

EDITORIALS



Letrozole after Tamoxifen for Breast Cancer — What Is the Price of Success?

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In this issue of the *Journal*, Goss et al.¹ report results from a trial that will have a considerable effect on the treatment of early-stage breast cancer. The study was led by the National Cancer Institute of Canada Clinical Trials Group and was a joint effort of the North American Intergroup and the Breast International Group. These organizations are to be commended for a well-conceived and well-conducted clinical trial. Their work is an excellent example of the way in which clinical-trial organizations can work together efficiently and expeditiously to investigate clinical questions of common interest.

Previous trials have shown that a five-year course of treatment with tamoxifen, an antagonist of the estrogen receptor, is effective in reducing the risk of recurrence or new breast cancers in women with hormone-receptor-positive tumors who have undergone successful primary treatment for early breast cancer. After five years of therapy, however, continued tamoxifen treatment has not been shown to provide additional benefit. The placebo-controlled study by Goss et al. investigated whether postmenopausal women with hormone-receptor-positive tumors who have completed five years of tamoxifen therapy would benefit from treatment with letrozole, an aromatase inhibitor that blocks the synthesis of estrogen.

At the first interim analysis, with a median follow-up of 2.4 years, 207 events had been reported in 5157 women — 75 in the letrozole group and 132 in the placebo group. The rates of locoregional recurrence, contralateral breast cancer, and distant recurrence were all reduced. On the basis of these results, the data and safety monitoring committee recommended that the findings be made public, the participants be informed of their treatment, and

women who had received placebo be given the opportunity to cross over to letrozole therapy.

The estimated magnitude of the benefit (a 43 percent reduction in the hazard of a recurrence or new contralateral breast cancer, corresponding to an absolute difference of 5 percent in disease-free survival after three years of follow-up) was substantially greater than expected. This finding is remarkable, given the well-known carryover effect of tamoxifen: in the five-year period immediately after the cessation of tamoxifen therapy, the rate of recurrence continues to be reduced by 30 percent relative to what would have been expected had tamoxifen not been administered.² Accordingly, it was anticipated by many that the initial effect of letrozole therapy after tamoxifen therapy would be moderate, with increased benefits becoming evident only with longer follow-up.

It is important to examine critically the interim analysis in this study. During the past five years, the results of several other breast-cancer trials have been made public after early interim analyses; these releases have evoked skepticism about the appropriate use of early-stopping rules. In the study by Goss et al., the interim analysis was conducted strictly according to protocol. The use of the Lan-DeMets alpha spending function, in conjunction with O'Brien-Fleming boundaries, was stipulated in the study protocol and was applied appropriately. Furthermore, the primary end point (the time to a first recurrence or new contralateral breast cancer), the number of events required to trigger the interim analysis, and the specific statistical tests used in the interim analysis were all specified a priori. Since the O'Brien-Fleming boundary was crossed by a substantial margin, we must concede, perhaps reluc-

tantly, that the recommendation of the data and safety monitoring committee that the data be released early was justified. In fact, because the model consent form for this study included the statement "If new side effects or information about my disease or treatment are discovered during the study, I will be told," one might argue that early disclosure not only was justified but also was actually dictated by the rules of the study.

On the other hand, the decision to close the study after a median follow-up of only 2.4 years, to inform all participants of the findings and the treatment they received, and to offer letrozole to the women who were originally assigned to placebo undeniably diminishes the clinical usefulness of the data. Moreover, the primary aim of the study was not fully achieved — namely, "to determine the disease-free survival and overall survival for women who have previously received ≥ 5 years of adjuvant tamoxifen randomized to receive either letrozole 2.5 mg daily or placebo daily for five years."³ Although the current report does show a relative reduction of 24 percent in the hazard of death from any cause in the letrozole group as compared with the placebo group, this reduction was not statistically significant ($P=0.25$), and it is possible that a survival advantage will never be documented, since ongoing follow-up will be confounded by crossover. Nor can the findings be used to support a recommendation of five years of letrozole treatment, since none of the participants have been followed that long. Indeed, only about one quarter of the patients have been followed for the analysis of efficacy for 30 months or more, and follow-up for adverse events has been even shorter. Thus, although the results demonstrate a meaningful biologic effect of letrozole therapy after tamoxifen therapy, they do not demonstrate a significant survival benefit, nor do they convey information about the optimal duration of treatment beyond two to three years. It is not even possible to quantify the magnitude of a potential benefit with respect to disease-free survival, not only because of the small number of events that have been reported to date, but also because of uncertainty about the interval for which the treatment benefit may persist.

If we are to make clinically appropriate treatment decisions, we need data on adverse events to support risk-benefit analyses.⁴ Although the data on toxic effects summarized by Goss et al. indicate that letrozole is generally well tolerated, concern about the consequences of long-term use remains. It is possible that the long-term adverse effects associated

with letrozole therapy have been underestimated because of the early cessation of the study. An obvious problem is the possible increased risk of osteoporosis. Indeed, there were more self-reported diagnoses of osteoporosis in the letrozole group than in the placebo group ($P=0.07$), and there were statistically significant increases in the rates of arthritis, myalgia, and arthralgia. Another potentially disquieting long-term effect is the possible excess in cardiovascular events among women taking letrozole. It would have been of great value to have been able to follow the women over a period of years in comparison with a blinded placebo group.

Moreover, ongoing placebo-controlled trials of treatment with aromatase inhibitors after five years of tamoxifen therapy (Trial B-33 of the National Surgical Adjuvant Breast and Bowel Project [NSABP], Study 2002-05 of the Grupo Español de Investigación en Cáncer de Mama, and Study 6A of the Austrian Breast Cancer and Colorectal Cancer Study Group) are virtually certain to be modified or terminated in response to the announcement of these study results. Therefore, there may be no opportunity to collect data from a placebo-controlled trial that will help to evaluate the risks of long-term adverse events. It is sobering to recall that, at a similar stage in its development, tamoxifen was generally regarded as having a fairly innocuous adverse-event profile.

The decision to unblind the trial reported by Goss et al. was dictated by the protocol and by the ethical need to inform patients about evolving data that clearly indicated a benefit for letrozole therapy. In consequence critical information will be lost to the degree that the primary aim of the study will not be fully achieved. It is likely that in the coming months there will be much debate over whether the data and safety monitoring committee made the best decision. In the interest of full disclosure, it must be stated that we are not without vested interest, since we are involved in the ongoing NSABP trial (B-33), which is similar in design to the study by Goss et al. and which is evaluating the aromatase inhibitor exemestane; this trial is in peril as a consequence of the release of the data on letrozole. It might appropriately be asked what we would have done with our trial had we been faced with the same situation and the same magnitude of benefit shown in the letrozole trial. After the customary remonstrance, laced with a hint of self-righteous indignation, protesting that observation must be allowed to continue until its scheduled completion, most as-

surely we would have disclosed the data in precisely the same manner. An inescapable truism of randomized trials is that we are condemned to bear the burden and the limitations of our incremental successes.

It would be fruitful to reflect on how future protocols might avoid similar problems — for example, by explicitly recommending that the data and safety monitoring board should not generally stop a trial early except for reasons of safety if doing so would compromise a primary aim of the trial. The protocol document might also specify a minimal level of follow-up to be completed before allowing early reporting if the reason for early reporting is efficacy. The development and implementation of more realistic early-stopping rules that incorporate risk–benefit tradeoffs and that recognize the possibility of nonproportional hazards would presumably also be of value. However, by their nature, early-stopping rules will always be based on overly simplified models of reality and will never capture all elements of the decision-making process. The really difficult decisions will always have to be confronted with the use of judgment rather than template-generated algorithms.

How, then, should the results from this trial influence the standard of care? Should letrozole therapy now be required after five years of tamoxifen therapy? At a minimum, suitable patients must be apprised of these important observations and must be given the opportunity to receive letrozole, with an understanding of the limitations of the data.

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2. Presented at the Early Breast Cancer Trialists' Collaborative Group Meeting, Oxford, England, September 21–23 2000.
3. A phase III randomized double-blind study of letrozole versus placebo in women with primary breast cancer completing five or more years of tamoxifen. Kingston, Ont., Canada: National Cancer Institute of Canada Clinical Trials Group, April 10, 2003.
4. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst* 1999;91:1829-46.

Beyond Tamoxifen — Extending Endocrine Treatment for Early-Stage Breast Cancer

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Five years of tamoxifen therapy is the standard adjuvant endocrine therapy for early-stage, hormone-receptor–positive breast cancer.^{1–3} Randomized trials have demonstrated the superiority of five years of treatment over shorter durations for the prevention of a recurrence,^{4,5} as well as a carryover effect that lowers the risk of recurrence for a decade after the completion of five years of tamoxifen therapy and reduces the incidence of contralateral breast cancer. By contrast, several randomized trials have shown that continuing tamoxifen therapy for longer than five years does not improve recurrence-free or overall survival^{6–9} and have raised the disturbing possibility that such a strategy might be deleterious.

Even after five years of tamoxifen therapy, women are at risk for a recurrence in the ipsilateral breast, new tumors in the contralateral breast, and distant metastases. These new events occur at an aggregate rate of 2 to 3 percent per year. Since most of these

recurrent or new tumors express hormone receptors, they may be sensitive to further endocrine manipulations. It is against this background that the results of the letrozole trial, led by the National Cancer Institute of Canada on behalf of several cooperative groups and the pharmaceutical company Novartis and reported by Goss et al.¹⁰ in this issue of the *Journal*, are greeted with interest. Letrozole, like other aromatase inhibitors, inhibits the peripheral conversion of androgens into estrogens and reduces the circulating levels of estrogens by more than 95 percent in postmenopausal women.¹¹ It has clinically significant activity in postmenopausal women with advanced breast cancer. The study by Goss et al. investigated whether extended adjuvant therapy with letrozole after five years of tamoxifen therapy confers a clinical advantage in patients with breast cancer. The question is of particular importance because postmenopausal women with hormone-