

Women with ER-positive breast Ca may soon extend tamoxifen therapy to 10 years

➔ A new study confirms that 10 years of tamoxifen significantly lowers the breast cancer mortality rate during the second decade after diagnosis, compared with 5 years of therapy

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Women who have hormone-sensitive breast cancer and who have taken tamoxifen for 5 years as adjuvant therapy stand to benefit from an additional 5 years of the drug, according to preliminary findings from the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial.¹

Tamoxifen is widely used to treat estrogen-receptor-positive (ER-positive) breast cancer and is generally prescribed for 5 years of daily use once the cancer has been excised. The drug substantially reduces the breast cancer mortality rate not only while treatment continues, but throughout the first 15 years after diagnosis.

It was known that 5 years of tamoxifen are more effective than 2 years. Until now, however, it was unclear whether continuation beyond 5 years further reduces the 15-year breast cancer mortality rate.

Details of the trial

In the trial of 12,894 women, investigators randomly assigned those who had received tamoxifen for 5 years to another 5 years of therapy or to no additional therapy, regardless of ER status. For the analysis, however, they included only the 6,847 women known to have ER-positive disease. Of these women, 3,428 were randomly assigned to continue

tamoxifen for another 5 years (10 years total), and 3,418 were allocated to stop the therapy immediately (5 years total).

Women who continued tamoxifen had a lower rate of recurrence and breast cancer mortality, but that benefit took several years to emerge. From the beginning of the ATLAS trial to year 15, the risk of recurrence was 21.4% among women who had continued tamoxifen to 10 years, and it was 25.1% among women who had only 5 years of therapy. Breast cancer mortality also declined significantly during years 5 to 15; it was 12.2% among women who continued tamoxifen to 10 years, and it was 15% among women who had only 5 years of therapy.

“Our results, taken together with results from previous trials of 5 years of tamoxifen versus none, suggest that 10 years of tamoxifen treatment can approximately halve breast cancer mortality during the second decade after diagnosis,” said Christina Davies, MBChB, lead investigator. “Good evidence now exists that 10 years of tamoxifen in ER-positive breast cancer produces substantial reductions in rates of recurrence and in breast cancer mortality, not only during the first decade, while treatment continues, but also during the second decade, long after it has ended.”

Implications of the ATLAS findings for gynecologic care



Mindy Goldman, MD

“The results of this trial have been long-awaited and are very exciting,” said Mindy Goldman, MD, director of the Women’s Cancer Care Program in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California, San Francisco. “I think these results will be translated into changes in clinical care right away.”

Because breast cancer is very common, gynecologists need to be aware of the gynecologic effects of drugs like tamoxifen, Dr. Goldman said. Gynecologists “need to ask their patients how long they have been on tamoxifen and about side effects they may be having.”

Although menopausal symptoms such as hot flashes improve over time in women who take tamoxifen, some women may continue to experience bothersome symptoms longer with the extended therapy, Dr. Goldman said.

Among her recommendations:

- **Be aware of nonhormonal treatments for menopausal symptoms** for breast cancer patients. Among the options are low doses of a number of different antidepressants, the neuropathic pain reliever gabapentin, and the antihypertensive clonidine. Some agents, such as gabapentin, cause sedation as a side effect and can be used for women having sleep disturbances. Doses of gabapentin are much lower than those used for neuropathic pain, and start as low as 100 mg or 300 mg per night, typically not exceeding 1,200 mg per day.
- **Know the uterine effects of tamoxifen**, which include increased endometrial thickening, cystic changes, benign polyps—and, in postmenopausal women, rare risks of uterine cancer. “Most endometrial cancers will present with bleeding, so gynecologists need to make sure they are discussing any abnormal bleeding with their patients on tamoxifen.”
- **Consider tamoxifen’s effects on bone.** In the ATLAS trial, there were fewer bone fractures among women who extended treatment.
- **Avoid overly aggressive scrutiny.** “In my Women’s Cancer Care Program, I see many patients who come for consults on a gyn issue related to their breast cancer,” Dr. Goldman said. “What I have found is that, many times, their gynecologists are too aggressive. They know that tamoxifen can increase the risk of uterine cancer, but they are doing routine ultrasounds in asymptomatic women and taking action based on endometrial thickness, like doing D&Cs for women who don’t necessarily need them—sometimes even hysterectomies.” Guidelines from the American College of Obstetricians and Gynecologists clearly state that routine ultrasound imaging is not indicated merely because a woman takes tamoxifen. “What I hope doesn’t happen is that ObGyns see these data as justification for more interventions.”



Because most endometrial cancers present with bleeding, be sure to ask patients about any abnormal bleeding on tamoxifen

Side effects were more common among postmenopausal women

Although tamoxifen has some side effects, they had a relatively small net effect on survival. The most significant effect was an increased risk—among postmenopausal women—of endometrial cancer. However, the excess risk of dying of endometrial cancer by year 15 was only 0.2% (0.4% among women who continued tamoxifen to 10 years vs 0.2% in the control group).

Investigators found no evidence that tamoxifen increases the risk of stroke, despite the fact that the US Food and Drug Administration lists stroke as a possible side effect of the drug. 📌

Reference

1. Davies C, Pan H, Godwin J, et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial [published online ahead of print December 5, 2012]. *Lancet*. doi:10.1016/S0140-6736(12)61963-1.