Randomized Trial of Adjuvant Tamoxifen and/or Goserelin in Premenopausal Breast Cancer

Self-rated Physiological Effects and Symptoms

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After primary surgery, 149 premenopausal breast cancer patients, with node-negative disease, were randomized to one of four treatment groups: goserelin, tamoxifen, goserelin plus tamoxifen or to a systematically untreated control group. The aim was to assess the effects of adjuvant endocrine therapy in terms of physical symptoms and perception of anxiety and depressive symptoms. Assessments were made before randomization, at 3–4 months and at 12 months. Treatment with goserelin resulted in early and more intense menopausal symptoms, while the effects of tamoxifen were slower and milder. The side effects with goserelin appeared to be alleviated by concurrent tamoxifen except for vasomotor symptoms (hot flashes, sweating, feeling warm). No significant group differences were found for anxiety and depressive symptoms. In conclusion, chemical castration with goserelin was associated with the highest level of physical symptoms. The group treated with tamoxifen alone showed the lowest levels of symptoms among the treatment groups, except for vaginal discharge and irregular bleedings.

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An overview of the randomized trials of ovarian ablation demonstrated a substantial and statistically significant survival benefit with this treatment among women aged under 50 years (1). The extent of this benefit in terms of reducing the probabilities of death was comparable with that reported in the overview of adjuvant prolonged polychemotherapy trials. However, ovarian ablation has been described as a mutilating procedure with many side effects (2). In recent years, luteinizing hormone releasing hormone (LHRH) analogues have become available in adjuvant settings. The hormonal effects in premenopausal women are the same as those with ovarian ablation (3, 4) but the treatment does not entail surgery or radiation therapy and has the potential advantage of being reversible. Goserelin acts on the hypothalamic-pituitary axis, achieving ovarian suppression by receptor down-regulation, decreasing luteinizing hormone and oestradiol levels to postmenopausal values (5). Recent results from a multicentre, randomized clinical trial involving more than 2600 patients indicated that adjuvant treatment with an LHRH analogue (goserelin) for 2 years among premenopausal women with early-stage breast cancer produces a statistically significant benefit in terms of event-free survival and a trend towards improved overall survival (6). Other recent trials have also indicated that adjuvant treatment with goserelin further improves treatment outcome when added to adjuvant cytotoxic chemotherapy (7, 8).

Adjuvant therapy with tamoxifen has been shown conclusively to improve both recurrence-free and overall survival in early-stage breast cancer (9). The treatment benefit was first established for women over the age of 50. The pharmacological effects of tamoxifen are complex, since the drug acts both as a partial oestrogen antagonist and as a partial agonist with a different balance between antagonism and agonism in different human tissues. Moreover, since tamoxifen is thought to act through competitive binding to oestrogen receptors, the pharmacological effects of the drug in a given organ system may be different in young and old women because of differing levels of circulating oestrogen (10–12).

A frequent consequence of breast cancer therapy for premenopausal women is that of menopause (13, 14). In the normal menopause the oestrogen levels decrease gradually and the symptoms vary from individual to individual.

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Hot flashes, changes in the vaginal epithelium and sleep alterations are described as early menopausal symptoms (15, 16). The oestrogen withdrawal is more acute when menopause is induced by drugs or surgery, and the symptoms and problems that women are likely to experience may be stronger (17). Several studies have mapped menopausal symptoms in breast cancer trials, but few studies are designed to capture the effects of adjuvant endocrine therapy alone and in premenopausal women.

Jaiyesimi et al. (18) concluded in a review article that tamoxifen can cause symptoms similar to those that may occur during 'normal' menopause, such as hot flashes, mild nausea, vaginal dryness, discharge and bleedings. Depressive symptoms, irritability, headache, dizziness, inability to concentrate, sleep disturbance and fatigue were observed only rarely. In the National Surgical Adjuvant Breast and Bowel Project (USA), breast cancer patients (pre- and postmenopausal) received adjuvant tamoxifen versus placebo (19). The proportion of hot flashes, vaginal discharge and irregular bleedings was higher in the tamoxifen group compared with that in the placebo group, but the difference between the groups decreased with age. In a study by Canney & Hatton (20), 93% of patients reported menopausal symptoms after ovarian ablation compared to 69% treated with tamoxifen and only 20% of patients who had no adjuvant therapy (women age <65 years in the study). Hot flashes, night sweats, vaginal dryness and musculoskeletal symptoms were more frequent in a sample of breast cancer patients than in an age-matched control group of healthy women in a study by Ganz et al. (21). For other symptoms, e.g. irritability, poor concentration and sad mood or social dysfunction, there were no between-group differences. A significant increase in hot flashes for the tamoxifen group (34%) compared to placebo (20%), for vaginal discharge (16% vs. 4%) and for menstrual irregularities (14% vs. 9%) was found in a chemoprevention study of healthy premenopausal women with an increased risk for breast cancer (22). The use of goserelin with or without tamoxifen was investigated in a study for pre- and perimenopausal women with advanced breast cancer. The prevalence of hot flashes, vaginal discharge and vaginal soreness was similar in both groups (23).

In 1990 a prospective, multicentre, randomized adjuvant trial was initiated in the Stockholm area with the aim of assessing the value of different types of adjuvant endocrine therapy in premenopausal women with invasive breast cancer. This study was conducted as a multicentre trial involving four European breast cancer trial groups: the ZIPP-trial (Zoladex in Premenopausal Breast Cancer Patients). The current report concerns patients, included by the Stockholm Breast Cancer Study Group, who contributed toward about 900 out of the more than 2600 patients who were included in all four trial groups. After primary surgery, the patients were randomly allocated to treatment with tamoxifen, tamoxifen plus the LHRH-analogue goserelin (Zoladex®), goserelin alone or to an untreated control group. The duration of all endocrine treatment was 2 years. Patients with axillary nodal involvement were offered six courses of concurrent adjuvant CMF chemotherapy. The trial permitted an unbiased and unconfounded assessment of the effect of the tested endocrine therapies alone in node-negative patients, as well as their effect in addition to chemotherapy in node-positive patients. The design of the trial is summarized in the Figure 1. The first results of the trial indicated a statistically significant benefit among the patients allocated to goserelin in terms of event-free survival and a trend towards overall survival (6).

To prevent possible confounding from the use of chemotherapy that may have endocrinological effects in premenopausal women, this report is based on patients without tumour spread to the axillary lymph nodes; that is, patients who did not receive adjuvant chemotherapy.

The purpose of the present study was to assess the symptoms and physiological effects that premenopausal breast cancer patients on goserelin and/or tamoxifen perceive during the first year after surgery in comparison to an untreated control group. Effects of the studied treatments on sexuality are reported separately.

MATERIAL AND METHODS

Participants and design

Between October 1990 and June 1994, patients in the Stockholm area, included in the randomized trial, were asked to participate in our study.

The inclusion criteria for the clinical trial were invasive breast cancer, premenopausal menstrual status (last menstruation <6 months earlier), primary surgery consisting of a modified radical mastectomy or sector resection plus axillary dissection, histopatholigical tumour size ≥ 10

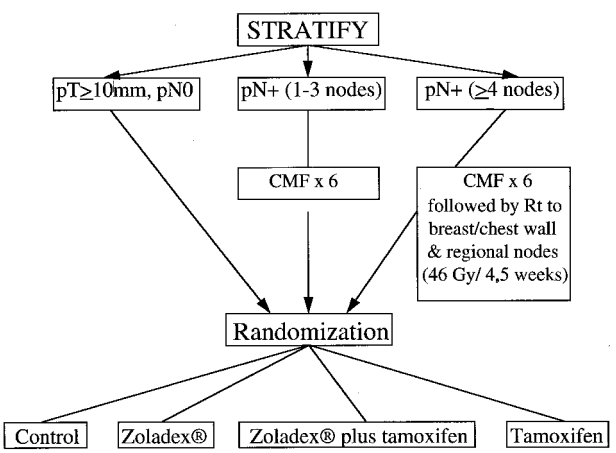

Fig. 1. Study design for the clinical trial. *Note:* All patients treated with breast conservation were offered radiotherapy (Rt) to the breast parenchyma (50 Gy/5 weeks).

mm, and no clinical evidence of distant metastases. The exclusion criteria were inoperable breast cancer, prior radiotherapy, prior neo-adjuvant chemotherapy and/or prior hormonal therapy, and current hormonal therapy.

Randomization was carried out by telephone to a central office, where the patient identifiers were recorded before the allocated treatment was revealed to the physician responsible. Treatment allocation was based on balanced lists using the permuted block technique. Informed consent was obtained from the patients before randomization, which was performed about four weeks after surgery. In conjunction with the information about the clinical trial, a research nurse informed the women both verbally and in writing about the present study. The voluntary aspect of the study was stressed and confidentiality was guaranteed. The randomized clinical trial, as well as the present study, was approved by the Karolinska Institute Regional Ethics Committee.

During October 1990 to June 1994, 194 node-negative patients were included in the randomized trial, and 149 (77%) of them were included in the present study. The remaining 45 patients were not included, for various reasons: never contacted (28), language difficulties (8), declined participation (8) and concurrent disease (1). There were no statistically significant differences between those who participated in this study and those who did not for allocated endocrine therapy, type of surgery and age (data not shown).

The patients were randomized to one of the following groups:

1. No endocrine therapy (control group) n = 37 (25%)
2. Goserelin (Zoladex®) (Z-group) n = 38 (25%)
3. Goserelin (Zoladex®) plus tamoxifen (ZT-group) n = 39 (26%)
4. Tamoxifen (T-group) n = 35 (24%)

Goserelin therapy was administered with a 3.6 mg depot s.c. injection every 4 weeks for 2 years. Tamoxifen at a dose of 40 mg daily was given orally for 2 years. A total of 67 patients (45%) underwent mastectomy. The remaining 82 patients (55%) had breast-conserving surgery, of which 78 patients were given radiotherapy to the breast (50 Gy/5 weeks). Sociodemographic data for the whole sample are presented in Table 1. There were no differences between the randomized groups for family structure, occupation or sick leave.

There were three time points of assessment using questionnaires. The pre-assessment was performed 3 to 4 weeks after surgery, before randomization and thus prior to any decision about adjuvant systemic treatment (n = 149), 3–4 months after randomization (n = 143) and 12 months after randomization (n = 136).

At 3–4 months, 6 patients had dropped out of the study: for medical reasons (1), administrative failure (4) and declined participation (1). At 12 months, 13 patients had dropped out: for medical reasons (6), administrative failure (3) declined participation (3) and death (1).

Table 1

Age and sociodemographic characteristics (n = 149)

Variable	n	%
Age, years[1]		
29–35	6	4
36–40	19	13
41–45	48	32
46–50	61	41
51–55	15	10
Living arrangements		
Alone	14	9
With husband/partner	42	28
With husband/partner and children	70	47
With children	20	14
Other	3	2
Type of occupation		
Office work	42	29
Health sector	27	18
Education	15	10
Professional job	25	17
Service sector	18	12
Other	22	14
Gainful employment	130	88
On sick leave, pre-assessment	109	73
On sick leave 3–4 months after randomization	28	20
On sick leave 12 months after randomization	12	9

[1] Mean 45 years.

The patients completed the questionnaires during their regular medical check-ups at the outpatient clinics. Completion of the questionnaire took about 20 min.

Instrument

When the present study was planned in 1989 some standardized instruments such as the Sickness Impact Profile (24) the Nottingham Health Profile (25) the FLIC (26) and the CIPS (27) were available. These instruments were all considered too general and did not include anticipated physiological effects of endocrine treatments.

The instrument used was partly taken from a questionnaire developed for breast cancer studies at our centre (28) and the Physical Symptoms and Problem List was complemented with questions that addressed the possible effects of endocrine therapy in premenopausal women. To ensure face validity, this list of symptoms was developed in collaboration with experienced oncologists. The new questionnaire was tested in a pilot study on patients and on healthcare professionals as controls. Content validity was assessed through interviews with physicians and nurses working in a dedicated breast cancer care unit.

The questionnaire included three parts:

1. *Sociodemographic Background*: questions related to age, occupation, sick leave and living arrangements.

2. *The Physical Symptoms and Problem List*: 24 items related to treatment side effects of endocrine treatment reported by at least 20% of the patients as a problem were analysed. The patients were asked to rate the perception of symptoms and problems during the preceding week. There were five response categories from 0 ('Not at all') to 4 ('Very much').
3. *The Hospital Anxiety and Depression scale (HAD scale)* (29): 14 items, each with four response choices, scored 0 to 3. The scores are summarized in two subscales (anxiety and depressive symptoms) with possible ranges of 0–21 for each subscale. The HAD scale has been found easy to administer, is well accepted by the patients and is sensitive to the mood changes that may occur during the course of a disease (30). The Swedish version was translated by Sullivan and found to be valid in a study of obese patients (31) and among patients with malignant melanoma (32). Zigmond & Snaith (29) recommended a cut-off point at scores ≥ 8 to identify cases with clinically significant levels of anxiety and depressive symptoms.

Statistical methods

A principal component analysis with orthotran/varimax rotation (33) was used to identify the basic dimensions of physical symptoms and problems reported by $\geq 20\%$ of the women (24 items). Assessment three at one year of endocrine treatment, was chosen for analysis (34).

Twenty-one symptoms formed seven factors with eigen values ≥ 1 explaining 71% of the total variance. Factor-based subscales were constructed for factors defined by at least two items. For each scale the mean of the assigned items was computed and used in subsequent analysis. For an item to be included, a factor loading ≥ 0.40 was required in one of the factors and less than 0.40 in the other factors. Consequently, 'Vaginal discharge', 'Dizziness' and 'Muscle weakness' were excluded from the factors. Internal consistency for each subscale was measured using Cronbach's alpha (35).

The factors deriving from the principal component analysis were:

1. Memory and concentration problems $\eta = 0.80$, (3 items: poor memory, concentration problems, irritability).
2. Vasomotor symptoms $\eta = 0.95$, (3 items: feeling warm, sweating, hot flashes).
3. Vaginal dryness and dry skin $\eta = 0.66$, (2 items: vaginal dryness, dry skin).
4. Mixed physical symptoms $\eta = 0.71$, (4 items: gastritis and/or heartburn, constipation, flushing, palpitations).
5. Changes in body image $\eta = 0.62$, (2 items: increased weight, changes in body image).
6. Sleep disturbances $\eta = 0.92$, (4 items: difficulty in sleeping, difficulty in falling asleep, waking up several times with difficulties in falling asleep again, waking up earlier than I want).
7. Fatigue $\eta = 0.69$, (3 items: tiredness, decreased physical fitness, headache).

The three single symptoms, excluded from the factors, were analysed separately and in addition 'irregular bleedings', because of its' high occurrence among women on tamoxifen.

ANOVA repeated measurement was used to analyse differences in group means over time and ANCOVA in the case of significant differences at pre-assessment. The Fisher's Protected Least Significant Difference (PLSD) test was applied to planned post hoc pairwise comparisons of means (33). Differences in categorical data between groups were explored by χ^2 test at each assessment (35). A p-value ≤ 0.05 was considered significant.

No randomized patient who entered the present study was excluded and all results were analysed in accordance with the intention to treat principle.

Missing values

For the HAD scale, missing data were imputed if a respondent answered at least half of the items in a subscale (36). The missing values were then replaced by the mean of the other scores in the subscale. With regard to physical symptoms, missing values were replaced by latest scores taken forward (37) or as the mean of the two adjacent scores. Missing data were imputed for 5 patients at 3–4 months and for 6 patients at 12 months.

RESULTS

Physical symptoms

Mean values and p-values for group, time and group-by-time interaction, for physical symptoms/problems grouped in seven factor-based scales and for single items are presented in Table 2. In Table 3, post hoc significant pairwise comparisons between groups are shown. The numbers and proportions of patients reporting problems (score > 0) at three assessment points are recorded in Table 4.

Factors

Memory and concentration problems increased significantly with time [$F\ (2,276) = 4.93$, $p < 0.01$]. There were no significant differences between the groups and no systematic group-by-time interaction.

Vasomotor symptoms were low in all four groups at pre-assessment but increased with time [$F(2,276) = 101.83$ $p < 0.0001$] and start of endocrine treatments (group-by-time interaction [$F(6,276) = 12.36$, $p < 0.0001$]). The highest levels of vasomotor symptoms were reported in the Z-group and the ZT-group (Table 2). These two groups (both including Zoladex®) had significantly higher levels of

problems than the control group and the T-group at 3–4 months and at 12 months. The T-group had significantly more problems than controls at both 3–4 months and at 12 months (Table 3).

Table 2

Mean values of physical symptoms/problems grouped in seven factor-based scales and three single items at three points of assessment and p-values. (Control group n = 36; Z-group n = 36; ZT-group n = 37; T-group n = 33)

	Mean values			Group	Time	Group by time
	Pre-assessment	3–4 months	12 months	p-value	p-value	p-value
Factors						
1. Memory-and concentration problems (3 items)				NS	<0.01	NS
Control	0.48	0.57	0.58			
Z-group	0.56	0.71	0.85			
ZT-group	0.47	0.55	0.67			
T-group	0.51	0.53	0.55			
2. Vasomotor symptoms (3 items)				<0.0001	<0.0001	<0.0001
Control	0.26	0.35	0.52			
Z-group	0.32	2.16	1.92			
ZT-group	0.37	2.00	1.65			
T-group	0.21	0.95	1.10			
3. Vaginal dryness and dry skin (2 items)				NS	<0.0001	<0.0001
Control	0.28	0.40	0.31			
Z-group	0.28	0.72	0.94			
ZT-group	0.34	0.49	0.59			
T-group	0.23	0.40	0.80			
4. Mixed physical symptoms (4 items)				NS	<0.0001	<0.05
Control	0.26	0.22	0.21			
Z-group	0.21	0.53	0.53			
ZT-group	0.14	0.36	0.31			
T-group	0.15	0.36	0.35			
5. Changes in body image (2 items)				NS	<0.01	<0.01
Control	0.44	0.50	0.42			
Z-group	0.43	0.54	0.78			
ZT-group	0.31	0.33	0.68			
T-group	0.55	0.42	0.44			
6. Sleep disturbances (4 items)				NS	NS	NS
Control	1.13	1.09	0.91			
Z-group	1.21	1.49	1.34			
ZT-group	1.01	1.23	1.22			
T-group	0.99	0.92	0.79			
7. Fatigue (3 items)				NS	NS	NS
Control	1.14	1.27	1.14			
Z-group	1.26	1.60	1.48			
ZT-group	1.12	1.06	1.14			
T-group	1.12	1.22	1.03			
Single items						
Vaginal discharge				NS	<0.0001	NS
Control	0.08	0.25	0.26			
Z-group	0.11	0.29	0.31			
ZT-group	0.16	0.38	0.19			
T-group	0.21	0.46	0.64			
Irregular bleedings				<0.05	NS	<0.05
Control	0.08	0.28	0.14			
Z-group	0.08	0.03	0.03			
ZT-group	0.08	0.00	0.00			
T-group	0.09	0.11	0.36			
Muscle weakness				NS	NS	<0.01
Control	0.56	0.36	0.36			
Z-group	0.36	0.61	0.94			
ZT-group	0.41	0.26	0.51			
T-group	0.52	0.61	0.47			

Table 3

Significant pairwise comparisons between groups, concerning factors and single items for significant group-by-time interactions

	Pre-assessment	3–4 months	12 months
Factors			
Vasomotor symptoms (3 items)			
Z-group—Control	NS	$p < 0.0001$	$p < 0.0001$
ZT-group—Control	NS	$p < 0.0001$	$p < 0.01$
T-group—Control	NS	$p < 0.05$	$p < 0.05$
Z-group—T-group	NS	$p < 0.0001$	$p < 0.005$
ZT-group—T-group	NS	$p < 0.0001$	$p < 0.05$
Vaginal dryness and dry skin (2 items)			
Z-group—Control	NS	$p < 0.05$	$p < 0.001$
T-group—Control	NS	NS	$p < 0.05$
Z-group—T-group	NS	$p < 0.05$	NS
Mixed physical symptoms (4 items)			
Z-group—Control	NS	$p < 0.05$	$p < 0.05$
Changes in body image (2 items)			
Z-group—Control	NS	NS	$p < 0.05$
Single items			
Muscle weakness			
Z-group—Control	NS	NS	$p < 0.05$
Z-group—T-group	NS	NS	$p < 0.05$
Vaginal discharge			
T-group—Control	NS	NS	$p < 0.05$
T-group—Z-group	NS	NS	$p < 0.05$
T-group—ZT-group	NS	NS	$p < 0.01$

Vaginal dryness and dry skin increased over time [$F(2,276) = 22.71$, $p < 0.0001$] but significantly more for the endocrine treatment groups as compared to the control group (group-by-time interaction [$F(6,276) = 4.03$, $p < 0.001$]). At 12 months the Z-group reported the highest level of symptoms followed by the T- and the ZT-groups (Table 2). While, the overall levels of vaginal symptoms in the control group were low during the year.

Significantly higher levels of *mixed physical symptoms* were reported by the Z-group compared to the control group at both 3–4 and 12 months (Table 3). There was a significant main effect of time [$F(2,276) = 13.01$, $p < 0.0001$] and significant group-by-time interaction [$F(6,276) = 2.69$, $p < 0.05$] (Table 2). However, the mean values were low and the number of patients reporting problems decreased over the year for all four groups (Table 4).

At 12 months, the women in the Z- and ZT-groups reported more changes in body image compared to the control- and T-groups. There was a significant main effect of time [$F(2,276) = 5.30$, $p < 0.01$] and significant group-by-time interaction [$F(6,276) = 3.32$, $p < 0.05$] (Table 2). Fisher's exact test showed significant a difference between the Z-group and the controls (Table 3).

There were no significant group-by-time interactions for sleep disturbances and fatigue but there was a tendency, although not statistically significant, for patients who received Zoladex® to report sleep disturbances more frequently than patients in the other groups. The clinical experience that night sweatings caused these patients to wake up is supported by the fact that the item 'Wake up several times'... showed significant differences at 3–4 and 12 months (Fisher: $p < 0.05$) between the two Zoladex® treated groups and those receiving tamoxifen alone. Almost all women (86–100%), regardless of treatment group, reported some degree of fatigue during the year (mean between 1.03 and 1.60).

Single items

'Vaginal discharge': In the T-group, 48% reported symptoms at 12 months while the corresponding number in the ZT, Z and control groups was about 20%. At 12 months, the differences were significantly different (Table 3).

'Irregular bleeding' increased over the year in the T-group, group-by-time interaction [$F(6,276) = 2.69$, $p < 0.05$)]. At 12 months, 21% in the T-group reported problems compared with 6% in the control group. 'Muscle weakness' increased over the year in the Z-group, group-by-time interaction [$F(6,276) = 3.61$, $p < 0.01$)]. There were no significant main effects or group-by-time interactions for 'Dizziness'.

Anxiety and depressive symptoms

The group means on the total HAD anxiety and depression subscales and the number of patients in the groups scoring above the cut-off point (≥ 8) are presented in Table 5. On the anxiety scale, 49% in the Z-group and 41% in the control group scored ≥ 8 at 12 months, compared

Table 4

Number of patients (χ^2 analysis) reporting symptoms (scores 1–4) in seven factor-based scales and three single items at three points of assessment. A p-value <0.05 was considered significant

	Pre-assessment		3–4 months		12 months	
	n	%	n	%	n	%
1. Memory-and concentration problems (3 items)						
Controls	21	(57)	23	(64)	23	(64)
Z-group	24	(63)	23	(61)	26	(72)
ZT-group	24	(62)	21	(54)	21	(57)
T-group	20	(57)	23	(66)	22	(67)
p-value	NS		NS		NS	
2. Vasomotor symptoms (3 items)						
Controls	13	(35)	15	(42)	15	(42)
Z-group	15	(39)	35	(92)	32	(89)
ZT-group	14	(36)	33	(85)	29	(78)
T-group	7	(20)	28	(80)	24	(73)
p-value	NS		<0.0001		<0.0001	
3. Vaginal dryness and dry skin (2 items)						
Controls	13	(35)	19	(53)	15	(42)
Z-group	15	(39)	25	(66)	26	(72)
ZT-group	18	(46)	22	(56)	22	(59)
T-group	11	(31)	17	(49)	20	(61)
p-value	NS		NS		NS	
4. Mixed physical symptoms (4 items)						
Controls	26	(70)	16	(44)	17	(47)
Z-group	27	(71)	24	(63)	22	(61)
ZT-group	26	(67)	21	(54)	20	(54)
T-group	28	(80)	19	(54)	17	(52)
p-value	NS		NS		NS	
5. Changes in body image (2 items)						
Controls	20	(54)	19	(53)	20	(56)
Z-group	18	(47)	23	(61)	29	(81)
ZT-group	14	(36)	15	(38)	20	(54)
T-group	23	(66)	19	(54)	17	(52)
p-value	NS		NS		<0.05	
6. Sleep disturbances (4 items)						
Controls	28	(76)	25	(69)	21	(58)
Z-group	26	(68)	29	(76)	26	(72)
ZT-group	25	(64)	26	(67)	27	(73)
T-group	26	(74)	24	(69)	17	(52)
p-value	NS		NS		NS	
7. Fatigue (3 items)						
Controls	34	(92)	31	(86)	31	(86)
Z-group	33	(87)	38	(100)	31	(86)
ZT-group	34	(87)	34	(87)	32	(86)
T-group	32	(91)	32	(91)	29	(88)
p-value	NS		NS		NS	
Single items						
Vaginal discharge						
Controls	3	(8)	7	(19)	8	(22)
Z-group	4	(11)	9	(24)	8	(22)
ZT-group	5	(13)	14	(36)	7	(19)
T-group	6	(17)	13	(37)	16	(48)
p-value	NS		NS		NS	
Irregular bleedings						
Controls	2	(5)	6	(17)	2	(6)
Z-group	2	(5)	0	(0)	0	(0)
ZT-group	2	(5)	0	(0)	0	(0)
T-group	3	(9)	2	(9)	7	(21)
p-value	NS		NS		NS	
Muscle weakness						
Controls	13	(35)	9	(25)	7	(19)
Z-group	10	(26)	17	(45)	17	(47)
ZT-group	13	(33)	7	(18)	12	(35)
T-group	13	(37)	14	(40)	10	(30)
p-value	NS		NS		NS	

Table 5

HAD, anxiety and depressive subscales: mean values and number of patients in the groups scored HAD anxiety and depression subscales ≥8 at three assessment points[1]

	Pre-assessment			3–4 months			12 months		
	Mean	n	%	Mean	n	%	Mean	n	%
Anxiety symptoms									
Controls	7.27	17	48	8.39	17	47	7.71	14	41
Z-group	6.69	11	29	7.14	16	43	6.65	17	49
ZT group	6.12	16	41	5.18	10	26	5.79	8	23
T-group	6.75	14	41	6.14	10	31	6.00	9	28
Depression symptoms									
Controls	3.76	4	11	4.49	8	22	4.06	5	15
Z-group	4.06	5	13	3.11	5	14	3.86	4	11
ZT-group	2.85	5	13	2.44	4	11	2.85	4	11
T-group	3.36	4	12	3.21	4	13	2.50	2	6

[1] No statistical differences between groups were found at any of the points of assessments.

with 28% in the T-group and 23% in the ZT-group. There were no statistically significant differences between the groups.

DISCUSSION

The randomized trial, which formed the basis for the current trial, was closed for patient entry in 1996. All patients allocated to systemic treatment as part of the trial have thus had the opportunity to conclude their 2-year treatment schedule. A first analysis of treatment efficacy at a median follow-up of about 4 years was recently presented (6). There was a statistically significant benefit among patients allocated to goserelin in terms of event-free survival. Their relative hazard (compared to patients not allocated to goserelin) was 0.77 (95% confidence interval 0.66–0.90, $p < 0.001$), which corresponds to a relative reduction of events by 23%. The benefit with goserelin appeared to be slightly less among those who received concurrent tamoxifen, but the difference compared to patients treated with goserelin alone was not statistically significant. There was also a survival difference favouring the goserelin-allocated patients (relative hazard 0.82, 95% CI = 0.67–1.05) but this difference was not statistically significant ($p = 0.12$). We believe that policy decisions on how the clinical trial results should be translated into clinical practice should take into account observations concerning psychological and physical side effects, such as those reported here.

This study reports on the self-rated physiological effects and symptoms perceived by premenopausal breast cancer patients on adjuvant endocrine therapy during the first year after surgery. One important aspect of the current study was that none of the patients received cytotoxic chemotherapy. Such treatment is associated with ovarian suppression. It may thus obscure the effects of endocrine therapies.

Significant differences between groups were found for vasomotor symptoms, vaginal dryness and dry skin, mixed physical symptoms, changes in body image, vaginal discharge, irregular bleedings and muscle weakness. However, the mean values of side effects were generally low; scoring less than 1 on a scale ranging from 0 to 4, with the exception of for vasomotor symptoms. Some symptoms were high (> 1), independent of endocrine treatment or not, e.g. sleeping problems and fatigue.

A wide range of symptoms has been attributed to 'normal' menopause (14, 15, 17). In a prospective study of healthy women going through the menopause, only vasomotor symptoms were significantly related to menopausal status (16). In the present study the burden of physical symptoms was significantly higher among patients receiving Zoladex® alone than in the other groups. Conversely, anxiety and depressive symptoms were fairly equal in all patient groups. Goserelin (Zoladex®) suppresses ovarian function and gives a reduction in oestrogen production to postmenopausal levels (5). The oestrogen levels decrease rapidly within three weeks, which is similar to the effects of surgical castration (2). In a study by Feldman et al. (15), almost all women (92%) suffered from hot flashes after surgical menopause. Canney & Hatton (20) reported menopausal symptoms in 93% after ovarian ablation, which may be a reflection of the change in oestrogen levels similar to that experienced by the women on Zoladex® therapy in the present study. Hunter (17) claimed that hot flashes are more prevalent in women who experience acute oestrogen withdrawal than in those experiencing a natural menopause, which could explain the differences between the Z- and control groups in the present study. Tamoxifen treatment gave lower levels of vasomotor symptoms than goserelin. After one year of treatment, 73% of the T-group scored symptoms > 0 compared with 42% in the control group. This is consistent with the results from Canney & Hatton (20), who reported menopausal symptoms in 69%

of women on tamoxifen and only 20% of patients who had no adjuvant therapy. A considerable proportion (51%) of the women in our study were perimenopausal, aged 46–55 years. Therefore, menopausal symptoms were expected over the year also for women in the control group.

Vaginal discharge has been reported as a problem for women on tamoxifen (18, 22). In our study, patients in the ZT-group reported fewer problems of vaginal discharge than the T-group, but reported having vaginal dryness to the same extent as the Z-group. The endocrine effect of tamoxifen varies depending on the hormonal status. In premenopausal women, serum oestrogen and progesterone levels increase with tamoxifen, whereas the drug has anti-oestrogenic effects on vaginal and uterine epithelium. In contrast, serum oestrogen and progesterone levels are unchanged in postmenopausal women on tamoxifen, and the drug has oestrogenic effects on vaginal and utherine epithelium (10–12). Our results indicate that premenopausal women, with medically induced menopause, have the same positive effect of tamoxifen on vaginal symptoms as postmenopausal women. However, at 12 months, 21% of the women on tamoxifen alone reported both vaginal discharge and vaginal dryness. This might be seen as a contradiction, but the two conditions may reflect different endocrine effects, so it is possible to suffer from both problems simultaneously.

Muscle weakness was more pronounced and was found to increase during the year for the patients treated with Zoladex® only. In our clinical practice, women on Zoladex® therapy have reported muscle weakness and joint problems, which is often reported in 'normal' menopause (13). Almost all women, whatever their group, suffered from tiredness and decreased physical fitness (fatigue). However, there was a steady decrease in sick leave, commensurate for the four groups, and at 12 months this had reached the 9% level. In concordance with Canney & Hatton (20), we found no support for the view that higher levels of menopausal symptoms lead to increased anxiety and depressive symptoms. Therefore these symptoms (measured by the HAD scale) should not be accounted for as side effects of adjuvant therapy.

The randomized nature of the underlying clinical trial ensured that chance variation and confounding factors could be adequately dealt with in the statistical analysis. However, the instruments that we used for assessing the effects of treatment do not fully accord with current standard methods. Guidelines for developing questionnaire modules were published some years after the initiation of the present study (38). The HAD scale has, however, been widely used in Europe for assessment of psychic distress (30). Today, the most appropriate choice would have been to add our symptom list to, for instance, the EORTC breast module, but it would still have been necessary to formulate novel questions specific to the purposes of the current study. The instrument seems to be valid, being able to detect clinically relevant differences between the randomization arms for physical symptoms. The principal components obtained formed a meaningful set of groups of items. The factor-based scales formed were sufficiently homogeneous in terms of Cronbach's alpha coefficient, even for scales consisting of only a few items.

In conclusion, the physiological effects of symptoms caused by the tested endocrine therapies were generally mild, with the exception of vasomotor symptoms. Ovarian suppression with the LHRH analogue goserelin as a post-surgical adjuvant therapy led, as expected, to menopausal symptoms. The addition of tamoxifen somewhat diminished the problem levels, while the effects of tamoxifen alone were slower and milder, with the exception of vaginal symptoms.

Further studies of this patient population during conclusion of treatment and thereafter to assess whether symptoms are reversible will increase our understanding of the complex interaction of endocrine manipulations and menopausal symptoms.

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