Aromatase inhibitors

RISKS VS BENEFITS OF EXTENDED ANASTROZOLE THERAPY

TRIAL SUMMARY: Extending AI therapy: 2 years vs 5 years

Gnant M, Steger G, Greil R, et al. A prospective randomized multi-centre phase-III trial of additional 2 versus additional 5 years of anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial. 2017 San Antonio Breast Cancer Symposium. December 2017. Abstract GS3-01.

In postmenopausal patients with hormone receptor-positive breast cancer, extended adjuvant therapy with aromatase inhibitors (AI) after initial tamoxifen has been shown to improve disease-free survival (DFS). However, the optimal duration of extended AI is unknown. In this study, 3,484 women with postmenopausal stage I-III hormone receptor-positive early breast cancer were randomized in 71 centers in Austria to receive either 2 years or 5 years of additional anastrozole (1 mg daily) as extended adjuvant therapy, after initial 5 years of adjuvant endocrine treatment. Inclusion criteria stipulated that patients had to be under 80 years of age and recurrence-free at 60 months after initial adjuvant therapy with tamoxifen (Tam) or AI, or Tam followed by AI. Patients were followed at least annually. The primary endpoint was DFS, with secondary endpoints of overall survival (OS), fractures, contralateral breast cancer, and toxicity. Median patient age was 64 years, 72% of patients had tumours smaller than 2 cm, 66% of patients were node-negative, 19% had high-grade tumours, 77% had tumours that were both estrogen receptor (ER)- and progesterone receptor (PR)-positive, and 80% had been treated with breast conserving surgery. Before randomization into ABCSG-16, 29% patients had undergone (neo)adjuvant chemotherapy and 51% patients had received 5 years of tamoxifen, whereas 49% patients had received other (AI-containing) regimens in the first 5 years.

Results: As of June 30, 2016, median followup was 105.9 months, 757 DFS events had been recorded: 22% in the 2-year group, and 22% in the 5-year group. There was no significant difference in DFS (HR 0.997, 95% CI: 0.86–1.15, log rank p=0.982), OS, time to secondary carcinoma or time to contralateral breast cancer. With respect to drug adherence, at 2 years, 81.2% of patients in the 2-year arm were still taking the study drug, as were 80.1% in the 5-year arm. At 5 years, 65.6% of patients in the 5-year arm were still on the assigned medication. Bone fractures were more frequent in the 5-year arm (6% vs 4 %, HR=1.405, 95% CI: 1.03–1.91, p=0.029). After 5 years of adjuvant endocrine therapy (tamoxifen or AI or sequence), 2 additional years of anastrozole are sufficient as extended adjuvant therapy: a further extension to 5 additional years did not yield additional outcome benefit, but added toxicity.

COMMENTARY: The inclusion of AIs in the adjuvant therapy of endocrine-positive, postmenopausal breast cancer patients is standard of care. AIs can be given using a number of different strategies: upfront for 5 years, in some combination with tamoxifen in the first 5 years, or as extended adjuvant therapy after 5 years of tamoxifen. While the improved efficacy of AIs is undisputed, their remain challenges in managing side effects of these drugs—arthralgias, myalgias, and loss of bone mineral density—which can limit their use in some patients.

Extended adjuvant (EA) therapy has been an area of ongoing debate for some time. The aTTOM[1] and ATLAS[2] trials addressed the question of adding an additional 5 years of tamoxifen (vs placebo) after an initial 5 years of adjuvant hormonal therapy, and found a reduction in both BC recurrence and BC death. EA treatment with AIs has been examined in 3 major trials: MA.17R (letrozole),[3,4] NSABP B-33 (exemestane),[5] and ABCSG-6a (anastrazole),[6] all of which showed modest improvements in DFS. The MA.17 trial was alone in showing an OS advantage, but only in node-positive women. As a result, current practice in Canada is often to reserve EA therapy for those at highest risk of

recurrence (node-positive, high-grade) given the side-effect profile of AIs and lack of survival benefit in low-risk patients.

The ABCSG-16 trial examined 2 vs 5 years of extended anastrazole after 5 years of endocrine therapy. With a median followup of 8.8 years, no differences in DFS or OS were found; there was a difference in compliance rates, as fewer patients were able to stay on anastrazole for the full 5 years. The majority of patients in this study were low-risk and, in many cases, although EA therapy may be discussed, they would not likely be encouraged to take EA hormonal treatment. These results are comparable to the DATA trial, which examined 3 vs 6 years of anastrazole after an initial 5 years of adjuvant hormonal therapy.[7] While it is encouraging that the same benefits were seen in patients who took 2 years instead of 5 years of AI, perhaps no EA was necessary at all. After all, 3 years of EA anastrazole given in ABCSG-6a did not yield any OS benefit. The debate will continue around whether there is value in improving DFS without an associated improvement in OS. At this point, extended adjuvant therapy with aromatase inhibitors should be discussed with those at highest risk of recurrence.

IN BRIEF

Already known

- Extended treatment with aromatase inhibitors (AI) after tamoxifen is thought to improve disease-free survival in postmenopausal women with hormone receptor-positive breast cancer.
- There is some uncertainty about the optimal duration of extended AI treatment.

What this study showed

- After 5 years of adjuvant treatment with tamoxifen or AIs or both in sequence, 2 additional years of anastrozole are sufficient as extended adjuvant therapy. Extending to 5 years did not provide additional benefit, but increased toxicity.

Next steps

- Reserve extended adjuvant AI therapy for those at highest risk of recurrence.
- Further investigate the benefits of extended adjuvant therapy.

References

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