AstraZeneca

INT0101

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Zoladex™ 3.6 mg depot injection

ACTIVE INGREDIENT: goserelin acetate (equivalent to 3.6mg goserelin)

Trial title (number): An Open, Randomized Trial Comparing Combination Chemotherapy (CAF) and Chemohormonal Therapy (CAF + ZOLADEX or CAF + ZOLADEX + Tamoxifen) in Premenopausal Women with Axillary Node-positive, Receptor-positive Breast Cancer (INT0101)

Developmental phase: IIIb
First subject recruited:15 July 1989
Last subject recruited:30 January 1994
Approval date: 05 October 2000

OBJECTIVES

In this trial, premenopausal women with axillary lymph node-positive, hormone receptor-positive breast cancer were randomized to 1 of the following 3 adjuvant therapy regimens:

- cyclophosphamide + doxorubicin + 5-fluorouracil (CAF)
- CAF followed by ZOLADEX (CAF + Z)
- CAF followed by ZOLADEX + tamoxifen (CAF + Z + T)

The objectives of this trial were:

- to compare recurrence rates, disease-free survival, and overall survival between the adjuvant therapy regimens
- to compare the relative toxicities of the adjuvant therapy regimens
- to assess the effect of the adjuvant therapy regimens on levels of luteinising hormone (LH), follicle-stimulating hormone (FSH) and estradiol

METHODS

Design: This was an open, randomized, collaborative group trial conducted in premenopausal women with axillary lymph node-positive, hormone receptor-positive early breast cancer. Adjuvant combination chemotherapy (CAF for 6 x 28-day cycles) was begun after randomization, and within 12 weeks (84 days) following surgery (modified radical mastectomy, or lumpectomy with axillary dissection). When planned, radiation therapy was administered within 4 weeks before or after completion of adjuvant chemotherapy. Immediately following treatment with CAF, patients received one of the following randomized (1:1:1 ratio) therapy regimens: no further trial treatment; ZOLADEX (3.6 mg monthly for 5 years); or ZOLADEX (3.6 mg monthly for 5 years) plus tamoxifen (20 mg daily for 5 years).

Population: This trial was designed to recruit 1500 premenopausal women with axillary lymph node-positive, hormone receptor-positive early breast cancer from ECOG, SWOG or CALGB institutions in the USA. Power calculations were based on the hazard rates for recurrence and survival.

Key inclusion criteria: undergone excision of the primary breast tumor mass (proven histologically to be invasive breast adenocarcinoma) and one or more pathologically involved axillary nodes; premenopausal; female; the interval between definitive surgery (ie, the date of mastectomy, or axillary dissection if a lumpectomy was performed) and randomization $\leq$12 weeks; estrogen and/or progesterone receptor-positive; no evidence of metastatic disease or

involvement of the other breast; agreement to use a non-hormonal barrier form of contraception for the duration of trial therapy; and written, informed consent to participate in the trial.
For surgical patients who did not undergo total mastectomy, the following additional inclusion criteria were applied: the primary lesion in the breast was to be ≤5 cm in its greatest dimension; patients had to receive post-operative radiotherapy either before CAF therapy (beginning within 4 weeks following axillary node dissection), or be willing to receive radiotherapy starting within 4 weeks from the last dose of CAF; and patients had to have histologically-negative inked margins of resection following excision of the primary tumor.

Key exclusion criteria: previous malignancy with the exception of basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or other cancer if the patient had been disease-free for ≥5 years; prior hormonal therapy or chemotherapy for breast cancer (except those patients who received tamoxifen for ≤14 days); bilateral breast malignancies; fixed lesions to chest wall, peau d'orange skin changes, skin ulceration, or inflammatory lesions; pregnancy or lactating; or brittle diabetes, poorly controlled hypertension, COPD which limits activity, major depression, other difficult to manage concurrent medical or neuropsychiatric problems, congestive heart failure, angina pectoris, cardiac arrhythmia or myocardial infarction within the previous 12 months.

Dosage: Patients were randomized (ratio 1:1:1) to one of the following 3 trial treatment arms:
- combination chemotherapy (CAF) for six 28-day cycles
- CAF for six 28-day cycles followed by ZOLADEX (one 3.6 mg depot monthly for 5 years)
- CAF for six 28-day cycles followed by ZOLADEX (one 3.6 mg depot monthly for 5 years) plus tamoxifen (20 mg daily for 5 years)

A cycle of CAF consisted of:
- cyclophosphamide - 100 mg/m^2 orally on Days 1 to 14 of a 28-day cycle
- doxorubicin - 30 mg/m^2iv on Days 1 and 8 of a 28-day cycle
- 5-fluorouracil - 500 mg/m^2 iv on Days 1 and 8 of a 28-day cycle

Key assessments:

Efficacy: The primary efficacy end-point of this trial (as defined in AstraZeneca's Statistical Analysis Plan) was disease-free survival (ie, the interval from randomization to the date of confirmed tumor recurrence, second primary breast cancer or death).
The secondary efficacy end-points of this trial (as defined in AstraZeneca's Statistical Analysis Plan) were:
- total recurrence-free time (ie, the interval from randomization to the date of local,regional or distant recurrence, or contralateral breast cancer)
- locoregional recurrence-free time (ie, the interval from randomization to the date of local or regional recurrence of breast cancer)
- distant recurrence-free time (ie, the interval from randomization to the date of distant recurrence or contralateral breast cancer)
- overall survival (ie, the interval from randomization to the date of death)
- number of new primary cancers (ie, the number of patients diagnosed after randomization with any new cancer, including contralateral breast cancer).

These end-points were assessed by following up patients until death, and by documenting any confirmed tumor recurrence or new primary cancer.

Serum concentrations of LH, FSH and estradiol were to be measured before starting, and at completion of CAF therapy, then 8 weeks after starting ZOLADEX therapy (or at an equivalent time for patients only receiving CAF), and then 1, 2 and 3 years after entry to the trial. Assays were performed by local laboratories, and there was considerable intra- and inter-patient variability in the laboratories and assays used.

Safety: Patients were assessed and follow-up forms completed 3 months into, and at the completion of CAF therapy, then every 4 months during the 5 years of randomized therapy, then every 6 months for the first 3 years of follow-up, and annually thereafter or until recurrence or death. Toxicity grading and adverse reaction reporting were based on the Common Toxicity Criteria (CTC).

RESULTS

Demography: A total of 1537 patients from 424 centers in the USA (212 ECOG centers, 125 SWOG centers, and 87 CALGB centers) entered the trial between 15 July 1989 and 30 January 1994, inclusive. Of these patients, 510 were randomized to receive adjuvant treatment with CAF alone, 511 with CAF followed by ZOLADEX (CAF + Z), and 516 with CAF followed by ZOLADEX + tamoxifen (CAF + Z + T).

The primary efficacy population (ie, the all-randomized population) was well balanced in terms of baseline demographic characteristics, primary tumor characteristics, and surgery and radiotherapy received at trial entry (see Table 1). Greater than 99% of patients were confirmed as having breast cancer that was both hormone receptor-positive (ie, ER and/or PgR-positive) and axillary lymph node-positive; 87% had ER-positive tumors, and 59% had 1 to 3 positive nodes.

Table 1	**Patient age, hysterectomy, and primary tumor characteristics in the primary efficacy population**					
Demographic characteristic	**CAF (n=510)**		**CAF+Z (n=511)**		**CAF+Z+T (n=516)**	
Age (years)						
Mean	42.4		42.2		42.5	
Standard deviation	5.7		5.9		5.9	
Minimum	25		25		24	
Maximum	57		54		57	
Age groups (number (%) of patients)						
<40 years of age	144	(28.2)	154	(30.1)	150	(29.1)
≥40 years of age	366	(71.8)	357	(69.9)	366	(70.9)
Hysterectomy (number (%) of patients)						
Yes	43	(8.4)	45	(8.8)	47	(9.1)
No	463	(90.8)	464	(90.8)	465	(90.1)
Unknown	4	(0.8)	2	(0.2)	4	(0.2)
Size of tumor						
≤10mm	27	(5.3)	31	(6.1)	31	(6.0)
11 to 20 mm	170	(33.3)	170	(33.3)	183	(35.5)
21 to 30 mm	158	(31.0)	144	(28.2)	135	(26.2)
31 to 40 mm	72	(14.1)	70	(13.7)	74	(14.3)
41 to 50 mm	34	(6.7)	47	(9.2)	48	(9.3)
>50 mm	42	(8.2)	44	(8.6)	42	(8.1)
Missing	7	(1.4)	5	(1.0)	3	(0.6)
ER and PgR status (number (%) of patients)						
ER positive and PgR positive	382	(74.9)	378	(74.0)	399	(77.3)
ER positive and PgR negative	60	(11.8)	60	(11.7)	57	(11.0)
ER negative and PgR positive	64	(12.5)	73	(14.3)	58	(11.2)
ER negative and PgR negative	0	(0.0)	0	(0.0)	0	(0.0)
Missing	4	(0.8)	0	(0.0)	2	(0.4)
Number of positive nodes (number (%) of patients)						
1 to 3	302	(59.2)	305	(59.7)	299	(57.9)

4 to 9	161	(31.6)	157	(30.7)	167	(32.4)
≥10	45	(8.8)	49	(9.6)	50	(9.7)
Missing	2	(0.4)	0	(0.0)	0	(0.0)

A total of 173 patients were not included in the secondary efficacy population because:

- they were protocol violators (as determined by a review of the case report forms by the ECOG Study Chair)
- they did not start receiving ZOLADEX or ZOLADEX + tamoxifen that was randomly allocated to them
- they were randomized to receive CAF only and had an event (ie, recurrence, second primary breast cancer or death) during the CAF treatment period; equivalent patients in the other 2 treatment groups did not go on to receive ZOLADEX or ZOLADEX + tamoxifen following chemotherapy.

Of the remaining patients, 492 were randomized to receive CAF alone, 436 with CAF followed by ZOLADEX, and 436 with CAF followed by ZOLADEX + tamoxifen.

Efficacy: Using a database copy date of 4 November 1999, a total of 202 (39.6%) patients randomized to receive CAF alone had had an event (ie, recurrence, second primary breast cancer, or death), compared to a total of 183 (35.8%) patients randomized to receive CAF followed by ZOLADEX (CAF + Z), and a total of 145 (28.1%) patients randomized to receive CAF followed by ZOLADEX + tamoxifen (CAF + Z + T). The lower incidences of events in the CAF + Z and CAF + Z + T groups compared to the CAF group were due to lower incidences of both local and distant recurrences in these groups. The median follow-up time for each group was 7.1 years. Sixty-six percent of patients in the CAF group were disease-free after 5 years compared to 70% in the CAF + Z group, and 76% in the CAF + Z + T group.

The results of the primary and secondary analyses of disease-free survival indicated that patients benefited from receiving hormonal therapy in addition to chemotherapy; differences approached or attained the conventional level of statistical significance (p = 0.05) for those patients who were randomized to CAF followed by ZOLADEX or ZOLADEX + tamoxifen compared to those patients who were randomized to CAF alone (see Table 2). A statistically significant benefit was also seen in favor of combination hormonal therapy (ie, ZOLADEX + tamoxifen) compared to ZOLADEX alone following chemotherapy. These findings were mirrored by the analyses of total recurrence-free time.

Table 2 Analyses of disease-free survival

Population/comparison	Hazard ratio[a]	95% confidence interval	p-value
Primary efficacy population			
CAF vs CAF + Z	0.831	0.680, 1.017	0.073
CAF vs CAF + Z + T	0.618	0.498, 0.767	<0.001
CAF + Z vs CAF + Z + T	0.747	0.600, 0.931	0.009
Secondary efficacy population			
CAF vs CAF + Z	0.806	0.651, 0.998	0.048
CAF vs CAF + Z + T	0.543	0.428, 0.688	<0.001
CAF + Z vs CAF + Z + T	0.675	0.527, 0.865	0.002

[a]A hazard ratio <1 indicates a better result for the second treatment compared to the first treatment.

A total of 124 (24.3%) patients randomized to receive CAF alone died, compared to a total of 112 (21.9%) patients randomized to receive CAF + Z, and a total of 103 (20.0%) patients randomized to receive CAF + Z + T. The median follow-up time for each group was between 7.0 and 7.2 years. The analyses of overall survival are presented in Table 3.

Table 3 Analyses of overall survival

Comparison	Hazard ratio[a]	95% confidence interval	p-value
Primary efficacy population			
CAF vs CAF + Z	0.884	0.684, 1.144	0.349
CAF vs CAF + Z + T	0.813	0.625, 1.058	0.123
CAF + Z vs CAF + Z + T	0.925	0.707, 1.211	0.573
Secondary efficacy population			
CAF vs CAF + Z	0.830	0.630, 1.092	0.183
CAF vs CAF + Z + T	0.694	0.518, 0.930	0.014
CAF + Z vs CAF + Z + T	0.841	0.619, 1.144	0.270

[a] A hazard ratio <1 indicates a better result for the second treatment compared to the first treatment.

Subgroup analyses by age indicated that patients aged <40 years at entry to the trial may have benefited more from adjuvant ZOLADEX therapy than patients aged≥40 years (see Table 4). However, the confidence intervals are wide, and within the statistical model, the treatment by age interaction was not significant.

Table 4 Analyses of disease-free survival by age (primary efficacy population)

Comparison	Hazard ratio[a]	95% confidence interval	p-value
Patients aged <40 years at entry to the trial			
CAF vs CAF + Z	0.764	0.542, 1.077	0.124
CAF vs CAF + Z + T	0.549	0.379, 0.795	0.002
CAF + Z vs CAF + Z + T	0.730	0.498, 1.069	0.106
Patients aged ≥40 years at entry to the trial			
CAF vs CAF + Z	0.896	0.697, 1.150	0.388
CAF vs CAF + Z + T	0.675	0.517, 0.880	0.004
CAF + Z vs CAF + Z + T	0.760	0.580, 0.995	0.046

[a] A hazard ratio <1 indicates a better result for the second treatment compared to the first treatment.

Comparisons and statistical analyses of the levels of LH, FSH and estradiol between the 3 treatment groups were not performed because of the considerable intra- and inter-patient variability in the laboratories and assays used to collect the data.

Safety: At least 1209 (78.7%) patients completed six 28-day cycles of CAF, and the median duration of CAF therapy was similar between the 3 treatment groups. A total of 882 out of 1027 (85.9%) patients randomized to receive ZOLADEX (with or without tamoxifen) started ZOLADEX therapy, and of these, at least 412 (46.6%) completed the 5-year treatment period. Median

duration of ZOLADEX therapy was similar between the CAF + Z and CAF + Z + T groups. A total of 442 out of 516 (85.7%) patients randomized to receive ZOLADEX + tamoxifen started tamoxifen therapy, and of these, at least 229 (51.8%) completed the 5-year treatment period.

Long-term ZOLADEX and ZOLADEX + tamoxifen therapies following chemotherapy appeared to be well tolerated. Expected side effects of hormonal therapy eg, hot flashes, were observed more frequently in the CAF + Z and CAF + Z + T groups, however, few toxicities related to ZOLADEX or tamoxifen led to withdrawal from trial therapy. Life-threatening toxicities were primarily limited to those related to CAF therapy eg, cytopenias, nausea, and vomiting.

Reference:

Davidson NE, O'Neill AM, Vukov AM et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer : results from INT 0101 (E5188) J Clin Oncol 2005; 23 (25): 5973-82

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Zoladex™ (goserelin acetate), Healthcare Professionals should view their specific country information.