CORRESPONDENCE

Anastrozole Is Superior to Tamoxifen as First-Line Therapy in Hormone Receptor–Positive Advanced Breast Carcinoma

I was surprised to read the recent article by Bonneterre et al.[1] The data presented in that article are the result of a retrospective analysis of a selected number of patients from two already published clinical trials that had previously reported conflicting results. The North American trial[2] had reported a significant advantage for anastrozole over tamoxifen in time to progression (median TTP: 11.1 vs. 5.6 months, respectively), whereas the larger European trial[3] did not show a significant improvement (median TTP: 8.2 months for anastrozole vs. 8.3 months for tamoxifen). This discrepancy was rationalized based on the fact that the North American trial enrollment was about 85% hormone receptor–positive patients, compared with about 44% in the European trial. However, statistical significance appears not to have been reached either in this subgroup in the European trial (TTP: 8.9 months for anastrozole vs. 7.8 months for tamoxifen).[3] Of further concern is the trend toward a worse TTP in the European trial in patients with receptor-unknown tumors (7.3 months with anastrozole compared with 8.3 months with tamoxifen).

In the European trial, *P* values were not provided for the subgroup analyses, and we can only infer from the data. However, notwithstanding that any retrospective analysis, even from a prospective trial, does not create Level I evidence, but at best Level III evidence, and as such weakens the conclusions that one can draw from the data,[4] it was resolved to combine the data from both trials to give more power to the analysis. The need for such a strategy appears questionable since neither trial was designed as a superiority trial in the first place, but as an equivalence trial. As prospectively planned, both trials achieved their primary objective, namely to show equivalence of tamoxifen and anastrozole. Although, statistically speaking, this is the only allowable conclusion, both the paper by Bonneterre et al.[1] and the original publications attempt to show superiority, and the latter have been criticized for this.[5,6] In the retrospective analysis, the conclusions of superiority that are reached are inconsistent with those from the original prospective trials, and they do not explain why the North American trial succeeded in achieving statistically significant superiority in hormone receptor-positive patients whereas the European trial did not although both trials enrolled a similar number of such patients (145 vs. 156 for anastrozole and tamoxifen, respectively, in the former, and 153 vs. 144 for anastrozole and tamoxifen, respectively, in the latter). An additional concern about the claim that anastrozole is superior to tamoxifen is the lack of survival data in the article, although the two-year survival data for both studies are available on the Food and Drug Administration web site.[7] In fact, the Center for Drug Evaluation and Research Medical Review reports less

favorable survival data for anastrozole compared with tamoxifen in both trials. In that report, two-year survival was 57.7% for the North American trial and 67.9% in the European trial for anastrozole, compared with 61.2% and 73.3% for tamoxifen, respectively. In the retrospective analysis under discussion, it would have been appropriate to show Kaplan-Meier estimates of TTP and survival in patients who had received previous adjuvant treatment with tamoxifen, because such patients who develop metastatic disease are encountered increasingly frequently in clinical practice.

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Author Reply

With regard to our previous article,[1] the author of the current letter is correct in his comments that while the North American trial (0030) showed a significant advantage for anastrozole over tamoxifen for time to progression (TTP),[2] the European trial (0027) did not.[3] It is our belief that this difference is mainly due to the imbalance in the number of patients with confirmed hormone-receptor positive tumors between these two trials (89% vs. 45%). In trial 0027, treatment with anastrozole was associated with increased TTP (8.9 vs. 7.8 months) in the 45% of patients with confirmed hormone receptor-positive tumors. However, no statistical analysis of these data was performed as both studies were prospectively designed for combined data analysis, and it was considered more appropriate statistically to perform subgroup analyses on the larger combined data set. Regarding the author's concern about the trend toward a lower TTP in the anastrozole group compared with the tamoxifen group in trial 0027, since receptor status was unknown in this subgroup, it is possible that patients with receptor positive disease may be distributed unequally between the two groups. Thus, one cannot compare the unknown subgroup with any meaningful certainty.

This combined data set for the hormone-receptor positive subgroup across both trials showed a statistically significant advantage in favor of anastrozole for TTP ($P = 0.022$). It was clearly stated within our article that the subgroup analysis was retrospective; however, we felt it was essential to emphasize strongly the importance of determining tumor hormonal receptor status before deciding on treatment strategy. In this context, for patients who were appropriate candidates for endocrine therapy, anastrozole was superior to tamoxifen in terms of TTP. In our view, these observations have an important practical clinical use, as they provide guidance in selecting hormonal therapy for receptor-positive patients.

The author is correct in his comment that both trials were designed as noninferiority trials. This was clearly identified in both papers. However, it is accepted by many regulatory agencies, including the Food and Drug Administration (FDA), that in some cases, trials designed to test for noninferiority can be used to show superiority, based on the nature of the studies and the larger sample size included in such trials.[4]

Regarding the author's comments on survival, the data quoted from the FDA website are immature, with approximately 60% of patients in trial 0030 and 70% of patients in trial 0027 still alive at the time of the report. The data contained in the website were submitted to the FDA as part of a routine safety update, and because of the immaturity of the results were not included in the publications discussed here. A mature survival analysis of the combined data from the two trials will be presented later this year.

Finally, the article by Bonneterre et al. reporting the results of the combined data from the two trials did not determine TTP in the subgroup of patients who had received prior adjuvant tamoxifen, as there were insufficient patients to allow a meaningful analysis. Only 77 patients in the anastrozole group and 68

patients in the tamoxifen group had received adjuvant tamoxifen therapy, either alone or in combination with chemotherapy.

In summary, we believe that the combined analysis of both trials indicates that anastrozole increased TTP compared with tamoxifen in patients with hormone receptor-positive disease. Given its favorable toxicity profile, with significantly fewer thromboembolic events and approximately half the incidence of vaginal bleeding compared with tamoxifen, these data support the use of anastrozole as first-line treatment for hormone-responsive advanced breast carcinoma in postmenopausal women. Furthermore, results from the first planned analysis of the Arimidex, Tamoxifen, Alone or in Combination trial (ATAC) for the adjuvant treatment of early breast carcinoma in postmenopausal women have shown anastrozole to produce significantly prolonged disease-free survival ($P = 0.013$) compared with tamoxifen, along with a significant reduction ($P = 0.007$) in the incidence of contralateral breast carcinoma,[5] and are, therefore, supportive of our findings in first-line therapy for patients with advanced breast carcinoma.

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