Quality of Life in Goserelin-Treated Versus Cyclophosphamide + Methotrexate + Fluorouracil–Treated Premenopausal and Perimenopausal Patients With Node-Positive, Early Breast Cancer: The Zoladex Early Breast Cancer Research Association Trialists Group

By H. de Haes, M. Olschewski, M. Kaufmann, M. Schumacher, W. Jonat, and W. Sauerbrei

Purpose: **To compare quality of life (QoL) in premenopausal and perimenopausal patients with node-positive, early breast cancer treated with the endocrine agent goserelin (Zoladex; AstraZeneca Pharmaceuticals LP, Wilmington, DE) or cyclophosphamide + methotrexate + fluorouracil (CMF).**

Patients and Methods: **Patients from 86 centers worldwide were randomly assigned to receive either goserelin (3.6 mg every 28 days for 2 years; n = 514) or CMF (six 28-day cycles; n = 496), and were included in the QoL study. QoL was assessed using a self-administered patient questionnaire that consisted of 39 items from the Rotterdam Symptom Checklist, including dimensions evaluating physical and psychological symptom distress, activities of daily living, hormonal effects, and an assessment of overall QoL.**

Results: **Early benefits were noted during months 3 to 6 of treatment, for goserelin compared with CMF. Significant differences were found for changes in overall QoL (eg, 6.96 ± 0.88 *v* 0.69 ± 0.92 at 6 months; $P < .0001$) and for physical symptom distress, activity levels, and "effort to cope with illness" dimensions. At 1, 2, and 3 years, there were no significant differences in overall QoL or specific QoL dimensions. Scores for hormonal symptoms were worse with goserelin during the 2-year goserelin treatment period; however, this trend was reversed at 3 years.**

Conclusion: **Goserelin offers improved overall QoL during the first 6 months of therapy compared with CMF chemotherapy in premenopausal and perimenopausal patients with early breast cancer. Coupled with equivalent efficacy in estrogen receptor-positive patients, these data support the use of goserelin as an alternative to CMF in premenopausal and perimenopausal patients with estrogen receptor-positive, node-positive early breast cancer.**

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THE ZOLADEX Early Breast Cancer Research Association (ZEBRA) study was a large, international trial to compare goserelin (Zoladex; AstraZeneca Pharmaceuticals LP, Wilmington, DE) with the cytotoxic chemotherapy regimen cyclophosphamide + methotrexate + fluorouracil (CMF) in premenopausal and perimenopausal patients with node-positive early breast cancer. This study demonstrated that, in terms of disease-free survival, goserelin was equivalent to CMF in patients with estrogen receptor- (ER-) positive tumors, while in patients with ER-negative tumors, CMF was superior to goserelin.[1] Goserelin has a favorable adverse effect profile, and, therefore, factors such as quality of life (QoL) and patients' preferences become important in deciding which treatment to choose in the ER-positive patient population.

Studies to date have shown a range of acute and late adverse effects of adjuvant chemotherapy that have the potential to substantially affect patients' QoL. Adverse effects that may be particularly debilitating include nausea, vomiting, alopecia, and fatigue. In two large-scale clinical trials conducted by the International Breast Cancer Study Group (IBCSG VI and VII), adjuvant chemotherapy (CMF) was shown to have a measurable effect on health-related QoL during the 6-month treatment period.[2] QoL measurements have been shown to worsen during adjuvant chemotherapy, but to improve after cessation of treatment.[3]

Both CMF chemotherapy and goserelin treatment induce amenorrhea; however, while it is reversible in the majority of patients following cessation of goserelin, it is generally permanent with chemotherapy.[4] Patients in whom treatment results in permanent amenorrhea will have to endure the short- and long-term effects of an early menopause, including hot flashes, psychological and genitourinary effects, bone loss, earlier onset of osteoporosis, and an increased risk of heart disease.[5,6]

In general, goserelin has been well tolerated, with the most common adverse effects being hormonal. In the ZEBRA study, menopausal symptoms, such as vaginal dryness and hot flashes, were initially lower with CMF than with goserelin (13.9% *v* 23.8% and 42.4% *v* 72.4% at 6 months, respectively).[1] However, after the end of goserelin treatment, the incidence of these effects

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in the goserelin group had fallen to below that seen in the CMF group. The incidence of cytotoxic adverse effects was substantially higher with CMF than with goserelin during the 6-month CMF treatment period. For example at 6 months, the incidence of nausea/vomiting, despite the use of antiemetics in over 97% of CMF patients for each cycle (56.4% *v* 5.3%), alopecia (43.4% *v* 3.5%) and infection (12.9% *v* 4.8%) were all higher for CMF than for goserelin. Loss of libido was reported in 47.4% of patients who received goserelin for the treatment of advanced breast cancer—a finding that has been reported in other studies of the endocrine treatment of breast cancer.[7,8] The role of goserelin in the treatment of breast cancer is emerging[9] and may offer a more acceptable treatment alternative for adjuvant therapy in younger women, avoiding both the short-term adverse effects associated with cytotoxic chemotherapy and the long-term effects of a premature menopause.

This article reports a protocoled substudy of the ZEBRA trial, which was designed to compare QoL during and following treatment with goserelin or CMF.

PATIENTS AND METHODS

Study Design

The ZEBRA study was an international, multicenter, open, randomized study initiated in 1990 to compare the efficacy and tolerability of goserelin with CMF in premenopausal and perimenopausal women with histologically proven, node-positive early breast cancer. Patients were recruited throughout a 6-year period, between October 1, 1990 and December 30, 1996, from 102 centers in 15 countries, from which a subgroup from 86 centers took part in the QoL study. Following local therapy for breast cancer (mastectomy or breast-conserving therapy ± radiotherapy, according to local practice), patients were randomized in a 1:1 ratio to receive goserelin or CMF chemotherapy. Randomization took place by the investigator contacting the Institute of Medical Biometry and Informatics at Freiburg, Germany, where the random assignment was performed centrally. If a patient fulfilled entry criteria, a patient number and treatment were assigned from a central randomization list. Patients were stratified for random assignment by center, and, within each center, randomized blocks were used with a random block length of six or eight.

The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and following local ethics committee approval. In a protocoled ZEBRA substudy, QoL was prospectively assessed in a subgroup of patients using a written, self-administered questionnaire. Patients were asked to complete the questionnaire before the start of treatment, and at 3 and 6 months and 1, 2, and 3 years after treatment commenced. Answers were based on the patients' experiences during the previous week.

Patients

Women were included if they were premenopausal or perimenopausal and ≤ 50 years of age, had node-positive Union Internationale Contre le Cancer stage II histologically proven operable invasive breast cancer with no evidence of metastatic disease, and had not received previous systemic therapy. All patients gave their informed consent to participate in the trial. Patients were excluded if they had concurrent or previous invasive malignancy (except squamous or basal cell skin carcinoma or cervical carcinoma), had received bilateral oophorectomy or radiation of the ovaries, were pregnant or breast feeding, had inadequate liver or renal function, or had evidence of blood disorders.

Patients were randomized to receive either goserelin 3.6 mg depot subcutaneously (every 28 days for 2 years [ie, 26 depots]) or CMF chemotherapy (six cycles, each cycle being 28 days unless treatment was delayed).[10] A cycle of CMF consisted of: cyclophosphamide (500 mg/m^2 given intravenously on days 1 and 8, or 100 mg/m^2 given orally on days 1 to 14), methotrexate (40 mg/m^2 given intravenously on days 1 and 8), and fluorouracil (600 mg/m^2 given intravenously on days 1 and 8).

For patients randomized after October 1, 1991, QoL was assessed. Patients were excluded from the QoL analysis if they were without a baseline QoL assessment or without any postbaseline data.

QoL Assessments

QoL was evaluated using a written, self-administered patient questionnaire. The questionnaire consisted of the 39 items of the Rotterdam Symptom Checklist (RSCL),[11] two additional items ("hot flashes/sweating" and "weight changes"), three social domain questions,[12] and an "effort to cope with illness" visual analog scale.[13] Validation studies have substantiated the reliability and validity of the RSCL.[14]

All symptom-related RSCL items and hot flashes/sweating and weight changes were on a 4-point scale, and overall QoL was assessed by one question on a 7-point scale that had proven to be sensitive to changes in patients with cancer.[15] The effort to cope with illness visual analog scale was recorded on a scale of 0 to 100.

The final questionnaire included seven dimensions, evaluating the following: overall QoL, physical symptom distress (sum of 23 items), psychological distress (sum of seven items), activities of daily living (sum of eight items), social effects (sum of three items), hormonal effects (hot flashes/sweating and weight changes), and effort to cope with illness.

All QoL scores were standardized to the range 0 to 100, with 0 representing the worst possible, and 100 representing the best possible condition. A positive change in QoL score from baseline represented an improvement.

Questionnaires were translated according to the forward-backward procedure in those countries for which a validated translation of the RSCL was not yet available.[16]

Statistical Analysis

Patients were included in the statistical analysis for QoL if they had a baseline score and at least one postbaseline score. Comparability at baseline of the two treatment groups was assessed in terms of age, type of surgery, medical, and social factors. QoL data after a recurrence were excluded from the analysis. Analysis of covariance was used on the change from baseline to each postbaseline assessment time. The dependent variable in the model was change from baseline and the independent variables were baseline value, treatment, and grouped country. In constructing the grouped country covariate, patients were grouped as follows: Germany; UK, Republic of Ireland, and Australia; Eastern Europe; France and Belgium; Finland; and Latin America.[16] Given the large sample size and the number of tests, the *P* value chosen for statistical significance was .01.

A factor analysis was performed to break the physical dimension into smaller symptom domains to enhance clinical interpretation while retaining psychometric properties. Five factor groupings were identified: nausea/vomiting (sum of three items), pain (sum of five items), fatigue (sum of four items), other therapy-related symptom (sum of 10 items), and sexual interest (one item).

Given that the ZEBRA trial demonstrated equivalence between CMF and goserelin in the ER-positive patients,[1] QoL was also retrospectively analyzed in the subgroup of patients with ER-positive tumors.

RESULTS

Patient Demographics

In total, 514 patients receiving goserelin and 496 patients receiving CMF treatment in 86 centers were initially included in the QoL substudy (Fig 1). Patient and disease characteristics of the two treatment groups were similar (Table 1). Baseline QoL scores and social factors were also similar for the two treatment groups. Baseline QoL scores are shown in Table 2.

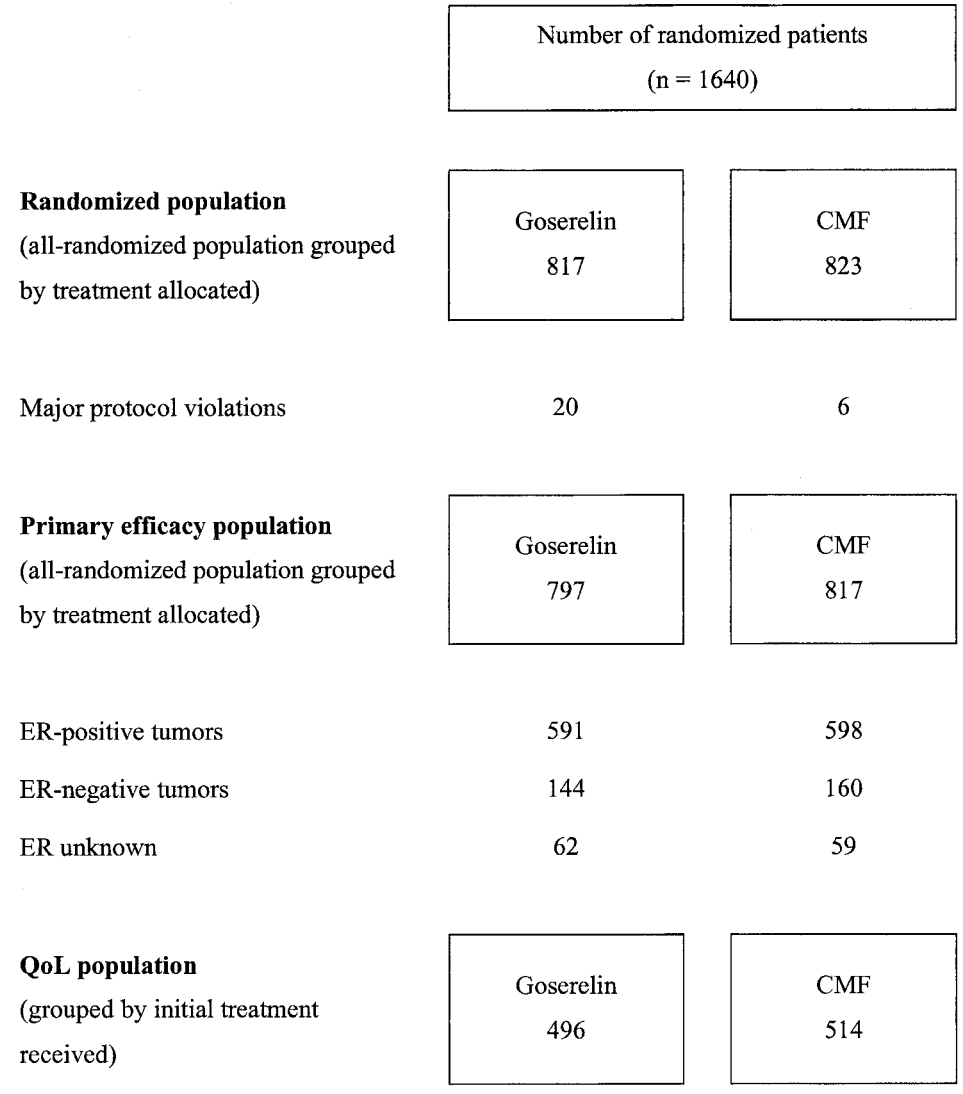

Fig 1. Defined patient populations within the Zoladex Early Breast Cancer Research Association quality-of-life subgroup study.

ER = Estrogen receptor
QoL = Quality of Life
CMF = Cyclophosphamide/methotrexate/5-fluorouracil

QoL Assessments

The number of patients available for QoL analysis at the various time points declined over time. For example, 1,010 patients provided physical scores at baseline. After 1 year, 803 patients were available, and after 3 years, 451 patients were available for analysis. Other QoL assessments exhibited similar decreases.

Overall QoL

The improvement in score for overall QoL from baseline was significantly greater ($P < .0001$) in the goserelin-treated group compared with the CMF-treated group during the first 3 to 6 months (4.86 ± 0.81 *v* -0.66 ± 0.87 at 3 months, and 6.96 ± 0.88 *v* 0.69 ± 0.92 at 6 months). However, at 1 year (7.90 ± 0.89 *v* 7.43 ± 0.92), 2 years (9.44 ± 0.96 *v* 11.05 ± 0.99), and 3 years (13.06 ± 1.18 *v* 11.15 ± 1.18), there were no differences in the change in overall QoL scores between the goserelin and CMF groups (Fig 2).

Physical Symptom Distress

During the first 3 to 6 months of therapy, early benefits in QoL were found for goserelin, with a significantly smaller decrease ($P < .0001$) in physical symptom distress than with CMF (-2.19 ± 0.44 *v* -7.11 ± 0.47 and -2.23 ± 0.51 *v* -6.37 ± 0.52 at 3 and 6 months, respectively, Fig 3). One to 3 years after the start of treatment, there were no significant differences in the change in physical symptom distress between the two treatment groups.

This difference at 3 to 6 months was primarily due to the significantly higher ($P < .0001$) incidence of nausea or vomiting,

Table 1. Patient and Disease Characteristics at Baseline

Characteristic	Goserelin (n = 514)		CMF (n = 496)	
	No. of Patients	%	No. of Patients	%
Mean age, years	42.6		42.8	
Menstrual/hysterectomy status				
Normal	436	84.8	442	89.1
Menorrhagia	6	1.2	11	2.2
Oligomenorrhea	27	5.3	20	4.0
Amenorrhea	5	1.0	3	0.6
Hysterectomy	40	7.8	20	4.0
Positive nodes				
0	1	0.2	0	0.0
1-3	355	69.1	361	72.8
4-9	134	26.1	116	23.4
≥ 10	18	3.5	16	3.2
Missing or unspecified	6	1.2	3	0.6
Local therapy				
Breast-conserving surgery	254	49.4	238	48.0
Mastectomy	260	50.6	258	52.0

Abbreviation: CMF, cyclophosphamide + methotrexate + fluorouracil.

and other therapy-related symptoms experienced by patients receiving chemotherapy. There was no significant difference in the amount of pain or fatigue reported by the two groups. Scores for the effect on sexual interest were worse in the goserelin group during treatment, though at 3 years, this effect was reversed (-1.09 ± 0.54 *v* 0.75 ± 0.56 at 2 years, and -0.99 ± 0.64 *v* 1.10 ± 0.64 at 3 years for goserelin and CMF, respectively).

Psychological Distress

No significant differences were observed between goserelin and CMF in terms of change in score on the psychological distress dimension during (4.99 ± 0.81 *v* 2.92 ± 0.85, and 4.40 ± 0.91 *v* 1.96 ± 0.93 at 3 and 6 months, respectively) or after treatment (12.49 ± 1.27 *v* 10.48 ± 1.25, respectively, at 3 years).

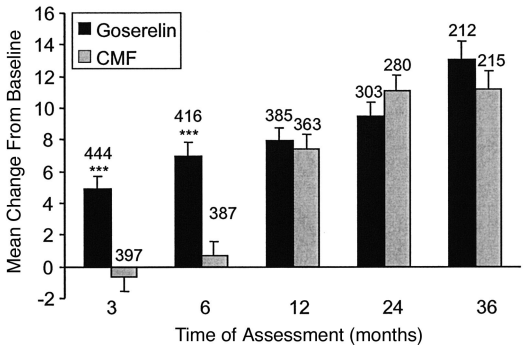

Fig 2. Improvement in overall quality-of-life (least square mean) after treatment with goserelin or cyclophosphamide + methotrexate + fluorouracil (CMF). (***), $P < .0001$ for goserelin versus CMF.

Activities of Daily Living

Patients receiving goserelin demonstrated a significantly greater ($P < .0001$) improvement in score on the activity level dimensions of the RSCL than those receiving CMF during months 3 to 6 of therapy (8.71 ± 0.52 *v* 5.37 ± 0.54, and 10.79 ± 0.55 *v* 6.47 ± 0.56, respectively, at 3 and 6 months). Again, there were no significant differences in the improvement in scores between the treatment groups 1 to 3 years after the start of treatment (Fig 4).

Hormonal Effects

The change in score for hormonal effects was significantly worse in the goserelin group during the 2-year goserelin treatment period compared with the CMF group ($P < .01$; -27.78 ± 1.07 *v* -14.51 ± 1.12 at 3 months, and -24.97 ± 1.35 *v* -19.07 ± 1.38 at 2 years). However, at 3 years (1 year after the cessation of goserelin therapy), this trend was reversed, with significantly better scores observed in the goserelin group (-5.77 ± 1.43 *v* -17.79 ± 1.42; $P < .0001$; Fig 5).

Table 2. Baseline QoL Scores of Patients in the QoL Population

QoL Category	Goserelin			CMF		
	Mean*	SD	No. of Patients	Mean*	SD	No. of Patients
RSCL dimension scores						
Physical symptom distress	88.2	8.4	513	87.9	9.0	492
Psychological distress	69.2	22.8	513	70.0	20.4	492
Activities of daily living	85.4	16.3	509	84.5	16.9	493
Other QoL scores						
Hormonal effects	89.3	15.2	514	88.4	15.2	493
Social effects	61.0	19.1	502	61.3	19.4	485
Effort to cope with illness	57.9	30.1	501	60.3	27.6	481
Overall QoL	69.7	19.4	496	69.3	18.9	473
RSCL subdimension scores of physical distress dimension						
Fatigue	74.8	18.7	513	74.9	19.0	494
Pain	86.2	12.7	513	87.8	12.3	492
Nausea/vomiting	95.0	9.4	512	92.1	14.5	491
Lack of sexual interest	77.2	30.0	501	76.5	30.3	470
Other therapy-related symptoms	93.6	7.1	513	93.1	7.4	492

Abbreviations: QoL, quality of life; CMF, cyclophosphamide, methotrexate, and fluorouracil; SD, standard deviation; RSCL, Rotterdam Symptom Checklist.
*Scores range from 0 to 100, with 0 representing the worst possible condition, and 100 representing the best possible condition.

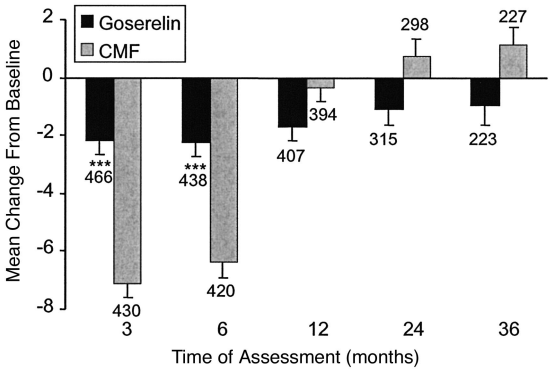

Fig 3. Changes in physical symptom distress (least square mean) after treatment with goserelin or cyclophosphamide + methotrexate + fluorouracil (CMF). (***), $P < .0001$ for goserelin versus CMF.

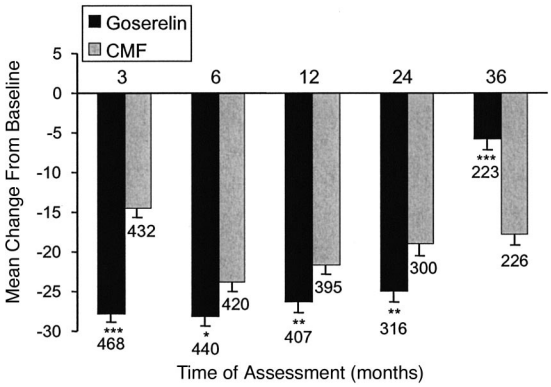

Fig 5. Changes in hormonal effects (least square mean) after treatment with goserelin or cyclophosphamide + methotrexate + fluorouracil (CMF). (*), $P < .01$; (**), $P < .001$; (***), $P < .0001$ for goserelin versus CMF.

Social Effects

Changes in social effects were small throughout the trial (-2.61 ± 0.92 *v* -2.06 ± 0.95 at 6 months, and -1.05 ± 1.38 *v* -1.12 ± 1.38, for goserelin and CMF at 3 years, respectively), and no significant differences were observed between the treatment groups.

Effort to Cope With Illness

Patients receiving goserelin required significantly less effort to cope with illness during the first 3 to 6 months of treatment ($P < .0001$) than those receiving CMF. The improvement in score was 13.41 ± 1.12 *v* 4.22 ± 1.18 and 15.91 ± 1.19 *v* 5.80 ± 1.23 for goserelin and CMF, respectively, at 3 and 6 months. However, no significant differences between treatment groups were observed at 1 to 3 years (Fig 6).

ER-Positive Patients

As the efficacy results demonstrated equivalence between goserelin and CMF in patients with ER-positive tumors, a retrospective analysis of QoL was performed in this subgroup. Treatment differences in women with ER-positive tumors were qualitatively identical to those obtained in the overall population for all QoL dimensions and subdimensions at all time points. For example, during the initial 6 months, the overall QoL for ER-positive patients was significantly better ($P < .0001$) in the goserelin-treated group (4.37 ± 0.98 at 3 months, and 6.38 ± 1.01 at 6 months) compared with the CMF-treated group (-1.25 ± 1.06 at 3 months, and -0.32 ± 1.08 at 6 months). As with the overall population, after 1 year (8.25 ± 0.98 *v* 7.27 ± 1.04), 2 years (8.84 ± 1.09 *v* 10.82 ± 1.19), and 3 years (12.38 ± 1.35 *v* 9.82 ± 1.38), no significant differences could be observed in QoL between the ER-positive goserelin and CMF groups, respectively.

DISCUSSION

The results of this study show that there was an improvement in overall QoL during the trial for patients in both treatment groups. Based on the mean level, in the goserelin group, there was a continual improvement in overall QoL throughout the treatment period, but in the CMF group, overall QoL improved markedly only when treatment had ceased.

During the first 3 to 6 months of therapy, patients receiving goserelin demonstrated a significantly better overall QoL than patients receiving CMF. These early advantages were mirrored in patients with ER-positive tumors, in whom equivalent efficacy of the two treatments was demonstrated.[1] In the period beyond 6 months after the start of treatment, no difference in overall QoL

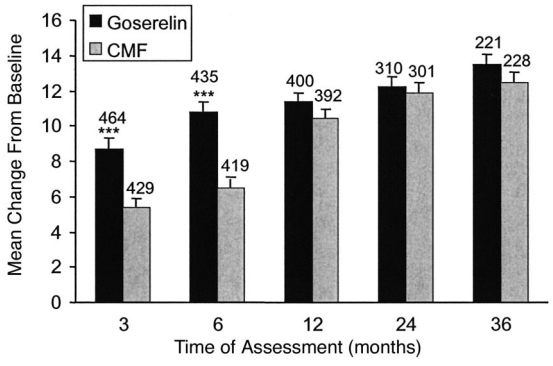

Fig 4. Improvement in activities of daily living (least square mean) after treatment with goserelin or cyclophosphamide + methotrexate + fluorouracil (CMF). (***), $P < .0001$ for goserelin versus CMF.

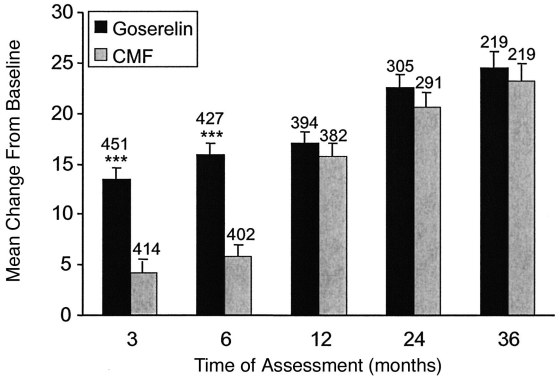

Fig 6. Improvement in effort to cope with illness (least square mean) after treatment with goserelin or cyclophosphamide + methotrexate + fluorouracil (CMF). (***), $P < .0001$ for goserelin versus CMF.

was observed, though patients randomized to goserelin were still receiving active treatment for as long as 2 years.

The improvements in overall QoL during the first 6 months were consistent with results seen in the physical dimension, activities of daily living, and the effort needed to cope with illness, in which significant differences were observed between goserelin and CMF in months 3 to 6, but no significant differences were seen thereafter. These differences are not unexpected considering the incidence of chemotherapy-related adverse events, such as nausea and vomiting, and alopecia as observed in this trial.

During the 2-year goserelin treatment period, a higher percentage of patients receiving goserelin became amenorrheic compared with patients who had received chemotherapy. Consequently, these patients experienced higher incidences of hormonal adverse effects as a result of reduced circulating levels of estradiol. However, at 3 years (1 year after the completion of goserelin therapy), menses returned for the majority of patients. In contrast, amenorrhea was generally permanent with CMF. This is reflected in the QoL assessment of hormonal effects; during the first 2 years after starting trial therapy, patients who received goserelin had markedly worse hormonal effects scores than those who received CMF. However, 1 year after completion of goserelin therapy, the effect was reversed, with the hormonal effects score being statistically significantly better for goserelin than for CMF.

These hormonal effects scores are also reflected in the single question on sexual interest included in the physical distress dimension of the RSCL, suggesting that individual patients who value sexuality highly might prefer chemotherapy as a matter of individual preference. The treatment choice then has to be discussed with individual patients to explore the value that they attach to the different outcomes and weighing these in their final treatment preference.[17] Similar effects on sexual interest have previously been reported.[8,18] In the study by Berglund et al,[18] goserelin alone and in combination with tamoxifen resulted in sexual dysfunction 1 to 2 years after inclusion, which was reversible following the withdrawal of therapy; patients receiving chemotherapy in this study also experienced sexual dysfunction that was still apparent 3 years after random assignment.[18]

While the absolute mean differences between treatments in the overall patient population may be small, they are highly significant and are considered to be clinically meaningful. It has recently been suggested that a change of 50% of the SD of any QoL measure can be considered clinically significant, and that a change of 8 to 10 points on a 100-point scale is similarly considered significant.[19] As can be seen from the data presented here, all the differences meet the former criteria for significance. In addition, a difference of 8 to 10 points is seen for the hormonal effects favoring CMF in the short term and goserelin in the longer term, and in the overall effort needed to cope with the illness that clearly favors goserelin.

In summary, compared with CMF, goserelin improved overall QoL during the 6-month CMF treatment period. This is attributable to similar differences that were seen on dimensions of physical activity and effort to cope with illness. No significant differences in overall QoL were seen after 6 months. Differences seen in the hormonal dimension were worse during the goserelin treatment period but reversed in favor of goserelin after cessation of therapy. However, these differences in hormonal effects did not impact on overall QoL. Coupled with the equivalent efficacy in ER-positive patients, these early benefits in QoL support the use of goserelin as an alternative to CMF in this patient population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Hanneke de Haes, AstraZeneca.

REFERENCES

1. Jonat W, Kaufmann M, Sauerbrei W, et al: Goserelin versus CMF as adjuvant therapy in premenopausal patients with node-positive breast cancer: the ZEBRA study. J Clin Oncol 20:4628-4635, 2002

2. Hurny C, Bernhard J, Coates A: Quality of life assessment in the International Breast Cancer Study Group: Past, present, and future. Recent Results Cancer Res 152:390-395, 1998

3. Shapiro CL, Recht A: Side effects of adjuvant treatment of breast cancer. N Engl J Med 344:1997-2008, 2001

4. Jonat W: Zoladex versus adjuvant therapy in pre/peri-menopausal breast cancer: tolerability and amenorrhoea comparisons. Proc Am Soc Clin Oncol 19:87, 2000 (abstr 333)

5. Bines J, Oleske DM, Cobleigh MA: Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol 14:1718-1729, 1996

6. Goodwin PJ, Ennis M, Pritchard K, et al: Risk of menopause during the first year after breast cancer diagnosis. J Clin Oncol 17:2365-2370, 1999

7. Blamey RW, Jonat W, Kaufmann M, et al: Zoladex depot in the treatment of premenopausal advanced breast cancer. Eur J Cancer 28:810-814, 1992

8. Fallowfield LJ, Leaity SK, Howell A, et al: Assessment of quality of life in women undergoing hormonal therapy for breast cancer: Validation of an endocrine symptom subscale for the FACT-B. Breast Cancer Res Treat 55:189-199, 1999

9. Kaufmann M, von Minckwitz G: The emerging role of hormonal ablation as adjuvant therapy in node + and node - pre-/perimenopausal patients. Breast 10:123-129, 2001 (suppl 3)

10. Bonadonna G, Brusamolino E, Valagussa P, et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405-410, 1976

11. de Haes JCJM, Van Knippenberg FCE, Neijt JP: Measuring psychological and physical distress in cancer patients: Structure and application of the Rotterdam Symptom Check List. Br J Cancer 62:1034-1038, 1990

12. Tempelaar R, de Haes JCJM, de Rutter JH, et al: The social experiences of cancer patients under treatment: A comparative study. Soc Sci Med 29:635-642, 1989

13. Hurny C, Bernhard J, Gelber RD, et al: Quality of life measures for patients receiving adjuvant therapy for breast cancer: An international trial—The International Breast Study Group. Eur J Cancer 28:118-124, 1992

14. de Haes JCJM, Olschewski M, Fayers P, et al: Measuring the quality of life of cancer patients with the Rotterdam Symptom Checklist (RSCL): A Manual. Groningen, the Netherlands, Northern Center for Healthcare Research, University of Groningen, 1996

15. de Haes JCJM, De Ruiter JH, Tempelaar R, et al: The distinction between affect and cognition in the quality of life of cancer patients: Sensitivity and stability. Qual Life Res 1:315-322, 1992

16. de Haes JCJM, Olschewski M: Quality of life assessment in a cross-cultural context: Use of the Rotterdam Symptom Checklist in a multinational randomized trial comparing CMF with Zoladex (Goserelin) treatment in early breast cancer. Ann Oncol 9:745-750, 1998

17. Stiggelbout AM, de Haes JCJM: Patient preference for cancer therapy: An overview of measurement approaches. J Clin Oncol 19:220-230, 2001

18. Berglund G, Nystedt M, Bolund C, et al: Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: A prospective randomized study. J Clin Oncol 19:2788-2796, 2001

19. Sloan J: Asking the obvious questions regarding patient burden. J Clin Oncol 20:4-6, 2002