From ATLAS to HORIZONTAL: musings on five key trials

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The ATLAS trial[1]

For decades, 5 years of tamoxifen has been the standard of care for the adjuvant therapy of women with estrogen receptor positive breast cancer, although in recent years for postmenopausal women this treatment has been largely replaced with aromatase inhibitors (AIs). Would extending tamoxifen therapy to 10 years provide further benefit or merely increase toxicity? Do the results of the ATLAS trial, in which nearly 13,000 women were recruited and randomized to receive 5 more years of tamoxifen or to stop tamoxifen at 5 years, provide us with a new standard of care for premenopausal women?

Which of the following clinical characteristic was *not* part of this study:

a) US patients were enrolled
b) 90% of patients were postmenopausal
c) About 50% of the patients were node positive
d) More than 6,000 patients were ER negative or unknown and were excluded from the analysis.

The results of this study showed that for women taking tamoxifen for 10 years one of the following was *false*:

a) There was a 25% lower recurrence rate, and 29% lower breast cancer mortality rate
b) The absolute gain in terms of breast cancer death was 2.8%
c) Most of the benefit was seen in years 5-10
d) The benefit far outweighed the small increase risk of death from endometrial cancer.

Key points

The benefit in the ATLAS trial was significant, with improvements in recurrence and overall survival. Most of the difference was observed in years 10-14, with very little increased benefit in years 5-10, which might indicate a carryover benefit of the initial 5 years of tamoxifen. The clinical niche for the use of prolonged tamoxifen therapy might be the premenopausal woman who has completed 5 years of tamoxifen and has remained premenopausal, or postmenopausal women who cannot tolerate AIs.

This new data is worthy of discussion with our patients, but might not represent a true new standard of care. Further information on prolonged tamoxifen therapy has become available with the recent presentation at ASCO of another 5- versus 10-year study, the aTTom (adjuvant Tamoxifen—to offer more?) trial from the UK. This study showed similar results to the ATLAS trial, and the final paper should be available for review soon.

Answers a, c

Clinical Cancer Genetics Community Research Network report[2]

Breast and ovarian cancer in families with Mexican heritage have a high prevalence of BRCA mutations and have been found to have a unique founder mutation of their own and another that is usually found in Ashkenazi Jews because of an interesting fluke of history. In this study, high-risk Hispanic families underwent BRCA testing, including BART (BRCA-Analysis Rearrangement Test). This is the largest study of Hispanic breast and ovarian cancer families in the United States and confirms earlier work by Weitzel and colleagues.[3]

One of the findings was significant number of Hispanic women with the BRCA1 185delAG mutation, which also has a 1% prevalence in Ashkenazi Jews, indicating that:

a) There is significant intermarriage between Mexicans and Jews
b) Conversos and Crypto-Jews escaped the Spanish Inquisition in 1492, immigrated to the New World bringing their Jewish founder mutation with them, but lost their identity as Jews and became Catholics for the past 500 years
c) The Ten Lost Tribes of Israel migrated to Mexico 2,700 years ago and learned Spanish

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d) Christopher Columbus was Jewish and his progeny populated New Spain, later known as Mexico.

Which of the following is true in terms of the results of this study:
a) The BRCA mutation prevalence of 25% in this high-risk population was as expected
b) Large rearrangements screening is not necessary in Hispanics in high-risk families
c) A first reported founder mutation BRCA1 ex9-12del has never been reported in Spain or South America, arose 1,480 years ago, and predates Spanish colonization
d) Genetic testing for BRCA mutations is rarely necessary in Hispanic families.

Key points
The BRCA1 185delAG is one of the 3 Ashkenazi Jewish founder mutations and was thought to arise in Eastern Europe around 1200 AD. However, it has been identified in some non-Ashkenazi families in Egypt, Morocco, Iraq, and Turkey, indicating that it might have arisen before the diaspora in 70 AD. Jews escaping the Spanish Inquisition in 1492 apparently brought the mutation with them to the New Spain, later known as Mexico, and then lost their identity as Jews. In the San Luis Valley of Colorado and New Mexico, some Hispanics, known as the "secret Jews" of San Luis Valley, ceremonially light candles on Friday night, don't eat pork, and in some cases, even circumcise their young.

The BRCA prevalence of 25% was higher than expected and indicates that Hispanics with strong family histories need to be considered for testing. The large deletions observed in this study would be missed by the usual Myriad screen, and BART (BRCAnalysis Rearrangement Test) testing needs to be requested to detect these mutations. A new founder mutation (BRCA1 ex9-12del) was discovered among these women of Mexican heritage, one not found in Spain.
Answers b, c

Effect of age and hormone receptor status[4]

Despite the findings in randomized clinical trials and decades of experience supporting breast conservation as an alternative to mastectomy, the tide seems to be turning back to mastectomy, particularly in affluent communities, for those undergoing MRI screening, in younger women, and surprisingly, in women with DCIS. Women diagnosed with early breast cancer often have the mistaken notion that their survival will be improved with more radical surgery. Does this paper stem the tide?

This large, population-based series of 112,154 women who underwent breast conserving therapy (BCT) or mastectomy between 1990 and 2004 were analyzed for disease-specific survival (DSS) and overall survival (OS).

The study results showed that:
a) DSS and OS were both improved in the BCT group compared with the mastectomy group
b) Only the DSS was improved – OS did not improve
c) The advantage of BCT over mastectomy was less apparent in women older than 50 with hormone receptor-positive disease
d) Mastectomy was superior to BCT for both DSS and OS
e) Mastectomy and BCT were the same.

The importance of this study was:
a) These results provide confidence in the efficacy of BCT even in young patients with hormone receptor-negative disease
b) Although the study was not a randomized clinical trial, but a population-based registry study, the numbers were very large
c) The benefit of BCT over mastectomy was seen regardless of hormone receptor status or patient age
d) All of the above
e) None of the above.

Key points
This paper should increase confidence that breast conservation is at least as good a choice as mastectomy and possibly better in terms of important outcomes. DSS and OS was improved across the board, but especially in women older than 50 with hormone receptor-positive disease.
Answers a, d

Women's Environmental Cancer and Radiation Epidemiology Study[5]

What can one say to women about their risk of contralateral breast cancer if they have a strong family history for breast cancer, but no BRCA mutation? This population-based case-control study of contralateral breast cancer (CBC) and unilateral breast cancer (UBC) from California, Seattle, and Denmark excluded BRCA mutation carriers.

Which of the following is incorrect?
a) Women carriers of BRCA who are older than 50 years have a 10-year CBC risk of 8.4%
b) Women carriers of BRCA who are younger than 40 have a 10-year CBC risk of 28.3%
c) Women aged 25-54 years without BRCA mutation but with a history of bilateral breast cancer in a first-degree relative had a 10-year cumulative risk of CBC of 5%
d) Women aged 25-54 years with a history of BRCA mutation had a 10-year cumulative risk of CBC of 18.4%

e) Women younger than 35 years and without a BRCA mutation, but with a first-degree relative with bilateral breast cancer, had a 10-year cumulative risk of CBC of 23.7%.

The best answer regarding the conclusion of this paper is:

a) Because women with family history of bilateral breast cancer have risks of CBC similar to those of mutation carriers, they should receive similar counseling for prevention measures

b) Women with negative BRCA test results don't have to worry about extremely high risks of CBC

c) Genetic testing is more important than family history

d) The risk of CBC is the same for BRCA mutation carriers regardless of age.

Key points

The women aged 25-54 years who do not have mutations but have a history of bilateral breast cancer in a first-degree relative had a 10-year cumulative risk of CBC of 15.6%, not much different than the 18.4% risk for women with BRCA mutations in the same age group. Family history is an important consideration in assessing the risk of CBC, even when BRCA testing is negative. The precise risk varies with age of diagnosis, family history of CBC, and the degree of relationship to an affected woman.

Answers c, a

The HORIZON trial[6]

Does any combination of AI and mTor inhibitor work for women with metastatic breast cancer, despite the line of therapy? In this large randomized phase 3 study, 1,112 patients were randomized to letrozole alone or letrozole plus temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer.

One can say the following about the HORIZON study and the similar BOLERO-2 trial:

a) Maurice Ravel, the French composer, wrote the score for BOLERO-2 after the huge success of his Bolero. In the second version, the music becomes thinner and softer instead of thicker and louder as in the original Bolero

b) In HORIZON, the AI was different, but the mTOR is the same

c) In BOLERO-2, the patients must have had previous AI therapy for metastatic disease

d) In HORIZON, there was more stomatitis, compared with BOLERO-2

The results of HORIZON are consistent with the following:

a) HORIZON confirms the results of BOLERO-2, showing an improved progression-free survival (PFS) of advanced breast cancer with the combination of an AI and mTOR inhibitor

b) HORIZON results were discordant with BOLERO-2 – BOLERO-2 showed an improvement in PFS in patients with advanced breast cancer who had previous treatment with nonsteroidal AIs, whereas HORIZON did not show an improvement in PFS

c) HORIZON showed an improvement in PFS but not in OS, whereas BOLERO-2 showed improvement in both

d) Oncology clinical trials should not use such silly acronyms for studies, and the names should be restricted to numbers like EST1199.

Key points

Patients in BOLERO-2 had previous nonsteroidal AI therapy for metastatic disease, were given a different mTOR inhibitor (everolimus), and had more mucositis (56% vs 14% in HORIZON patients), which might indicate an inadequate dose of mTOR in the HORIZON study. There was no difference in PFS in the HORIZON study, whereas BOLERO-2 showed a PFS of 10.6 months versus 4.1 months ($P < .0001$).

Answers c, b

References

1. Davies C, Pan H, Godwin J, et al. 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. *Lancet*. 2013;381:805-816.
2. Weitzel JN, Clague J, Martir-Negron A, et al. Prevalence and type of BRCA mutations in Hispanics undergoing genetic cancer risk assessment in the Southwestern United States: a report from the Clinical Cancer Genetics Community Research Network. *J Clin Onc*. 2013;31:210-216.
3. Weitzel JN, Lagos V, Martir-Negron A, et al. Prevalence of BRCA mutations and founder effect in high risk Hispanic families. *Cancer Epidemiol Biomarkers Prev*. 2005;14(7):1666-1671.
4. Hwang ES, Lichtensztajn DY, Gomez SL, Fowble B, Clarke CA. Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. *Cancer*. 2013;119:1402-1411.
5. Reiner AS, John EM, Brooks JD, et al. Risk of asynchronous contralateral breast cancer in noncarriers of BRCA1 and BRCA2 mutations with a family history of breast cancer: a report from the Women's Environmental Cancer and Radiation Epidemiology Study. *J Clin Oncol*. 2013;31:433-439.
6. Wolff AC, Lazar AA, Bondarenko I, et al. Randomized phase III placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer. *J Clin Oncol*. 2013;31:195-202.