



Estrogen receptor positive early breast cancer: the long road

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Comment on: Ruhstaller T, Giobbie-Hurder A, Colleoni M, *et al.* Adjuvant Letrozole and Tamoxifen Alone or Sequentially for Postmenopausal Women With Hormone Receptor-Positive Breast Cancer: Long-Term Follow-Up of the BIG 1-98 Trial. *J Clin Oncol* 2019;37:105-14.

Received: 15 March 2019; Accepted: 27 March 2019; Published: 03 April 2019.

doi: 10.21037/abs.2019.03.02

View this article at: <http://dx.doi.org/10.21037/abs.2019.03.02>

The risk of recurrence with early estrogen receptor positive breast cancer continues for decades (1). Because of that risk, long-term follow-up (LTFU) from trials of adjuvant endocrine therapy is quite important. The recent report of the BIG 1-98 trial from Ruhstaller and colleagues (2) provides us with another opportunity to view breast cancer through a longer time course.

The BIG 1-98 trial randomized patients to 5 years of letrozole, 5 years of tamoxifen, 2 years of letrozole followed by 3 years of tamoxifen, and 2 years of tamoxifen followed by 3 years of letrozole (3).

The primary end point was disease free survival with relevant events defined as follows: recurrence at local, regional, or distant sites, new invasive contralateral breast cancer, any second non-breast cancer, or death without a prior cancer event.

BIG-1-98 was originally a Novartis sponsored study; however, funding for follow-up stopped at 8.4 years. Realizing the importance of additional follow-up, the academic partners in this study created and activated a LTFU cohort in 2011.

Unfortunately, some patients were not able to be part of the LTFU, so only 4,460 out of the original 8,010 trial patients were eligible. Eighty-six percent of that subgroup (3,833 patients) had at least one LTFU report and that group constituted the final study group with a median follow-up of 12.6 years.

The results of this study found that patients assigned to receive letrozole at any point had a 9% reduction in the hazard of a disease-free survival (DFS) event compared to tamoxifen alone and an 11% reduction in cancer mortality. Neither of these findings achieved statistical significance.

Letrozole therapy led to a decrease in contralateral breast cancer compared to tamoxifen in years 1–5, and for years 5–10, but not in years 10–15.

Reporting of long-term toxicity data remains an important endpoint with endocrine therapies. Adverse event reporting demonstrated no increase in fractures in the letrozole arm. No differences were seen between treatment arms for myocardial infarction or cerebrovascular events; however, as had been previously reported (4), more overall cardiac events were seen in the letrozole arm.

Disease free survival at 14 years was not significantly different between letrozole and tamoxifen at 62.9% *vs.* 60.2% (HR 0.91). Overall survival was also not significantly different, 72.9% with letrozole *vs.* 71.1% with tamoxifen. Breast cancer mortality was approximately 15% for both groups.

This is the fourth report of the BIG1-98 trial. How have the results changed over time? In the initial report on the BIG1-98 trial published in 2005 with median follow-up of 25.8 months, there was a 2.6% improvement in DFS for letrozole compared to placebo, mostly related to a 1.4% decrease in distant recurrence. This benefit was seen only in the higher risk, node positive group where there was a 6.5% increase in DFS (3).

In a subsequent report after a median follow-up of 51 months, there was a 2.7% improvement in DFS with Letrozole due to a 1.2% improvement in DDFS and 0.9% improvement in contralateral breast cancer (4). Five-year overall survival in the letrozole arm was 90.8% *vs.* 90.1% for tamoxifen.

Following the release of these results, patients still on active study therapy with tamoxifen were offered crossover

to letrozole. A proportion of 25.2% of the tamoxifen treated women crossed over prior to a primary end point event, with a greater percentage of node positive women crossing over (46.9%) compared to node negative women (29%) (5).

Given these results it is helpful to review several other adjuvant endocrine therapy studies which have reported long term follow-up results.

Cuzick and colleagues reported 10-year analysis of the ATAC trial with median follow-up of 120 months (6). They found a 4.3% improvement in DFS with anastrozole compared to tamoxifen with a 2.6% improvement in distant DFS. Interestingly, the greatest reduction was seen in the first 2 years. The reduction in contralateral breast cancers with anastrozole increased from 0.8% at 5 years to 1.7% at 10 years. Overall survival did not differ, 76.5% for anastrozole and 76% for tamoxifen. In this study there was minimal crossover to anastrozole.

More fractures were seen during the study in anastrozole treated patients; however, this effect did not carry over into the post treatment follow-up period, when rates were the same for both groups.

Another report with extended follow-up is the recent study by Goss and colleagues (7) who reported on extending aromatase inhibitor therapy out to 10 years. In their study, involving 1,918 patients, there was a median follow-up of 10.6 years at randomization and an additional 6.3 years of follow-up at the time of the study report. Seventy percent of patients had received 5 years of tamoxifen followed by 5 years of AI therapy prior to randomization between no further therapy and 5 additional years of AI therapy. Medication adherence was 62% in a group of patients that had already had at least 5 years of prior therapy and presumably had tolerated AI therapy well enough to be willing to continue.

The results of this study demonstrated a non-significant 3% overall decrease in recurrence or new contralateral primary favoring the AI arm. Importantly there was no difference in breast cancer specific survival with letrozole at 93% *vs.* placebo at 94%. There was better preservation of bone density and fewer fractures in the placebo arm.

Ruhstaller and colleagues are to be commended for recognizing the importance of LTFU and completing their study in spite of losing their industry support. In spite of the loss of a significant portion of the original study group they were still able to follow a substantial number of patients with over 83,000 patient years of follow-up. It is unclear how the significant crossover from tamoxifen to letrozole impacted the results; however, differences between the

therapies could have certainly been affected by crossover.

What can we learn from the long-term results of BIG 1-98 and similar studies?

First, events continue to occur after the 5- and 10-year marks, consistent with what we know about the natural history of this disease.

Second, AI therapy is highly effective in reducing the risk of contralateral breast cancer with continued benefit past the cessation of therapy, at least for 5 years.

Third, the benefit of AI therapy over tamoxifen seems to wane over longer follow-up with both BIG 1-98 and ATAC demonstrating significant benefit primarily in the first 2 years. Delineating breast cancer events that ultimately affect morbidity and mortality is important since a significant proportion of the DFS benefit in these studies comes from reductions in contralateral breast cancers, whose impact on mortality may be negligible.

Ultimately the decisions regarding adjuvant endocrine therapy should be made on efficacy and safety. Another factor that may be the most important of all is tolerability. High rates of non-compliance have been reported for AI therapy (8) with 40% or more of patients failing to take their medication as prescribed. The 62% compliance rate reported by Goss, in what could be argued is a group that was highly selected for likely medication compliance, illustrates this point.

Given the uncertainties of benefit from prolonged AI therapies (9-13) and the apparently modest survival benefits from standard duration AI therapy, perhaps we should rethink our treatment strategies and look to minimize AI toxicities such as fractures, which can be reduced by limiting AI exposure (BIG 71 M), and urogenital effects which often have major impact on the quality of life for breast cancer survivors.

Hopefully, in the future, additional guidance from biomarkers will allow us to refine our approach to patients with early, estrogen receptor positive breast cancer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Ji-Qiao Yang (West China Hospital, Sichuan University, Chengdu, China).

Conflicts of Interest: The author has completed the ICMJE

uniform disclosure form (available at <http://dx.doi.org/10.21037/abs.2018.01.01>). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/abs.2019.03.02

Cite this article as: Cole JT. Estrogen receptor positive early breast cancer: the long road. *Ann Breast Surg* 2019;3:7.