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NATIONAL BREAST CANCER COALITION FUND

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Fact Sheet on the Arimidex, Tamoxifen Alone or in Combination (ATAC) Clinical Trial

Background

For the past 30 years, Tamoxifen (brand name Nolvadex) has been a standard therapy for estrogen-receptor positive metastatic breast cancer, and a standard adjuvant treatment for early-stage breast cancer. Tamoxifen is a selective estrogen receptor modulator (SERM) that inhibits growth of estrogen receptor positive tumors by preventing estrogen from stimulating cancer cells. Tamoxifen has shown the ability to reduce cancer recurrence and to prolong life for many women. Tamoxifen treatment also has some significant side effects, including hot flashes, vaginal dryness and bleeding, blood clots, and endometrial cancer.

Aromatase inhibitors (AI) are another class of hormonal treatments that target estrogen-receptor positive tumors. Aromatase inhibitors exhibit a very different mechanism of action than SERM's. Aromatase inhibitors prevent the conversion of androgens into estrogen in fat, muscle, breast, and brain. In premenopausal women the ovaries make their own estrogen so aromatase inhibitors are not appropriate. Rather than preventing production of estrogen, SERM's work by blocking estrogen from stimulating the breast cells themselves. In this situation the drugs work equally well in pre- and postmenopausal women. The difference between these two classes of drugs will likely translate into different long-term effects.

In the mid-1990's, Anastrozole (brand name Arimidex) became one of several aromatase inhibitors made available for postmenopausal women with metastatic breast cancer. Anastrozole is currently used to treat postmenopausal women whose cancer has progressed to metastasis during Tamoxifen treatment, and also as a first-line treatment for women diagnosed with metastatic cancer. Anastrozole has shown itself to be comparable, if not slightly more effective than Tamoxifen in the treatment of estrogen-receptor positive metastatic breast cancer, without the same side effects as Tamoxifen.

Since Anastrozole has been effective in the metastatic setting, the Arimidex, Tamoxifen Alone or in Combination (ATAC) Group designed a trial to compare Anastrozole with Tamoxifen in the adjuvant setting. This trial, summarized below, focused on three questions:

- Is Anastrozole as effective as Tamoxifen in treating postmenopausal women with early, operable breast cancer?

- Does Anastrozole offer safety and side effect benefits over Tamoxifen in the adjuvant setting?
- Is a combination of Anastrozole and Tamoxifen more effective or safe than Tamoxifen alone?

Study Design

The study enrolled 9366 women from 21 countries. All patients were postmenopausal women with newly diagnosed operable invasive breast cancer, who had finished surgery and chemotherapy, were eligible for adjuvant therapy, and who were willing to suspend all hormonal therapies including HRT. Enrollment included both estrogen-receptor positive and receptor negative women, since at the time of trial initiation, hormone receptor status was not known to be an important contributor to the success of hormone treatments.

Women were randomized to one of three treatment arms: Anastrozole alone, Tamoxifen alone, or Anastrozole and Tamoxifen taken together (Combination). Estrogen receptor negative women, who composed about 8% of the study population, were distributed evenly among the study arms. Patients were assessed for disease recurrence at the initiation of adjuvant treatment, again at 3 months, at 6 months, and then periodically for every 6 months. The first sign of cancer recurrence was referred to as a “first event” and included any local or distant cancer recurrence, or the presence of contralateral cancer (cancer in the other breast). The statistical values used to assess treatment effectiveness were based upon the presence and timing of “first events” during treatment. They include:

- Percent disease free survival (the number of patients cancer-free at a point in time)
- Recurrence rate (the percentage of patients exhibiting the return of their cancer)
- Incidence of primary contralateral tumors (the percentage of patients with a new tumor in their other breast)

Investigators also recorded incidence of a variety of predetermined adverse events, although no diagnostics were performed to assess severity of these problems. Enrollment was open between July of 1996 and March of 2000, and the cutoff date for follow-up was June of 2001. The median follow-up length was 33 months.

Results

- Disease-free survival estimates at the three-year follow up were 89.4% for Anastrozole, 87.4% for Tamoxifen, and 87.2% for the Combination group.
- The percentages of women who died during the course of the trial, due to any causes, were 6.4% for Anastrozole, 6.5% for Tamoxifen, and 6.9% for the Combination group.

- There was no difference in recurrence rates among the groups during the first year of treatment, but Anastrozole yielded lower recurrence rates in the second and third year of treatment.

Recurrence Rates at Two and Three Years of Follow Up

Year 2:	Year 3:
Anastrozole: 2.6%	Anastrozole: 2.9%
Tamoxifen: 4.3%	Tamoxifen: 3.7%
Combination: 4.1%	Combination: 3.7%

- The beneficial effects of Anastrozole over Tamoxifen were not seen in the receptor negative women. Most importantly, recurrence rates were 3 times higher in receptor negative women than in receptor positive women.
- Anastrozole reduced the incidence of primary contralateral tumors by 58% in comparison with the Tamoxifen group and by 50% in comparison with the combination group. There were 14 cases of contralateral cancer out of 3125 women in the Anastrozole group, compared with 33 cases out of 3116 women in the Tamoxifen group and 28 cases out of 3125 women in the Combination group.
- Women who took Anastrozole reported a reduction in the incidence of hot flashes, vaginal bleeding, blood clots, and endometrial cancer in comparison to the Tamoxifen group or the Combination group.

	Anastrozole	Tamoxifen	Combination
Hot flashes	34.3%	39.7%	40.1%
Vaginal bleeding	4.5%	8.2%	7.7%
Blood clots	2.1%	3.5%	4.0%
Endometrial cancer	0.1%	0.5%	0.3%

- Anastrozole was associated with significant increases in the incidence of musculoskeletal disorders and bone fractures in comparison with Tamoxifen.

	Anastrozole	Tamoxifen	Combination
Musculoskeletal	27.8%	21.3%	22.1%
Bone fractures	5.9%	3.7%	4.6%

- No data comparing the effects of Anastrozole, Tamoxifen, and combination treatment on the cardiovascular health, cognition, mood, or sexual function were collected

Conclusion

At three years of follow up, adjuvant treatment with Anastrozole offers an incremental improvement in disease free survival, tumor recurrence rate, and incidence of contralateral tumors over Tamoxifen in postmenopausal women with estrogen receptor positive breast cancer. Despite these differences in disease recurrence and incidence, there was no difference between Tamoxifen and Anastrozole in terms of survival. Anastrozole did offer slight reductions in several side effects associated with

Tamoxifen. Anastrozole was no more efficacious than Tamoxifen for patients with hormone-receptor negative disease. Overall, the combination treatment was equivalent to Tamoxifen and worse than treatment with Anastrozole alone. The reasons for this effect are not well understood. One theory is that since Tamoxifen binds estrogen receptors and exhibits some estrogen-like signaling, the impact of estrogen reduction achieved by Anastrozole would be minimized when the two are given together. This illustrates the complicated and largely unexplored role of hormone activity in breast cancer.

Since Anastrozole and Tamoxifen function in different ways, Anastrozole may be associated with side effects not normally experienced by patients on Tamoxifen. The presence of musculoskeletal disorders is potentially one example, although no data was gathered in this study to specifically examine the effects of Anastrozole on this system. Bone mineral studies have been proposed to investigate this question. Currently, the effects of Anastrozole on blood lipid metabolism and cognition are unknown, and long-term follow up is necessary in order to examine these factors. While research has shown that the optimal treatment length for Tamoxifen is five years, there are no comparable studies that evaluate the optimal treatment length for Anastrozole. Long-term follow up will enable us to further establish how women can gain the most benefit from this treatment.

Further Questions Raised by this Study

The following questions should be evaluated before Anastrozole becomes the standard for adjuvant therapy:

- How long should Anastrozole treatment last to balance safety and effectiveness?
- How effective is Anastrozole compared to Tamoxifen at the five year treatment point, or in the longer term?
- What are the risks of a five year treatment with Anastrozole?
- How should Anastrozole treatment be sequenced with Tamoxifen?
- Is it possible to switch from Tamoxifen treatment to Anastrozole, or vice versa?
- What will be the systemic consequences of such a change?
- What are the effects of withdrawal from Anastrozole?

