SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ZOLADEX™ 3.6 mg depot injection

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

Trial title (number): An Open, Randomised Trial Comparing Combination Chemotherapy (CMF) Versus ZOLADEX + Tamoxifen (NOLVADEX™) in Premenopausal, Hormone Receptor-Positive, Lymph Node-positive or Lymph Node-negative Patients With Operable Breast Cancer (ACO5)

Clinical phase: IIIb

First patient recruited: 18 December 1990
Last patient recruited: 29 June 1999
Database copy date: August 1999
AstraZeneca approval date: 2 October 2000

Publications: Jakesz R, Gnant M, Hausmaninger H et al. European Journal of Surgical Oncology 2000;26(3):281 Abs 110.
Jakesz R, Gnant M, Hausmaninger H et al. Breast 1999;8(4):233 Abs 071.
Jakesz R, Gnant M, Hausmaninger H et al. Breast Cancer Resarch and Treatment 1999; 57(1):25 Abs 2.
Jakesz R, Hausmaninger H, Samonigg H et al. Proceedings of the 35th Annual Meeting of the American Society of Clinical Oncology; 1999 May 15-18;18:67a Abs 250.
Jakesz R, Hausmaninger H, Samonigg H et al. European Journal of Cancer 1999; 35 (suppl 4): S83 Abs 268a.

OBJECTIVES

The objectives of the trial were:

- to compare the effectiveness of 2 adjuvant therapy regimens (cyclophosphamide, methotrexate and 5-fluorouracil (CMF) versus ZOLADEX + tamoxifen) in respect of effects on the prognosis (disease-free survival and overall survival) in premenopausal patients who had undergone potentially curative surgery of hormone receptor-positive breast cancer
- to record and compare the acute, subacute and chronic toxicity of the 2 therapy regimens in the same patient population

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METHODS

Design: This was an open, randomised, parallel-group, multi-centre trial conducted in pre-/perimenopausal patients with hormone receptor-positive, early breast cancer. Both lymph node-positive and lymph node-negative patients were included in the trial. Before randomisation to 1 of the 2 treatment groups, patients were stratified according to tumour stage, nodal stage, locoregional therapy, receptor status, tumour grading and centre.

Population: This Austrian trial was planned to recruit at least 660 patients within 4 years of its initiation, with evaluation of the efficacy data occurring 5 years after the end of recruitment. The sample size calculation was based on a 10% difference in survival (65% to 75%). However, recruitment was subsequently increased as the mortality rate in the trial was less than predicted.

Key inclusion criteria: Pre- or perimenopausal breast cancer patients who had undergone successful, potentially curative surgery following exclusion of distant metastases; either lymph node-positive, or lymph node-negative with the primary tumour having a minimum cross section of at least 1 cm; hormone receptor-positive tumour; complete healing after successful operation; time since surgery no longer than 4 weeks.

Key exclusion criteria: T4 tumour stage; inflammatory breast cancer; in situ cancer of any size with or without Paget's disease; simultaneous or sequential bilateral breast cancer; received pre-operative tumour reductive radiation and/or pre-operative tumour-specific medication therapy; male patients; existing pregnancy or lactation; manifest secondary malignoma or previous secondary malignoma (except curatively treated epidermoid cancer or in situ cervical cancer).

Dosage: Patients received 1 of the following 2 trial treatment regimens:

- CMF for 6 cycles, with each cycle lasting 28 days. A cycle of CMF consisted of:
  - cyclophosphamide (600 mg/m^2 given intravenously on Days 1 and 8),
  - methotrexate (40 mg/m^2 given intravenously on Days 1 and 8), and
  - 5-fluorouracil (600 mg/m^2 given intravenously on Days 1 and 8).
- One ZOLADEX 3.6 mg depot subcutaneously every 28 days for 3 years, plus 20 mg tamoxifen (1 x 20 mg or 2 x 10 mg oral tablets) every day for 5 years.

Where postoperative radiation was indicated, it was administered simultaneously with trial treatment for patients randomised to ZOLADEX + tamoxifen therapy, and was administered between Cycles 3 and 4 of CMF therapy for patients randomised to combination chemotherapy.

Key assessments:

Efficacy: The primary end-point of this trial was disease-free survival (ie, the interval from randomisation to the date of confirmed tumour recurrence, contralateral breast cancer or death). The secondary end-points of this trial were overall survival (ie, the interval from randomisation to the date of death) and the number of patients with new primary cancers. End-points were assessed by following up patients until first tumour recurrence and/or death.

For patients in the CMF treatment group only, an assessment of whether amenorrhoea following CMF treatment was indicative of an increased risk of recurrence or death was performed.

Safety: Safety assessments involved the reporting of specific expected side effects of trial therapy pre-printed on the case report forms; no other adverse events were collected. Expected side effects were assessed before each course of CMF and before each injection of ZOLADEX 3.6 mg. In addition, assessments were also performed for both treatment groups every 3 months during the first 3 years following the start of trial therapy, and every 6 months during the 4th and 5th years. No relationship to trial treatment was recorded.

Clinical laboratory data were also assessed during the trial but have not been presented in this report due to the poor quality of the data collected.

RESULTS

Demography: A total of 1122 patients from 63 centres in Austria entered the trial between 18 December 1990 and 29 June 1999, inclusive. Of these patients, 559 were randomised to receive treatment with ZOLADEX + tamoxifen, and 563 were randomised to receive treatment with CMF. These 2 groups were well balanced in terms of baseline demographic characteristics, primary tumour characteristics, and locoregional therapy and radiotherapy received. Key demographic and primary tumour characteristics are presented in Table I.

Table I Patient age, menopausal status and primary tumour characteristics in the primary efficacy (all-randomised) population

Demographic characteristic[a]	ZOLADEX + tamoxifen (N = 559)		CMF (N = 563)	
Age (years)				
Mean[b]	44.3		44.2	
Standard deviation	5.7		5.8	
Minimum	24		23	
Maximum	60		58	
Age (number (%) of patients)				
<40 years	102	(18.2)	116	(20.6)
40 to 50 years	381	(68.2)	366	(65.0)
>50 years	70	(12.5)	79	(14.0)
Unknown	6	(1.1)	2	(0.4)
Menopausal status (number (%) of patients)				
Premenopausal	516	(92.3)	530	(94.1)
Postmenopausal[c]	4	(0.7)	5	(0.9)
Unknown	39	(7.0)	28	(5.0)
Primary tumour (pT) stage				
pT1a (≤0.5 cm)	2	(0.4)	2	(0.4)
pT1b (>0.5 to 1.0 cm)	20	(3.6)	27	(4.8)
pT1c (>1.0 to 2.0 cm)	269	(48.1)	278	(49.4)
pT2 (>2.0 to 5.0 cm)	209	(37.4)	208	(36.9)
pT3 (>5.0 cm)	22	(3.9)	22	(3.9)
Unknown	37	(6.6)	26	(4.6)
Oestrogen receptor (ER) and progesterone receptor (PgR) status				
Both positive	422	(75.5)	429	(76.2)
One positive and one negative	82	(14.7)	93	(16.5)
One negative and one unknown	1	(0.2)	2	(0.4)
Unknown	54	(9.7)	39	(6.9)
Primary node (pN) stage				
No metastatic lymph node involvement	270	(48.3)	268	(47.6)
1 to 3 lymph nodes involved	174	(31.1)	186	(33.0)
4 to 10 lymph nodes involved	66	(11.8)	71	(12.6)
>10 lymph nodes involved	13	(2.3)	12	(2.1)
Unknown	36	(6.4)	26	(4.6)

[a] No data regarding patients' race were collected in this trial.
[b] ZOLADEX + tamoxifen group, n = 553; CMF group, n = 561.
[c] Major protocol violation leading to exclusion of patients from the secondary efficacy population.

A total of 1026 (91.4%) patients were known to have had hormone receptor-positive tumours (ie, ER and/or PgR positive); 954 (85.0%) had ER-positive tumours, and 923 (82.3%) had PgR-positive tumours.
One-hundred-and-forty-four (12.8%) patients were excluded from the secondary efficacy population for one or more of the following reasons: they were postmenopausal at entry to the trial (9 patients), they may have received trial treatment before randomisation (18 patients), and/or they had no record of receiving the randomised trial treatment (122 patients). Patients in this population were grouped according to treatment allocated (which was the same as the treatment received); 497 patients in the ZOLADEX + tamoxifen group, and 481 patients in the CMF group. All patients who started therapy with ZOLADEX also received tamoxifen.
Efficacy: In the primary efficacy population, 80 (14.3%) patients randomised to receive ZOLADEX + tamoxifen had an event (ie, disease recurrence, contralateral breast cancer or death) compared to 105 (18.7%) patients randomised to receive CMF. The median follow-up times for the 2 trial treatment groups were 3.8 and 3.7 years, respectively. Based on these results, patients in the ZOLADEX + tamoxifen group fared statistically significantly better than those in the CMF group. A very similar statistically significant result was also seen for the secondary efficacy population (see Table II).

Table II Analyses of disease-free survival

Efficacy population	Hazard ratio[a]	95% confidence interval	p-value
Primary	0.69	0.51, 0.93	0.013
Secondary	0.67	0.50, 0.91	0.011

[a] ZOLADEX + tamoxifen/CMF: a hazard ratio <1.0 favours ZOLADEX + tamoxifen.

In the primary efficacy population, 34 (6.1%) patients randomised to receive ZOLADEX + tamoxifen died compared to 44 (7.8%) patients randomised to receive CMF. The median follow-up time was 3.8 years for both trial treatment groups. Based on the hazard ratio these results, though early, suggest that there may be a benefit in terms of survival for those patients who were randomised to receive ZOLADEX + tamoxifen compared to those who were randomised to receive CMF (see Table III).

Table III Analyses of overall survival

Efficacy population	Hazard ratio[a]	95% confidence interval	p-value
Primary	0.78	0.50, 1.22	0.271
Secondary	0.78	0.49, 1.24	0.296

[a] ZOLADEX + tamoxifen/CMF: a hazard ratio <1.0 favours ZOLADEX + tamoxifen.

The menstrual status of 456 out of the 489 patients who received CMF was known at or near completion of trial therapy. Of these 456 patients, 275 (60.3%) had amenorrhoea, and these amenorrhoeic patients fared statistically significantly better in terms of disease-free and overall survival than those patients who were not amenorrhoeic (see Table IV).

Table IV Analyses of disease-free and overall survival by menstrual status at the completion of CMF therapy (primary efficacy population)

Efficacy end-point	Hazard ratio[a]	95% confidence interval	p-value
Disease-free survival	0.53	0.36, 0.80	0.003
Overall survival	0.47	0.25, 0.90	0.022

[a] Amenorrhoea/ no amenorrhoea: a hazard ratio <1.0 favours amenorrhoea.

Fifteen (2.7%) patients randomised to ZOLADEX + tamoxifen had second primary cancers (including contralateral breast cancer) that led to withdrawal from the trial compared to 21 (3.7%) patients randomised to CMF.

Safety: Only the specific expected side effects of chemotherapy and ZOLADEX + tamoxifen pre-printed on the case report forms were recorded during the trial. No relationship to trial treatment was recorded.

Of those expected side effects recorded using the WHO scale to indicate severity, the most common experienced by patients who received ZOLADEX and tamoxifen were pain (20%), nausea/vomiting (11%), hair loss (8%) and infection (8%). None of these 4 side effects reached Grade 4 severity. The most common side effects experienced by patients who received CMF were nausea/vomiting (86%), hair loss (58%), stomatitis (24%), constipation (24%), pain (23%), infection (16%), diarrhoea (15%), cutaneous toxicity (13%) and fever (10%). For 2 to 3% of patients, nausea/vomiting and hair loss reached Grade 4 severity.

Of those expected side effects recorded on an absent/present basis, the most common experienced by patients who received ZOLADEX and tamoxifen were amenorrhoea (97%) and hot flushes (89%). These are both expected side effects of ZOLADEX which reduces circulating oestradiol levels to within the postmenopausal range. These were also the most common side effects reported on the pre-printed case report forms by patients who received chemotherapy (81% and 56%, respectively), however, the frequency of these effects was lower than for patients who received ZOLADEX + tamoxifen.