Sequential Adjuvant Hormonal Therapy Following Tamoxifen

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8

Since the first International Breast Cancer Overview presented at the 1985 NIH Consensus Conference, tamoxifen was considered the mainstay of adjuvant hormonal therapy for women with early breast cancer. However, the selection of optimal adjuvant hormonal therapy for postmenopausal women is currently controversial. Recent trials — NCIC-MA17, ITA and EU-20149 – have evaluated the role of aromatase inhibitors as follow-up therapy to adjuvant tamoxifen. NCIC-MA17 randomly assigned postmenopausal women who had completed 4.5 to 6 years of adjuvant tamoxifen to five years of placebo or adjuvant letrozole. ITA and EU-20149 randomly assigned postmenopausal women who had completed two to three years of adjuvant tamoxifen to two to three years of continued tamoxifen, or two to three of anastrozole and exemestane, respectively. These trials of sequential adjuvant hormonal therapy demonstrated significant therapeutic advantages for women receiving aromatase inhibitors following adjuvant tamoxifen. The results from these and other ongoing trials will better define optimal adjuvant hormonal therapy regimen.

RANDOMIZED PHASE III STUDY OF LETROZOLE VERSUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER WHO HAVE COMPLETED AT LEAST FIVE YEARS OF ADJUVANT TAMOXIFEN

Protocol IDs: CAN-NCIC-MA17, CLB-49805, E-JMA17, EORTC-10983, IBCSG-BIG97-01, JRF-Vor-Int-10, NCCTG-CAN-MA17, NCCTG-JMA.17, SWOG-CAN-MA17, SWOG-JMA17
Accrual: 5,187 (Closed)

Eligibility	Postmenopausal patients with ER/PR-positive breast cancer previously treated with adjuvant tamoxifen for 4.5 to 6 years
ARM 1	Letrozole x 5 y
ARM 2	Placebo x 5 y

DISEASE-FREE SURVIVAL (DFS) AND RECURRENCES OR A NEW CONTRALATERAL PRIMARY TUMOR (MEDIAN FOLLOW-UP 2.4 YEARS)

	Letrozole (n=2,575)	Placebo (n=2,582)	*p*-value
Estimated 4-year DFS	93%	87%	<0.001
Recurrences, or a new contralateral primary	75 (2.9%)	132 (5.1%)	<0.00008

SOURCES: NCI Physicians Data Query, October 2004.

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802.

ITA TRIAL: ANASTROZOLE (A) VERSUS TAMOXIFEN (T) IN WOMEN ALREADY RECEIVING ADJUVANT TAMOXIFEN (MEDIAN FOLLOW-UP 24 MONTHS)[1]

Protocol IDs: ITA (Italian Tamoxifen Arimidex®)
Accrual: 448 (Closed)

Eligibility	Postmenopausal patients with ER/PR-positive primary breast cancer previously treated with adjuvant tamoxifen for two to three years
ARM 1	Anastrozole x 2-3 y
ARM 2	Tamoxifen x 2-3 y

Treatment	Event-free survival		Progression-free survival	
	Hazard ratio	*p*-value	Hazard ratio	*p*-value
Tamoxifen n=225	1.0		1.0	
Anastrozole n=223	0.36 (95% CI 0.21-0.63)	0.0004	0.35 (95% CI 0.18-0.69)	0.002

"These findings confirm the role of A in the treatment of early breast cancer. Furthermore, the findings show that switching patients on adjuvant T to treatment with adjuvant A appears to decrease their risk of relapse and death. A was found to be more effective and induce less serious adverse effects than T in women already on treatment with this antiestrogen."

A = anastrozole; T = tamoxifen

SOURCE: [1] Boccardo F. Presentation. SABCS, 2003;Abstract 3.

PHASE III TRIAL OF EXEMESTANE VERSUS TAMOXIFEN FOLLOWING TWO TO THREE YEARS OF ADJUVANT TAMOXIFEN

Protocol IDs: CRC-TU-TEAM, EU-20149
Accrual: 4,742 (Closed)

Eligibility	Postmenopausal women with ER/PR-positive breast cancer who have received two to three years of adjuvant tamoxifen
ARM 1	Tamoxifen x 2-3 y
ARM 2	Exemestane x 2-3 y

UNADJUSTED HAZARD RATIOS FOR THE EXEMESTANE GROUP COMPARED TO THE TAMOXIFEN GROUP

Endpoints	Unadjusted hazard ratio (95% CI)	*p*-value
Disease-free survival	0.68 (0.56-0.82)	<0.001
Estrogen receptor-positive (ER+) ER+, progesterone receptor-positive ER+, progesterone receptor-negative	0.64 (0.52-0.79) 0.66 (0.51-0.87) 0.58 (0.38-0.90)	
Breast cancer-free survival	0.63 (0.51-0.77)	<0.001
Time to contralateral breast cancer	0.44 (0.20-0.98)	0.04
Overall survival	0.88 (0.67-1.16)	0.37

INCIDENCE OF SIGNIFICANTLY DIFFERENT ADVERSE EVENTS BETWEEN GROUPS

Type of event	Exemestane any Grade	Tamoxifen any Grade	*p*-value
Visual disturbances	7.4%	5.7%	0.04
Osteoporosis	7.4%	5.7%	0.05
Gynecologic symptoms	5.8%	9.0%	<0.001
Arthralgia	5.4%	3.6%	0.01
Diarrhea	4.3%	2.3%	<0.001
Vaginal bleeding	4.0%	5.5%	0.05
Cramps	2.8%	4.4%	<0.001
Thromboembolic events	1.3%	2.4%	0.007

SOURCE: Coombes C et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92.

ANASTROZOLE VERSUS TAMOXIFEN AFTER TWO YEARS OF ADJUVANT TAMOXIFEN

Protocol ID: ABCSG-08, ARNO-95
Accrual: 3,123 (Closed)

Eligibility	Postmenopausal patients with ER/PR-positive breast cancer previously treated with adjuvant tamoxifen for 2 years
ARM 1	Anastrozole x 3 y
ARM 2	Tamoxifen x 3 y

SOURCES: www.abcsg.at. Jakesz R et al. Presentation. SABCS, 2004.

SELECT PUBLICATIONS

Baum M et al; The ATAC Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *The Lancet* 2002;359(9324):2131-9.

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;83(Suppl 1):60;Abstract 3.

Coombes C et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92.

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802.

SEQUENTIAL ADJUVANT ENDOCRINE THERAPY

For postmenopausal patients who are on tamoxifen for any length of time, our practice today is to switch to an aromatase inhibitor. There was a time when we would leave patients on tamoxifen if they were already on tamoxifen, because there was really no evidence that crossing over was beneficial. But, after all three of the crossover trials came out this past year, there was really no justification in our minds to continue tamoxifen.

– Gabriel N Hortobagyi, MD

We have completed accrual to an adjuvant trial (IBCSG-18-98) comparing five years of tamoxifen, five years of letrozole, two years of tamoxifen followed by three years of letrozole, and two years of letrozole followed by three years of tamoxifen in postmenopausal patients with endocrine-responsive disease. This trial accrued 8,028 patients. A lifelong treatment strategy for patients with an increased risk of breast cancer recurrence might be reasonable. I think maintaining the cells under control and suppressing new tumors requires a sequential approach that includes endocrine therapy for tumors that are endocrine responsive.

– Aron Goldhirsch, MD

ADJUVANT LETROZOLE FOLLOWING FIVE YEARS OF ADJUVANT TAMOXIFEN

"We found a significant improvement in disease free survival, including a substantial reduction in the rate of distant metastasis in the letrozole group as compared with the placebo group; the rate of death due to breast cancer was almost halved. Letrozole was equally effective in women with node-negative disease and those with node-positive disease. The reduction in the rates of recurrent and new disease in the letrozole group confirms the continuous dependence of hormone-receptor-positive breast cancer on estrogen. …

"On the basis of these findings, postmenopausal women with hormone-receptor-positive tumors who have completed about five years of adjuvant tamoxifen therapy should be considered for letrozole treatment. However, our results, which necessitated the discontinuation of the study, leave the optimal duration of treatment undefined and the question of long-term toxicity unanswered."

— Goss PE et al. N Engl J Med *2003;349(19):1793-802.*

BIOLOGICAL RATIONALE FOR THE SEQUENCING OF ADJUVANT HORMONAL THERAPY

If the ATAC trial data from the patients with ER-positive and PR-negative disease were confirmed, it would be difficult to substantiate the use of adjuvant tamoxifen followed by adjuvant letrozole in that group of patients. The relapse rate was too high with adjuvant tamoxifen to suggest such a sequential strategy, and it may be best to use an aromatase inhibitor early in that group of patients. In the patients with ER/PR-positive disease, in whom the relapse rates for tamoxifen and anastrozole were more similar, one could argue for the use of such a sequential strategy. However, I suspect even in that group of patients it is best to accept the gain associated with the aromatase inhibitors as initial adjuvant therapy, rather than allow a few patients to relapse and have to treat their metastatic disease.

— Mitchell Dowsett, PhD

ADJUVANT EXEMESTANE FOLLOWING TWO TO THREE YEARS OF ADJUVANT TAMOXIFEN

"We found that switching patients to adjuvant treatment with exemestane after two to three years of tamoxifen therapy was associated with a statistically and clinically significant improvement in disease-free survival, which included a reduction in the incidence of metastic disease. This strategy also reduced the risks of contralateral breast cancer, endometrial cancer, and intriguingly, other primary cancers. At the time of this report, the observed number of deaths over the relatively short follow-up period precludes the detection of a statistically significant difference in overall survival."

— Coombes C et al. N Engl J Med *2004;350(11):1081-92.*