planned 'a priori' at the time the ITA trial was designed and with regard to the 2 trials performed by 1 collaborative group sharing the same design and comparable selection criteria. In addition, it includes a relatively large number of patients (more than 800) and the median follow-up time was quite long for both studies included. Thus, the results are quite mature.

However, it must be said that the study suffers from weaknesses as well. Both our trials were concluded without having reached the planned recruitment size and, therefore, we note that each of them lacks the adequate statistical power to correctly analyze the impact on mortality of switching. The reasons for trial closure have been detailed previously.6,14 However, it is not to be undervalued that the slow recruitment rate and the availability of a new, more potent aromatase inhibitor like anastrozole played a major role in interrupting recruitment in the GROCTA4B trial. The problem of 'slow recruitment' was also a reason for trial closure in the case of the ITA trial.6 However, in this case we should also consider the role played by the interim analysis of efficacy performed by our group soon after the release of the preliminary results of the ATAC trial, showing the superiority of switching to anastrozole. This interim analysis prompted trial investigators to consider that it might no longer be ethical to allow trial entry. However, they decided to keep the patients randomly assigned to tamoxifen on this antiestrogen, first, because only 33% of these patients were still receiving this treatment and most of them were expected to discontinue it within a few months and, second, due to the very preliminary nature of the results achieved by available trials with aromatase inhibitors and the lack of any actual evidence of mortality benefit.4,7,10 The lack of a strict standardization of treatment for recurring patients might be a further source of bias for a mortality analysis, as in
our case. However, administering an aromatase inhibitor to patients relapsing after 5 years of tamoxifen is not likely to represent a major confounding factor in this case. In fact, 32% of the women who continued with tamoxifen in the GROCTA 4B trial received an aromatase inhibitor on recurrence. It is also worth noting that 27% of the women who switched to AG were also rechallenged with an endocrine treatment (including third-generation imidazolic or steroidal aromatase inhibitors) on recurrence in this trial. Comparative figures are not available for the women recruited to the ITA trial. However, both trials were performed by the same collaborative group and there is very little risk, if any, that treatment policy of recurring patients might have changed from 1 trial to the other. Moreover, the results of the most recent overview of adjuvant tamoxifen trials show a clear carryover effect of the tamoxifen treatment also with respect to mortality, suggesting that the survival advantage seen in these patients is more likely to be the early use of tamoxifen rather than that related to the treatment selected at the time of recurrence. Finally, AG was employed in the GROCTA 4B trial. This drug is no longer used in the treatment of breast cancer and, given the low dose employed in our previous trial, it should be expected to be much less effective than a more potent and selective compound like ANA, the inhibitor tested in the ITA trial.

This might explain the different effect of switching on breast cancer-related mortality observed in the 2 studies, and the finding that this effect was greater and statistically significant only for the patients who switched to anastrozole in the ITA study.

Although the number of breast cancer deaths recorded so far in this trial was smaller than in the GROCTA 4B trial due to the shorter duration of follow-up, it is worth noting that there was no difference between the 2 studies in the interaction of treatment with the aromatase inhibitor, either AG or ANA, with breast cancer-related mortality. In fact, a clear benefit of breast cancer-related mortality was achieved by switching in both trials. It is also of importance to consider that both all-cause and breast cancer-related mortality

### TABLE 3
Multivariate Analysis of Mortality

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality</th>
<th>Breast cancer-related mortality</th>
<th>Breast cancer-unrelated mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAM*</td>
<td>1.0</td>
<td>.016</td>
<td>1.0</td>
</tr>
<tr>
<td>AG/ANA</td>
<td>0.64 (0.44–0.92)</td>
<td>0.003</td>
<td>0.65 (0.41–1.00)</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2 cm</td>
<td>1.0</td>
<td>.003</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
<td>1.88 (1.23–2.85)</td>
<td>2.03 (1.21–3.43)</td>
<td>1.60 (0.79–3.25)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1-G2</td>
<td>1.0</td>
<td>.006</td>
<td>1.0</td>
</tr>
<tr>
<td>G3</td>
<td>1.21 (0.71–2.05)</td>
<td>1.04 (0.55–1.95)</td>
<td>1.77 (0.69–4.58)</td>
</tr>
<tr>
<td>Gx undetermined (lobular carcinoma) or missing information</td>
<td>1.69 (1.10–2.59)</td>
<td>1.56 (0.93–2.62)</td>
<td>1.97 (0.93–4.20)</td>
</tr>
<tr>
<td>No. involved nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
<td>.02</td>
<td>1.0</td>
</tr>
<tr>
<td>1-3</td>
<td>1.38 (0.75–2.51)</td>
<td>1.65 (0.72–3.78)</td>
<td>1.10 (0.45–2.66)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>2.16 (1.15–4.04)</td>
<td>3.12 (1.34–7.27)</td>
<td>1.09 (0.38–2.99)</td>
</tr>
<tr>
<td>Treatment of primary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>1.0</td>
<td>.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Mastectomy plus irradiation of the chest wall</td>
<td>0.87 (0.37–2.05)</td>
<td>0.97 (0.38–2.48)</td>
<td>0.61 (0.08–4.76)</td>
</tr>
<tr>
<td>QUAD/tumorectomy plus axillary dissection and irradiation of residual breast</td>
<td>0.78 (0.51–1.18)</td>
<td>0.76 (0.46–1.26)</td>
<td>0.80 (0.39–1.67)</td>
</tr>
<tr>
<td>Prior adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td>.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>0.91 (0.59–1.42)</td>
<td>1.06 (0.64–1.78)</td>
<td>.57 (0.23–1.41)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>1.0</td>
<td>.002</td>
<td>1.0</td>
</tr>
<tr>
<td>≥65 years</td>
<td>1.88 (1.27–2.78)</td>
<td>1.50 (0.94–2.37)</td>
<td>3.38 (1.51–7.57)</td>
</tr>
</tbody>
</table>

* TAM indicates women who continued with tamoxifen.

1 AG/ANA indicates women who switched to aminoglutethimide or anastrozole.
mortality benefits achieved by switching were still statistically significant even after multivariate analysis by patient age, tumor size and grade, nodal status, and prior local and/or systemic treatment.

The analysis of breast cancer-unrelated mortality is more complex for several reasons. First, because, as previously noted, the 2 trials differ in their median duration of follow-up. This aspect might be crucial for this type of estimation as we have shown that, overall, median time to death for women who apparently died in the absence of proven disease recurrence was about double that of women who died after breast cancer recurrence. Second, because cardiovascular events represent the actual and sole cause of death reported on most death certificates, it might well be that in both trials breast cancer-related deaths have been misclassified and the incidence of cardiovascular deaths has been overestimated. In addition, the lack of information on most of the patients enrolled in our 2 trials on factors such as, for example, being overweight, diet, smoking habits, physical activity, hypertension, and diabetes, which are recognized as risks of cardiovascular mortality, might also represent a further source of bias. On the basis of what has been previously reported for long-term tamoxifen trials, one would expect that switching from tamoxifen to an aromatase inhibitor would imply a decrease in death due to strokes. Indeed, this was the case in the combined analysis. However, we also observed fewer cardiovascular deaths among women who switched to the aromatase inhibitor and, more important, there were fewer lethal cardiac ischemic events, in spite of the progressive increase in plasma cholesterol levels reported in these women in the ITA trial (this information was not available for the GROCTA 4B trial women).

Our findings in this regard should be considered with particular caution both on the basis of the small numbers involved and the previous considerations, together with the finding that instead a higher incidence of cardiac ischemic deaths was reported by BIG-98 trial investigators. However, it should not be underestimated that no increase in cardiac ischemic events was reported in any of the other adjuvant trials with aromatase inhibitors reported so far. Recently, a reduced risk of acute myocardial infarction or angina among tamoxifen users resulted from a nested case-control study reported by Bradbury et al. Even on the basis of these findings, and of the known hypolipidemic effects of tamoxifen, one would expect more ischemic cardiac deaths among the women who switched to the aromatase inhibitor in our trials. However, the Bradbury et al study shows that the protective effect of tamoxifen was statistically significant only in current tamoxifen users. In both our studies, all patients randomized to continue tamoxifen had discontinued this treatment at the time of the present analysis and it is worth noting that the slight increase in breast cancer-unrelated mortality risk observed in the ITA trial among the women switched to ANA was exclusively due to just 1 more death caused by a homicide.

In conclusion, this pooled analysis provides solid evidence that switching to an aromatase inhibitor after a few years of tamoxifen treatment implies a mortality benefit over continued tamoxifen and that the benefit on breast cancer-related mortality is mainly due to the effect of switching. Although the numbers are small and the findings are likely to be less reliable in this regard, our analysis also appears to exclude that switching might result in an increased risk of death for causes other than from breast cancer, namely, for cardiovascular events.

The present data and mortality benefits emerging from the most recent reports of the other switching trials, together with those from a recent metanalysis of the 3 switching trials with ANA (which includes the ITA trial as well), reinforce the indication of early switching to an aromatase inhibitor in women presently receiving adjuvant treatment with tamoxifen.

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