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Adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression: patient-reported outcomes in the TEXT and SOFT randomised trials

Jürg Bernhard, Ph.D.,

International Breast Cancer Study Group Coordinating Center and Bern University Hospital, Inselspital, Bern, Switzerland

Weixiu Luo, M.D., M.S.,

International Breast Cancer Study Group Statistical Center, Dana-Farber Cancer Institute, Boston, MA, USA

Karin Ribí, Ph.D.,

International Breast Cancer Study Group Coordinating Center, Bern, Switzerland

Marco Colleoni, M.D.,

Division of Medical Senology, European Institute of Oncology and International Breast Cancer Study Group, Milan, Italy

Harold J. Burstein, M.D., Ph.D.,

Dana-Farber Cancer Institute and Alliance for Clinical Trials in Oncology, Boston, MA, USA

Carlo Tondini, M.D.,

Medical Oncology, Osp. Papa Giovanni XXIII and International Breast Cancer Study Group, Bergamo, Italy

Graziella Pinotti, M.D.,

Medical Oncology, Ospedale di Circolo and Fondazione Macchi and International Breast Cancer Study Group, Varese, Italy

Simon Spazzapan, M.D.,

Medical Oncology, Centro di Riferimento Oncologico and International Breast Cancer Study Group, Aviano, Italy

Corresponding Author: Jürg Bernhard, Ph.D. International Breast Cancer Study Group (IBCSG) Coordinating Center, Effingerstrasse 40, 3008 Bern, Switzerland; tel: +41-031-389-9391, fax +41-031-389-9229, juerg.bernhard@ibcsg.org. TEXT and SOFT Investigators and the International Breast Cancer Study Group (IBCSG) are listed in Supplementary Material, available with the full text of this article at [journal website].

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DISCLOSURES

All other authors declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

J.B., K.R., O.P., P.A.F., G.F.F., B.A.W., A.S.C., A.G., and R.D.G. participated in the design. M.C., H.J.B., C.T., G.P., S.S., T.R., F.P., L.P., V.P., O.P., G.F.F., P.A.F., A.G., B.A. W. participated in data collection. W.L., M.M.R., J.B., K.R., K.N.P., R.D.G. participated in data analysis. All authors participated in data interpretations, drafting and finalising the report.

Thomas Ruhstaller, M.D.,

Breast Center, Kantonsspital St. Gallen, Swiss Group for Clinical Cancer Research (SAKK) and International Breast Cancer Study Group, St. Gallen, Switzerland

Fabio Puglisi, M.D., Ph.D.,

Department of Oncology, University Hospital of Udine, University of Udine and International Breast Cancer Study Group, Udine, Italy

Lorenzo Pavesi, M.D.,

Oncology Unit, Salvatore Maugeri Foundation and International Breast Cancer Study Group, Pavia, Italy

Vani Parmar, MBBS, MS, DNB,

Surgical Oncology, Breast Services, Tata Memorial Hospital and International Breast Cancer Study Group, Mumbai, India

Meredith M. Regan, Sc.D.,

International Breast Cancer Study Group Statistical Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Olivia Pagani, M.D.,

Institute of Oncology of Southern Switzerland, Swiss Group for Clinical Cancer Research (SAKK), and International Breast Cancer Study Group, Lugano Viganello, Switzerland

Gini F. Fleming, M.D.,

The University of Chicago Medical Center and Alliance for Clinical Trials in Oncology, Chicago, IL, USA

Prudence A. Francis, M.D.,

Peter MacCallum Cancer Center, St Vincent's Hospital, University of Melbourne, Melbourne and Australia & New Zealand Breast Cancer Trials Group, Newcastle, Australia; International Breast Cancer Study Group

Karen N. Price, B.S.,

International Breast Cancer Study Group Statistical Center, Frontier Science and Technology Research Foundation, Boston, MA, USA

Alan S. Coates, M.D.,

International Breast Cancer Study Group and University of Sydney, Sydney, Australia

Richard D. Gelber, Ph.D.,

International Breast Cancer Study Group Statistical Center, Dana-Farber Cancer Institute, Harvard Medical School, Harvard School of Public Health, Frontier Science and Technology Research Foundation, Boston, MA, USA

Aron Goldhirsch, M.D., and

Program for Breast Health (Senology), European Institute of Oncology, Milan, Italy & International Breast Cancer Study Group, Bern, Switzerland

Barbara A. Walley, M.D.

Tom Baker Cancer Centre and NCIC Clinical Trials Group, Calgary, AB, Canada

Abstract

Background—Efficacy analysis of the combined IBCSG TEXT and SOFT trials showed a significant disease-free survival benefit for exemestane plus ovarian function suppression (OFS) compared with tamoxifen +OFS. We present patient-reported outcomes from these trials.

Methods—Between 7 November 2003 and 7 April 2011, 4717 premenopausal patients with hormone-receptor positive breast cancer were enrolled in TEXT or SOFT to receive unblinded adjuvant treatment with 5 years of exemestane+OFS or tamoxifen+OFS. Chemotherapy use was optional. Randomization was performed via IBCSG's internet-based system with the use of permuted blocks and was stratified by chemotherapy use and lymph nodes status. Patients completed a quality of life (QoL) form including several global and symptom-specific indicators at baseline, every 6 months for 24 months, then annually during years 3 to 6. Differences in change of QoL from baseline between the two treatments were tested at short-, mid-, and long-term using mixed-models for repeated measures, for each trial with and without chemotherapy and overall. The analysis was intention-to-treat using treatment as randomly assigned. At the time of analysis, the median follow-up was 5.7 years (IQR, 3.7 to 6.9 years), with treatment and follow-up of patients ongoing.

Findings—Patients reported considerable worsening from baseline in key endocrine symptoms. Those on tamoxifen+OFS were more affected by hot flushes and sweats over five years than those on exemestane+OFS, although these symptoms improved. Patients on exemestane+OFS reported more vaginal dryness, greater loss of sexual interest, and difficulties becoming aroused. These differences persisted over time. An increase in bone/joint pain was more pronounced, particularly in the short-term, in patients on exemestane+OFS. Changes of global QoL indicators from baseline were small and similar between treatments over the whole treatment period.

Interpretation—Overall, from a QoL perspective, there is no strong indication to favor either exemestane+OFS or tamoxifen+OFS. The differential effects of the two treatments on endocrine symptoms burden need to be addressed with patients individually.

Funding—TEXT and SOFT receive financial support for trial conduct from Pfizer, the International Breast Cancer Study Group and the US National Cancer Institute. Pfizer and Ipsen provide drug supply. See Acknowledgment for grants and grant numbers.

Keywords

adjuvant therapy; aromatase inhibitor; breast cancer; endocrine therapy; exemestane; GnRH agonist; ovarian function suppression; premenopausal; quality of life; sexual functioning; tamoxifen; triptorelin

INTRODUCTION

In premenopausal patients with hormone receptor-positive breast cancer, the TEXT and SOFT combined analysis showed a significant disease-free survival benefit for exemestane plus ovarian function suppression (OFS) compared with tamoxifen+OFS, providing a new treatment option for premenopausal women who receive OFS as part of adjuvant endocrine therapy.¹ Whether or not to give chemotherapy was decided by the physician and patient. In TEXT, chemotherapy was administered concurrently with OFS after randomization. In

SOFT, patients who received chemotherapy were eligible for randomization only if they remained premenopausal after completion.²

Comparisons of tamoxifen with an aromatase inhibitor have been extensively studied in postmenopausal patients. The arimidex, tamoxifen, alone or in combination (ATAC) trial,^{3,4} and the intergroup exemestane study (IES)⁵ assessed patient-reported symptoms related to endocrine therapy. These trials revealed no major effect on overall quality of life (QoL) and total symptom scores according to endocrine agents. Patients reported hot flushes as the most prevalent side-effect but indicated no differences between tamoxifen and anastrozole^{3,4} or exemestane.⁵ Self-reported gynecological symptoms (i.e. vaginal dryness, diminished libido, pain with intercourse) were more frequent with anastrozole compared to tamoxifen, whereas dizziness, cold sweats and vaginal discharge were more frequent with tamoxifen.^{3,4} Comparisons between exemestane and tamoxifen revealed no differences for any of the endocrine symptoms except for vaginal discharge, which was greater with tamoxifen up to 24 months following 2–3 years of treatment with tamoxifen.⁵ Patient-reported bone or joint pain was not assessed in these trials.

Placebo-controlled breast cancer prevention trials in postmenopausal women showed more vasomotor^{6,7} and gynecologic symptoms as well as sexual problems for tamoxifen⁶ and worse menopausal-related QoL for exemestane⁸. In the recent mammary prevention 3 (MAP.3) trial, exemestane had small negative effects on vasomotor symptoms, sexual symptoms, and pain, which occurred mainly in the first 6 months to 2 years after random assignment. No treatment differences were observed in general QoL domains.⁹

Little is known about the influence of chemotherapy on patients' perception of endocrine symptoms. In the Zoladex® in premenopausal patients (ZIPP) trial, the endocrine therapy (goserelin, goserelin plus tamoxifen or tamoxifen alone) had differential effects on patient-reported symptoms only in those patients who did not receive chemotherapy.¹⁰

The QoL analysis in the TEXT and SOFT trials was conducted in parallel to the efficacy analysis¹ to elucidate differential effects of exemestane as compared to tamoxifen on QoL among patients who are treated with OFS during adjuvant endocrine therapy.

METHODS

Study design and participants

Details of the trials have been described elsewhere.^{1,2} Eligibility for both trials included operable hormone receptor-positive breast cancer and premenopausal status, defined by regular menses without exogenous hormones during the prior six months and/or estradiol level in the premenopausal range. All TEXT patients and SOFT patients who did not receive chemotherapy were randomized within twelve weeks of definitive surgery; SOFT patients who received (neo)adjuvant chemotherapy were randomized within eight months of completing chemotherapy, as soon as a premenopausal estradiol level was confirmed.

TEXT was designed to evaluate five years of exemestane with the gonadotropin-releasing hormone agonist triptorelin versus tamoxifen with triptorelin for women who received OFS

from the start of adjuvant therapy. Eligible women were randomized 1:1 to five years of exemestane 25mg orally daily plus triptorelin 3.75mg by intramuscular injection every 28 days, or to five years of tamoxifen 20mg orally daily plus triptorelin. As an alternative method of OFS, bilateral oophorectomy or ovarian irradiation could be performed after at least 6 months of triptorelin. Chemotherapy was optional, and if administered, was started concomitantly with triptorelin; oral endocrine therapy started after completion of chemotherapy. If chemotherapy was not administered, then oral endocrine therapy started 6 to 8 weeks after initiation of triptorelin, to allow for a prior decline in ovarian estrogen production.

SOFT was designed to evaluate five years of exemestane+OFS versus tamoxifen+OFS versus tamoxifen for women who remained premenopausal within eight months after completion of pre- or post-operative adjuvant chemotherapy, or for whom adjuvant tamoxifen alone was selected as suitable treatment. Eligible women were randomized 1:1:1 to exemestane+OFS (triptorelin, bilateral oophorectomy or ovarian irradiation), tamoxifen +OFS, or tamoxifen. Results of patients randomized to tamoxifen alone are not included in this report. Consistent with this design, patients in SOFT (but not TEXT) were allowed to receive adjuvant oral endocrine therapy before randomization.

In TEXT and SOFT, protocol-assigned endocrine therapy was to cease 5 years from randomization with annual follow-up thereafter unless the patient withdrew consent for further participation. At this point in follow-up, 30% of patients continued on some or all protocol-assigned treatments, 56% of patients had completed treatment and 14% had stopped all protocol-assigned treatments early (16% exemestane+OFS and 11% tamoxifen +OFS).¹ The ethics committees of each participating center approved the study protocols and all patients gave written informed consent.

Randomisation and masking

In both trials, random allocation of unblinded treatment assignment was generated and performed via IBCSG's internet-based system with the use of permuted blocks and was stratified by chemotherapy use (yes/no) and lymph nodes status (N0/N1+). The Participating Center Principal Investigator or designee accessed the randomisation system.

Procedures: QoL assessment

Patients completed the IBCSG QoL Core Form¹¹ and a trial-specific module at baseline, every 6 months for 2 years, and then annually in years 3 through 6. The forms were to be completed at the clinic, before diagnostic procedures (exception: baseline) or treatment was given and regardless of disease status. The forms were faxed to the IBCSG Data Management Center in Amherst, NY. The baseline assessment in TEXT was prior to any adjuvant therapy, whereas some SOFT patients had received chemotherapy and initiated oral endocrine therapy. Eligibility exceptions were cognitive or physical impairment that interfered with the QoL assessment, or inability to read any of the 26 languages available on the core form. The core form includes global indicators for physical well-being,¹² mood,¹³ coping effort,¹⁴ and subjective health estimation,¹⁵ and five indicators specific to symptoms and side-effects.¹⁶ The module consisted of 12 endocrine symptom indicators, one global

indicator for treatment burden¹⁷ and a question regarding sexual activity during the past 6 months (yes/no). The selection of symptoms was based on the findings of two breast cancer prevention trials^{6,7} including a symptom checklist developed for the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial^{18,19} subsequently validated²⁰, providing the most convincing evidence for endocrine symptom burden when we designed TEXT and SOFT. An expanded module was used for centers with English as primary language to provide cross-validation between selected LASA indicators and the Center for Epidemiologic Studies-Depression Scale (CES-D)²¹ and the Medical Outcomes Study (MOS) sexual problems measures 22; these data will be presented elsewhere.

All indicators were in the linear analogue self-assessment (LASA) format.¹⁶ They were transformed to range from 0 to 100, with higher numbers reflecting a better condition. For all indicators, a clinically significant change was defined conservatively as at least ± 8 points.²³

We prospectively defined the following hypotheses:

a. Primary

1. There will be no difference in frequency of hot flushes, as measured by LASA format, between patients receiving exemestane+OFS versus tamoxifen+OFS in the short, intermediate and long-term. We expected an improvement of hot flushes at 24 months compared to six months.
2. In patients without chemotherapy, there will be a differential effect on specific menopausal symptoms, i.e., more vaginal discharge in patients receiving tamoxifen+OFS, more vaginal dryness and more bone or joint pain in patients receiving exemestane+OFS.
3. In patients without chemotherapy, there will be no difference in loss of sexual interest between those receiving exemestane+OFS versus tamoxifen+OFS.

b. Secondary

1. There will be no difference in global QoL domains (physical well-being, mood, coping effort) between patients receiving exemestane+OFS versus tamoxifen+OFS.
2. Patients in TEXT receiving chemotherapy after randomization will report worse menopausal symptoms (primary endpoint: hot flushes), sexual functioning (primary endpoint: sexual interest) and global QoL domains (primary endpoint: coping effort) compared to those without chemotherapy at six month after randomization, and worse menopausal symptoms and sexual functioning at 60 months. Patients in SOFT with prior chemotherapy will have worse baseline scores and thus less worsening during endocrine therapy compared to those with concurrent chemotherapy in TEXT.

3. Patients who report worse menopausal symptoms (primary endpoint: hot flushes) during the first 6 months on endocrine therapy will also report delayed adaptation in global QoL domains both during and beyond that time.

Outcomes

For each of the global and symptom-specific indicators in the QoL assessment, the changes from baseline to each timepoint were calculated, as timepoint score minus baseline score. The changes were summarized as mean with 95% confidence interval at each timepoint.

Statistical Analysis

The following patients were excluded from the QoL analysis: (1) patients with a QoL eligibility exemption; (2) patients at participating centers with poor overall QoL submission compliance (<60% of QoL assessments completed between baseline and 24 months; 7% of centers); (3) patients who otherwise had no QoL data submitted (Fig. 1).

Mixed-effects linear modeling for repeated measures was used to test the short- (month 6), intermediate- (month 24) and long-term (month 60) effects of treatment on changes from baseline in each QoL indicator. The models included cohort (trial and chemotherapy use), treatment assignment (exemestane+OFS vs. tamoxifen+OFS), QL assessment timepoint, and the interactions of the three variables, without regard for statistical significance of the interaction parameters. Models were adjusted for baseline covariates: age, race/ethnicity, BMI, menstruation status, family history of breast or ovarian cancer, nodal status, tumor size, tumor grade, and HER2 status. An unstructured covariance was selected based on comparison of Akaike information criterion (AIC) and likelihood ratio tests. Within each cohort and overall, the estimated difference between treatment groups, 95% confidence intervals, and Wald P-values, were summarized at 6, 24 and 60 months. To address the primary hypotheses and secondary hypothesis 1, model contrasts compared treatment groups overall and separately according to cohort at the three specified timepoints. Tests of the cohort-by-treatment interaction were also performed.

To address secondary hypothesis 2, the difference between chemotherapy versus no chemotherapy was tested. To address secondary hypotheses 3, we added a new covariate, severity of menopausal symptoms during the first 6 months of therapy, by categorizing the patients into two groups (more vs. less severe) using the median value of the change in hot flushes from baseline to 6 months overall. The mean difference between the two severity groups in QoL change from baseline to 6, 12, 18, and 24 months was estimated and tested. The statistical analysis plan changed the approach to longitudinal modeling, rather than independent two-sample tests at each timepoint as specified in the original protocols, because follow-up at the time of analysis was much longer than anticipated in the protocols and the modeling incorporated correlation of measurements over time and the multiple cohorts (defined by trial and chemotherapy use) analyzed.

To examine potential bias introduced by excluding patients at centers with poor QoL submission compliance, characteristics of those patients were summarized (Supplemental Table S3) and the analysis of 9 global and symptom-specific indicators specified in the hypotheses were re-run using all patients.

Although the hypotheses are stated as one-sided, tests were two-sided, consistent with the protocol. The reported P-values were not adjusted for testing of multiple QoL indicators over time, in order to look for consistency of the signal among comparable QL indicators. Power was considered within each trial protocol, but not re-estimated for the combined analysis. To have 80% power to detect an 8-unit difference between two treatment groups in the mean short-term change in hot flushes score (i.e., from baseline to 6 months), and in the mean intermediate-term change (baseline to 24 months), a sample size of 950 patients was estimated; for the indicator loss of sexual interest, approximately 1250 patients were required. The analysis used SAS version 9.4 (SAS Institute Inc., Cary, NC). The trials are registered with clinicaltrials.gov NCT00066703 (TEXT) and NCT00066690 (SOFT).

Role of the funding source

IBCSG was responsible for the TEXT and SOFT trial designs, including QoL, and for data collection and analysis. Pfizer and Ipsen, the manufacturers of exemestane and triptorelin, provided drug and Pfizer provided financial support; neither imposed restrictions on the investigators with respect to trial design or data collection, analysis or interpretation. The manuscript was prepared entirely by the authors. The Steering Committee (including employees of Pfizer and Ipsen) reviewed and approved the manuscript content. The statisticians (WL, MMR) and corresponding author (JB) had full access to all the data and the corresponding author had final responsibility to submit for publication.

RESULTS

Study Population

Between 7 November 2003 and 7 April 2011, 4717 premenopausal women were randomized to exemestane+OFS or tamoxifen+OFS. After exclusions (27 patients excluded from ITT efficacy analysis; 42 patients with a QoL eligibility exemption; 546 patients at participating centers with poor QoL submission compliance; 6 patients who had no QoL data submitted), 4096 remained in the intent-to-treat (ITT) QoL population (Fig. 1). The median follow-up was 5.7 years (IQR, 3.7 to 6.9 years).

The median age at randomization was 43 years and 42% (1726/4096) had node-positive disease (Table 1, Table S1). In TEXT, 59% (1400/2381) received concurrent chemotherapy, in SOFT, 55% (951/1715) received prior chemotherapy. Patient and disease characteristics at randomization were balanced across the treatment groups (Table S2). Patient, disease and treatment characteristics were generally balanced between the ITT QoL population and those excluded, though excluded patients had lower rates of physician-reported symptoms at randomization (Supplemental Table S3).

The QoL form submission rates for the QoL population was similar in both trials, with 88% (14915/16856) submission of forms expected between baseline and 60 months in TEXT and 85% (10274/12037) in SOFT. The rates declined over time, with 90% (3606/4016) at six months, 86% (3337/3871) at 24 months, and 79% (2019/2542) at 60 months, and were balanced by treatment arm.

Treatment comparisons

Baseline scores most impaired included tiredness, sleep disturbance, being irritable, mood, coping effort, and health perception (Table 2). Vasomotor symptoms showed the greatest early change from baseline, as shown for hot flushes by cohort (Fig. 2). Hot flushes thereafter improved continuously (overall mean change months 24 - 6: exemestane+OFS= 6; tamoxifen+OFS= 8; both $p<0.0001$), but without reaching baseline scores. Overall, patients receiving exemestane+OFS experienced less worsening of hot flushes at six months than those receiving tamoxifen+OFS ($=8$, $P<0.0001$; primary hypothesis 1). This difference persisted over time, although it became smaller. Patients receiving exemestane+OFS also experienced less worsening of sweats than those receiving tamoxifen+OFS (Fig. 3; Fig. S1; overall, month six: $=7$, month 24 $=4$, month 60: $=5$, each $P=0.0001$).

Gynecological and sexual symptoms were notable over the whole treatment period (Fig. 3 and 4 A, B; Fig. S2, S5–S8). Patients receiving exemestane+OFS experienced a greater exacerbation in vaginal dryness (overall, month six: $=-7$, month 24: $=-8$, month 60: $=-7$, each $P<0.0001$), and less vaginal discharge than patients receiving tamoxifen+OFS (overall, month six: $=5$, month 24: $=6$, month 60: $=5$, each $P<0.0001$; primary hypothesis 2) though the changes in vaginal discharge were not clinically meaningful (<8 points) in both treatment groups. Patients receiving exemestane+OFS also indicated a greater decline in sexual interest than those with tamoxifen+OFS. This difference increased over time (overall, month six: $=-5$, month 24: $=-7$, month 60: $=-8$, each $P<0.0001$; primary hypothesis 3). At baseline, 76% (1548/2033 and 1556/2045) of the patients reported being sexually active in both treatment groups, and these percentages declined at six months to 69% (1261/1819) for patients receiving exemestane+OFS and 74% (1348/1827) for those receiving tamoxifen+OFS, at 24 months 70% (1171/1682) and 75% (1284/1705), and at 60 months 62% (641/1030) and 71% (702/992), respectively. If sexually active, patients receiving exemestane+OFS experienced greater changes in difficulties becoming aroused than patients receiving tamoxifen+OFS (overall, month six: $=-5$, month 24: $=-6$, each $P<0.0001$; month 60: $=-4$, $P=0.0068$). There was no treatment difference in vaginal itching/irritation.

Irrespective of chemotherapy, patients receiving exemestane+OFS experienced a substantially greater worsening in bone or joint pain than patients receiving tamoxifen+OFS (Fig. 3 and 4C; overall, month six: $=-15$, month 24: $=-7$, month 60: $=-5$, each $P<0.0001$; primary hypothesis 2).

Patients in each treatment group felt similarly troubled by weight gain over the whole treatment period (Fig. 4D) and reported significant sleep disturbance in the short- and mid-term (Fig. S3). There were also no differences between the randomized treatments in appetite, feeling sick (nausea/vomiting), tiredness, headaches, being irritable or feeling dizzy (Fig. 3).

In general, patients reported small changes in physical well-being, mood and health perception in short-, mid- and long-term (all <8 points), but indicated less effort to cope over time (Fig. 5). There was no treatment difference in these global domains between patients

receiving exemestane+OFS compared to those receiving tamoxifen+OFS (secondary hypothesis 1). Changes in treatment burden were smaller than those of the key symptoms.

Impact of chemotherapy

Patients treated without chemotherapy indicated no difference in treatment burden between the randomized treatments. In patients who received chemotherapy, those receiving exemestane+OFS reported being more bothered by treatment in short-term than those receiving tamoxifen+OFS, especially patients with prior chemotherapy (Fig. S5–S8; SOFT; month six: -7 , $P=0.00061$, month 24: -5 , $P=0.021$).

Patients in SOFT who received prior chemotherapy were randomized on average 8 months from final surgery, substantially later than the other three cohorts (Table 1). In general, patients with prior chemotherapy reported worse baseline scores for symptoms, possibly caused by chemotherapy, and thus smaller changes thereafter compared to those without chemotherapy, as shown for hot flushes (Fig. 2; secondary hypothesis 2).

Patients in TEXT receiving chemotherapy initiated it concurrently with triptorelin, but initiated exemestane or tamoxifen on average 19 weeks after randomization, later than the other three cohorts. They indicated a much smaller difference in bone or joint pain between exemestane+OFS and tamoxifen+OFS over the first 6 months (Fig. 4C; of changes -9) compared to the other three cohorts (ranged -17 to -15). To note, there were no intermediate- to long-term QoL differences by chemotherapy in TEXT or SOFT.

Adaptation

At baseline, patients in SOFT reported better coping scores (with prior chemotherapy: 69, without: 70) than those in TEXT (with planned chemotherapy 59, without: 64). After 12 months, these differences disappeared.

Overall, patients with more severe hot flushes during the first 6 months had less improvement in coping scores in short- to mid-term than those with less severe menopausal symptoms during the first six months. This was most expressed in TEXT patients receiving concurrent chemotherapy (month six: -10 , $P<0.0001$; month 24: -6 , $P=0.00019$; secondary hypothesis 3). For changes in mood and physical well-being, the difference between the two severity groups was consistent although smaller (data not shown).

DISCUSSION

In these premenopausal trials with OFS, the comparison of exemestane with tamoxifen showed differential QoL findings. Patients assigned exemestane+OFS reported significantly more detrimental effects of bone or joint pain, vaginal dryness, greater loss of sexual interest and difficulties becoming aroused, while patients assigned tamoxifen+OFS were significantly more affected by hot flushes, sweats and vaginal discharge. In general, patients reported considerable changes in key endocrine symptoms in the short-, mid- and long-term, but differences between the randomized treatments were small. The changes in global QoL domains were similar between the randomized treatment groups. The differential findings

are in contrast to no differences (except for vaginal discharge) in IES in postmenopausal women.⁵

Vasomotor symptoms were most expressed over the whole treatment period, although they improved in the mid- and long-term. Contrary to our hypothesis, patients receiving tamoxifen+OFS were more affected by hot flushes than patients on exemestane+OFS.

The continuous impact of gynecological and sexual symptoms are a serious concern. Patients on exemestane+OFS reported more vaginal dryness, greater loss of sexual interest, more difficulties in becoming aroused, and were less likely to remain sexually active while patients on tamoxifen+OFS reported more but small changes in vaginal discharge. These differences persisted over time. Worsening in bone or joint pain was more expressed in patients with exemestane+OFS, particularly in the short-term, than in patients with tamoxifen+OFS.

Patients indicated a clinically-relevant change in their treatment burden mainly in the short-term. The changes in this summative measure were smaller than might be expected from the side-effect profile. An early difference in favor of tamoxifen+OFS in patients who received chemotherapy did not persist. Similarly, there were no differences between the randomized treatments in any of the other global domains, in agreement with previous trials.^{4,5,9} The relatively low treatment burden may reflect patients' adaptation, as suggested by their decreasing coping effort. This interpretation is supported by preference studies.^{24,25} However, a substantial minority of patients is expected to suffer from burdensome endocrine symptoms,⁹ as reflected in the 14% of patients in the total sample who had stopped all protocol-assigned treatments early (16% exemestane+OFS and 11% tamoxifen+OFS), most reporting targeted adverse events.¹ In general, the patient-reported symptoms corresponded to the reported adverse events. The patient-reported outcomes show the perceived time course of these symptoms and thus give a more comprehensive and accurate picture of the net impact of a given symptom (e.g., long-term impact on sexual function).

An early recognition of symptom burden is imperative for patient care. Some of the main menopausal symptoms can be ameliorated by a multidisciplinary approach.^{26,27} As shown for hot flushes, pronounced symptom burden had a relevant impact on patients' adaptation.

Chemotherapy was optional in both trials, and therefore associated with prognostic factors. In the context of OFS for all patients, and thus in contrast to the ZIPP trial,¹⁰ the differential endocrine effects were similarly present in patients with or without chemotherapy. In TEXT, patients with or without concurrent chemotherapy required comparable effort to cope¹⁴ at month 6. This differs from the Zoladex Early Breast Cancer Research Association (ZEBRA) trial and IBCSG Trial VIII, both with OFS as a randomized intervention, in which patients receiving goserelin required substantially less effort to cope¹⁴ at month 6 than those receiving chemotherapy (CMF).^{28,29}

Chemotherapy had a clinically-relevant short-term impact in that patients with prior chemotherapy (in SOFT) had lower baseline scores in chemotherapy-related domains and subsequently a greater improvement. However, these patients had more time to adapt than those with planned chemotherapy and reported less coping effort at baseline. A timing effect

was obvious by the smaller difference between exemestane and tamoxifen in bone or joint pain in short-term changes in TEXT patients with planned chemotherapy. These patients received chemotherapy and triptorelin concurrently after randomization, and exemestane or tamoxifen several months later than the other three cohorts.

The inclusion of the four cohorts in the analysis adds complexity to the interpretation of the results. On the other hand, the use or not of chemotherapy is a decision for each patient; when chemotherapy is used, OFS will be initiated concurrently for some patients and may be initiated after chemotherapy when premenopausal status is established or re-established. The analysis provides insight into the patterns of QoL over time for each of these scenarios.

When we developed these trials at the beginning of the last decade, we were not aware of any endocrine symptom questionnaire ready to be used in the required languages. Due to feasibility reasons, specific QoL domains which are especially relevant in this clinical context (e.g., depression, body image, sexual function, cognitive function) could not be investigated in depth in these large-scale trials. Instead, we used a pragmatic measurement approach based on LASA indicators as previously used in IBCSG trials. Depression, sexual and cognitive functioning are under further investigation in a subset of TEXT and SOFT.

Longitudinal QoL data submission always presents a challenge. More than 500 centers world-wide participated in the trials and we excluded 7% of centers with poor QoL form submission rates. As well, the QoL form submission rate decreased in the long-term, but overall was balanced between the randomized treatments. Sensitivity analysis confirmed that results were robust to the analysis approach for missing data.

In conclusion, from a QoL perspective, there is no strong indication to favor either exemestane+OFS or tamoxifen+OFS, and the benefit in disease-free survival of exemestane +OFS over tamoxifen+OFS observed in TEXT and SOFT is achieved without a detrimental impact on global QoL. The differential effects of the two treatments on endocrine symptoms should be considered with each patient individually.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT PANEL**Evidence before this study**

We searched PubMed for clinical trials published in English between Jan 1, 1998, and Jan. 1, 2003, and updated it on February 26, 2015, that assessed patient-reported symptoms and QoL in premenopausal women with early breast cancer undergoing adjuvant endocrine treatment. We used the search terms “premenopausal”, “tamoxifen”, “aromatase inhibitors”, “QoL”, and “patient-reported outcome”. We manually reviewed the results and found no randomized phase III trial reporting on patient-reported symptoms and QoL on the specific comparison of tamoxifen with an aromatase inhibitor in premenopausal women. Existing data is based on data from postmenopausal women^{3–5} or placebo-controlled breast cancer prevention trials.^{6–9}

Added value of this study

In TEXT and SOFT trials, patients assigned exemestane+OFS reported more detrimental effects of bone or joint pain, vaginal dryness, greater loss of sexual interest and difficulties becoming aroused, while patients assigned tamoxifen+OFS were more affected by hot flushes and sweats. Global QoL domains were similar between the randomized treatment groups. The differential impact on endocrine symptoms is only partly consistent with the findings of previous trials of an aromatase inhibitor compared with tamoxifen in postmenopausal patients (without OFS). In the IES, comparisons between exemestane and tamoxifen revealed no differences for any of the endocrine symptoms except for vaginal discharge, which was greater with tamoxifen up to 24 months following 2–3 years of treatment with tamoxifen.⁵ In the ATAC trial, self-reported gynecological symptoms were more frequent with anastrozole compared to tamoxifen, whereas dizziness, cold sweats and vaginal discharge were more frequent with tamoxifen.^{3,4} Patient-reported bone or joint pain was not assessed in these trials.

Implication of all the available evidence

In premenopausal patients with hormone receptor-positive breast cancer, the TEXT and SOFT trials combined analysis showed a disease-free survival benefit for exemestane plus ovarian function suppression (OFS) compared with tamoxifen+OFS, providing a new treatment option for premenopausal women who receive OFS as part of adjuvant endocrine therapy.¹ From a QoL perspective, there is no strong indication to favor either exemestane+OFS or tamoxifen+OFS. The differential effects of the two treatments on endocrine symptoms should be considered with each patient individually.

Figure 1.

CONSORT Flowchart to identify the 4096-patient intention-to-treat (ITT) quality-of-life population.

Abbreviations: E=Exemestane; OFS=Ovarian Function Suppression; QoL=quality-of-life; SOFT=Suppression of Ovarian Function Trial; T=Tamoxifen; TEXT=Tamoxifen and Exemestane Trial.

Figure 2.

Hot flush scores (mean with 95% confidence intervals (CI); higher score indicates better condition) over time according to treatment assignment and patient cohort: (A) Hot flush scores from baseline to 60 months, separately according to chemotherapy cohort (side by side), and according to trial and treatment assignment (within chemotherapy cohort); (B) Change of hot flush scores from baseline to 6, 24, and 60 months according to patient cohort as defined by chemotherapy stratum and trial. The dashed vertical line at ± 8 indicates the minimal clinically-meaningful change of quality-of-life (QoL) scores.

Abbreviations: CI=confidence interval; E=Exemestane; HF=hot flushes; OFS=Ovarian Function Suppression; QoL=quality-of-life; SOFT=Suppression of Ovarian Function Trial; T=Tamoxifen; TEXT=Tamoxifen and Exemestane Trial.

Figure 3. Change of quality-of-life (QoL) symptom indicator scores from baseline to 6, 24, and 60 months, according to treatment assignment, overall across patient cohorts. The dashed vertical line at ± 8 indicates the minimal clinically-meaningful change of QoL scores. Abbreviations: CI=confidence interval; E=Exemestane; OFS=Ovarian Function Suppression; QoL=quality-of-life; T=Tamoxifen.

Figure 4.

Vaginal dryness (A), loss of sexual interest (B), bone or joint pain (C), and troubled by weight gain (D) (mean with 95% confidence intervals (CI); higher score indicates better condition) from baseline to 60 months, separately according to chemotherapy cohort (side by side), and according to trial and treatment assignment (within chemotherapy cohort). Abbreviations: CI=confidence interval; OFS=Ovarian Function Suppression; SOFT=Suppression of Ovarian Function Trial; TEXT=Tamoxifen and Exemestane Trial.

Figure 5. Change of quality-of-life (QoL) global domain scores from baseline to 6, 24, and 60 months, according to treatment assignment, overall across patient cohorts. The dashed vertical line at ± 8 indicates the minimal clinically-meaningful change of QoL scores. Abbreviations: CI=confidence interval; E=Exemestane; OFS=Ovarian Function Suppression; QoL=quality-of-life; T=Tamoxifen.

Characteristics of patients in the TEXT and SOFT quality-of-life population, overall and according to patient cohort as defined by trial and chemotherapy stratum.¹

Table 1

	Patient Cohort												Overall	
	No chemotherapy TEXT			No chemotherapy SOFT			Chemotherapy TEXT			Prior Chemotherapy SOFT				
	N	%		N	%		N	%		N	%		N	%
<i>Number of patients</i>	981			764			1400			951		4096		
<i>Age, years</i>														
<35	35	3.6		10	1.3		170	12.1		198	20.8	413	10.1	
35–39	110	11.2		50	6.5		256	18.3		264	27.8	680	16.6	
40–44	344	35.1		216	28.3		500	35.7		300	31.5	1360	33.2	
45–49	381	38.8		347	45.4		419	29.9		158	16.6	1305	31.9	
50+	111	11.3		141	18.5		55	3.9		31	3.3	338	8.3	
Median [IQR]	45	[41,47]		46	[43,49]		42	[38,46]		40	[35,44]	43	[39,46]	
Nodal status														
Negative	774	78.9		701	91.8		480	34.3		415	43.6	2370	57.9	
Positive	207	21.1		63	8.2		920	65.7		536	56.4	1726	42.1	
Tumor size > 2cm	186	19.0		121	15.8		720	51.4		437	46.0	1464	35.7	
Mo. from final surgery to randomization, median [IQR]	1.5	[1.1, 1.9]		1.9	[1.3, 2.5]		1.2	[0.9, 1.6]		8.1	[5.9, 10.3]	1.6	[1.1, 2.7]	
Endocrine therapy before randomization²	-	-		41	5.4		-	-		405	42.6	-	-	

Abbreviations: IQR=interquartile range; SOFT=Suppression of Ovarian Function Trial; TEXT=Tamoxifen and Exemestane Trial.

¹ A more complete summary of characteristics is provided in Table S1. Characteristics were well balanced according to treatment assignment (Table S2 in the Supplementary Materials).

² In SOFT, oral endocrine therapy before randomization was allowed while premenopausal status was established or re-established. In the SOFT prior chemotherapy cohort, average duration was 16 weeks (IQR, 10–22 weeks); in the SOFT no chemotherapy cohort, average duration was 5 weeks (IQR, 2–7 weeks).

Table 2

Baseline quality-of-life scores¹ in the TEXT and SOFT quality-of-life population, overall and according to patient cohorts as defined by trial and chemotherapy stratum.

	Patient Cohort												Overall (n=4096)	
	No Chemotherapy TEXT (n=981)		No Chemotherapy SOFT (n=764)		Chemotherapy TEXT (n=1400)		Prior Chemotherapy SOFT (n=951)							
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Quality of Life Indicator														
Symptom Indicators														
Vasomotor														
Hot flushes	92	16	90	19	92	18	71	32	87	23				
Sweats (including night sweats)	88	19	86	20	88	20	75	29	85	23				
Gynecological / Sexual														
Vaginal discharge	90	16	88	17	90	17	80	23	87	19				
Vaginal dryness	93	13	92	15	94	13	81	25	90	18				
Vaginal itching/irritation	93	15	92	15	93	14	86	22	91	17				
Loss of sexual interest	80	26	80	27	79	27	66	31	76	28				
Difficulties in becoming aroused	84	21	83	23	85	20	73	27	82	23				
Musculoskeletal / neurology pain														
Bone or joint pain	86	21	84	22	88	19	76	28	84	23				
Headaches	86	20	84	22	84	21	82	24	84	22				
Gastrointestinal														
Appetite	84	19	82	21	80	22	81	21	82	21				
Feeling sick (nausea/vomiting)	94	13	93	14	92	15	92	16	93	15				
Constitutional / psychological														
Sleep disturbance	74	26	72	27	71	27	67	29	71	28				
Tiredness	64	27	61	27	65	26	54	27	62	27				
Troubled by weight gain	87	22	85	24	88	20	69	32	83	26				
Being irritable	76	23	75	23	74	24	72	24	74	24				
Feeling dizzy	92	15	91	16	91	16	88	19	90	17				

	Patient Cohort											
Quality of Life Indicator	No Chemotherapy TEXT (n=981)		No Chemotherapy SOFT (n=764)		Chemotherapy TEXT (n=1400)		Prior Chemotherapy SOFT (n=951)		Overall (n=4096)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Global indicators												
Physical well-being	79	21	78	21	77	22	77	21	78	22		
Mood	72	23	72	23	70	24	75	22	72	23		
Coping effort	64	27	70	25	59	28	69	25	65	27		
Treatment burden	80	23	78	23	76	24	73	23	77	24		
Health perception	74	20	73	21	70	22	73	21	72	21		

Abbreviations: SD=standard deviation; SOFT=Suppression of Ovarian Function Trial; TEXT=Tamoxifen and Exemestane Trial.

/ All indicators range from 0 to 100, with higher scores indicating a better condition.