Abstract  

**Purpose:** To review the health-related quality of life (QOL) of women treated with adjuvant hormonal therapy.

**Experimental Design:** To review the limited QOL data from randomized trials of tamoxifen versus placebo and ovarian ablation versus none. To discuss QOL results from randomized trials of aromatase inhibitors compared with tamoxifen or placebo for adjuvant therapy of postmenopausal women with estrogen receptor–positive and/or progesterone receptor–positive breast cancer.

**Results:** QOL is generally good in up to 3 years of follow-up with either tamoxifen or aromatase inhibitors. Vasomotor and sexual complaints remain problematic, however, in only a small proportion of women. There are fewer data regarding the QOL effects of ovarian ablation, which may nonetheless be more substantial.

**Conclusion:** Tamoxifen and aromatase inhibitors cause specific vasomotor or gynecologic symptoms, which may affect sexual function. However, clinical benefits of these agents are generally achieved without major detrimental effect on overall QOL.

Cancer therapies can result in substantial toxicities that may impair the quality of life of patients. Health-related quality of life (QOL) may be described as the wide variety of subjective experiences related to health, such as symptoms, and their effects on physical, emotional, and social functioning (1). Information on the effect of cancer therapy on QOL is useful to physicians and patients when making decisions about treatment. In addition to providing important information about the direct experience of patients, QOL provides a global impression of the effect of a number of coincident toxicities on a patient’s ability to function. For example, adjuvant chemotherapy, which is associated with a wide range of adverse effects, including nausea, vomiting, alopecia, fatigue, and sequelae, such as premature menopause, arthritic complaints, mood disorders, and cognitive effects, has been shown in randomized trials and observational studies to substantially impair the QOL of women in both the short term (2) and potentially the long term (3). Despite the importance of QOL information, its regular use by physicians and patients in treatment decision making has been hampered by lack of familiarity with the instruments used, problems with interpretation of measured differences, and the relative lack of methodologically rigorous studies. Increasing use of QOL assessment in cancer trials and better methods of analysis are likely to improve the interpretation and use of QOL data.

The effect of adjuvant hormonal therapy on QOL is an important consideration in treatment decision making. Standard hormonal therapies now include not only adjuvant tamoxifen and ovarian suppression but the relatively new third-generation aromatase inhibitors. Hormonal therapies are often given for a long duration. Five years of such therapy is now standard, and 10 years is increasingly being used. The duration of adjuvant endocrine therapies may be extended even longer in the future. These therapies are accompanied by a number of toxicities related to estrogen withdrawal or antagonism, including vasomotor symptoms, vaginal dryness, urogenital and sexual dysfunction, and in some instances, muscle or joint pain (4). Hormonal therapies are also at least anecdotally associated with other symptoms, including weight gain, hair loss, fatigue, and depression. Until recently, there have been limited QOL information from randomized trials of endocrine therapy, but now, such data are being collected and reported more frequently.

**Tamoxifen**

The effects of tamoxifen on QOL are best obtained from two randomized trials (Table 1). The Wisconsin Tamoxifen Trial included 140 postmenopausal women with lymph node–negative breast cancer who were randomly assigned to receive tamoxifen or placebo (5). Investigators collected data on symptoms and overall QOL over 24 months. Women receiving tamoxifen were found to have increased hot flashes (67% versus 45% at 6 months, *P* < 0.01). Gynecologic symptoms, such as bleeding, irritation, and vaginal discharge, were also more common (30% versus 15% at 6 months; *P* < 0.05) in...
those receiving tamoxifen. No differences were reported with respect to nausea, fatigue, joint pain, depression, irritability, gastrointestinal distress, or overall QOL.

The largest and most comprehensive assessment of patient-reported symptoms and QOL comes from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 Breast Cancer Prevention Trial in which over 13,000 healthy, high-risk women were randomized to tamoxifen or placebo (6). The QOL assessment in this study was extensive and recorded data on 11,064 women over 36 months. Women were assessed for self-reported symptoms, sexual functioning, depression, and overall QOL using the Medical Outcomes Short Form 36 (SF-36) general health survey. There was an increase in vasomotor symptoms, such as hot flashes (78% versus 65%; P < 0.05), cold sweats (21% versus 14%; P < 0.05), and vaginal discharge (55% versus 34%; P < 0.05), in women receiving tamoxifen compared with those receiving placebo. Women on tamoxifen also reported a slight increase in problems related to sexual function, such as difficulty being sexually aroused and having orgasm. These problems were reported relatively uncommonly, in <15% of patients over 36 months. The mean difference between groups in proportion of patients reporting these symptoms was ≤1%. There were no differences in depression or overall QOL in women receiving tamoxifen versus those on placebo (7).

### Ovarian Suppression

There has been less evaluation of QOL in premenopausal women undergoing ovarian suppression. In a substudy of the Zoladex in Premenopausal Patients trial, 149 women with node-negative breast cancer who did not receive adjuvant chemotherapy were randomized to no endocrine treatment (n = 37), goserelin (n = 38), goserelin plus tamoxifen (n = 39), or tamoxifen alone (n = 35; ref. 8). QOL was assessed with the Hospital Anxiety and Depression Scale and a symptom checklist at baseline, 3.5 months, and 12 months after randomization. Anxiety and depression were not significantly different in any of the arms. There were more intense and earlier vasomotor symptoms (e.g., flushing and palpitations) and vaginal dryness in women treated with goserelin compared with those treated with tamoxifen. More vaginal discharge and irregular bleeding were reported by women treated with tamoxifen, however.

#### Aromatase Inhibitors

Aromatase inhibitors in postmenopausal women are now proving very successful in increasing distant and overall disease-free survival and in preventing contralateral breast cancer compared with tamoxifen when given immediately after surgery, after 2 to 3 years of tamoxifen, and particularly extended adjuvant therapy after 5 years of tamoxifen, a setting in which there was no previous consensus on any useful endocrine therapy. Aromatase inhibition results in a marked decrease in estrogen synthesis, leading to minimal levels of circulating estrogen. Treatment with aromatase inhibitors seems to be associated with a number of adverse effects that are similar but perhaps less intense than those experienced by premenopausal women treated with ovarian suppression. Hot flashes, arthritis, arthralgia, muscle pain, and an increase in osteoporosis and in the rate of bone fracture have been reported (9–11). To date, there have been quite a number of randomized trials of these agents in the adjuvant setting (12). Fortunately, four of the largest trials examining these agents have included extensive QOL studies (see Table 2).

**Aromatase inhibitors as extended adjuvant therapy.** Only one trial in this setting has reported QOL data. The MA.17 trial compared the use of letrozole with placebo in postmenopausal women with stage I to III breast cancer who were disease free after 4.5 to 6 years of adjuvant tamoxifen. Of the 5,170 women in the trial, 3,612 (69.9%) participated in the QOL substudy (4). QOL was assessed with the SF-36 and the Menopause-Specific QOL instrument at baseline, 6 months, and annually. The median follow-up was 30 months. Compliance with the QOL assessment was >90% for all time points. QOL as measured by mean change of scores from baseline decreased in both groups in the majority of QOL domains at the 6-month

### Table 1. Randomized trials evaluating QOL of tamoxifen and ovarian ablation in premenopausal and postmenopausal women

<table>
<thead>
<tr>
<th>Trial (menopausal status)</th>
<th>Intervention</th>
<th>Timing</th>
<th>Sample size</th>
<th>Instrument</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisconsin (5) (postmenopausal)</td>
<td>Placebo × 2 y Tamoxifen × 2 y</td>
<td>0-10 y Postsurgery</td>
<td>140</td>
<td>Symptom check list trial specific QOL</td>
<td>† Vasomotor and gynecologic symptoms; no difference in overall QOL</td>
</tr>
<tr>
<td>NSABP-P1 (7) (premenopausal and postmenopausal)</td>
<td>Placebo × 5 y Tamoxifen × 5 y</td>
<td>Prevention</td>
<td>11,064</td>
<td>SF-36; symptom checklist</td>
<td>† Vasomotor, gynecologic symptoms and sexual dysfunction; no difference in overall QOL</td>
</tr>
<tr>
<td>ZIPP (8) (premenopausal)</td>
<td>No treatment Tamoxifen × 2 y Goserelin × 2 y Goserelin + tamoxifen × 2 y</td>
<td>Postsurgery</td>
<td>149</td>
<td>HADS; symptom checklist</td>
<td>† Vasomotor symptoms and vaginal dryness for goserelin versus tamoxifen</td>
</tr>
</tbody>
</table>

Abbreviation: NSABP, National Surgical Breast and Bowel Project; ZIPP, Zoladex in Premenopausal Patients; HADS, Hospital Anxiety and Depression Scale.
anastrozole, 347 tamoxifen, and the combination. The primary treatment (14). In this substudy, 1,021 of the 9,366 postmenopausal women with early breast cancer following Fallowfield et al. studied QOL over a period of 24 months in the Arimidex, Tamoxifen, Alone, or in Combination trial, has been the most widely studied with respect to QOL. In this context for the use of aromatase inhibitors therapy.

Switching to aromatase inhibitors after about 2 years of tamoxifen. To date, only one trial has reported on QOL assessment for aromatase inhibitors following 2 years of tamoxifen. The Intergroup Exemestane Study (IES) randomized postmenopausal women with early breast cancer who remained disease free after 2 to 3 years of tamoxifen to receive exemestane or further tamoxifen to complete a total of 5 years of adjuvant therapy (10). Of 4,742 women randomized, 582 participated in the QOL substudy over 24 months (13). QOL was assessed with the Functional Assessment of Cancer Therapy-Breast questionnaire and an endocrine subscale at months 3, 6, 12, 18, and 24 months. There were no differences in QOL between the two treatment groups. Endocrine symptoms, in particular vasomotor symptoms, improved over time. No differences were noted between the groups for any endocrine symptoms aside from vaginal discharge, which decreased in patients treated with exemestane.

Aromatase inhibitors versus tamoxifen as initial adjuvant therapy. This context for the use of aromatase inhibitors has been the most widely studied with respect to QOL. In the Arimidex, Tamoxifen, Alone, or in Combination trial, Fallowfield et al. studied QOL over a period of 24 months in postmenopausal women with early breast cancer following primary treatment (14). In this substudy, 1,021 of the 9,366 patients randomized were evaluated: 335 patients received anastrozole, 347 tamoxifen, and 339 the combination. The Functional Assessment of Cancer Therapy-Breast and endocrine subscale were used in this study. Compliance with the QOL assessment was 85%. Overall QOL improved over time, and there was no significant difference between groups. Fallowfield et al. did, however, observe a decrease in QOL related to endocrine symptoms from baseline to 3 months for all treatments. For specific endocrine symptoms, the differences between the groups were small. There were more patients reporting cold sweats (8% versus 11%, \( P < 0.05 \)), vaginal discharge (1% versus 5%, \( P < 0.05 \)), and irritation (3% versus 5%, \( P < 0.05 \)) in the tamoxifen-alone arm, and more patients reporting vaginal dryness (16% versus 8%, \( P < 0.05 \)), pain on intercourse (18% versus 8%, \( P < 0.05 \)), and loss of sexual interest (16% versus 9%, \( P < 0.05 \)) in the anastrozole-alone arm. These results were recently updated to 5 years of follow-up (13). Overall, QOL continued to improve slightly over time with no differences seen between groups. Following the initial worsening at 3 months, the endocrine subscale scores stabilized. No differences were observed between groups in the endocrine subscale, but differences in specific endocrine symptoms seen previously remained.

In another upfront adjuvant therapy trial, symptoms were recorded for the first 12 months in 997 postmenopausal women randomized to tamoxifen or exemestane following primary surgical treatment or adjuvant chemotherapy (16). Exemestane was associated with a decrease in the proportion of patients reporting vaginal discharge and an increase in the proportion reporting vaginal dryness and bone or muscle aches.

Comparison of the QOL studies of aromatase inhibitors is problematic because of the differences related to the timing of adjuvant therapy, the aromatase inhibitors evaluated, the comparison arm of the studies, and the instruments used to assess QOL. The QOL instruments used in these studies have been widely validated. The Functional Assessment of Cancer

<table>
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</table>
| MA17 (4)            | Placebo \(\times 5\) y  
Letrozole \(\times 5\) y | Following tamoxifen \(\times 5\) y | 3,612       | SF-36; MENQOL               | Small differences in bodily pain and vasomotor symptoms; no difference in overall QOL. |
| IES (15)            | Exemestane \(\times 2-3\) y  
Tamoxifen \(\times 2-3\) y | Following tamoxifen \(\times 2-3\) y | 582         | FACT-B; endocrine subscale  | No difference in overall QOL or the endocrine subscale                   |
| ATAC (14)           | Anastrozole \(\times 5\) y  
Tamoxifen \(\times 5\) y  
Combination \(\times 5\) y | Post-surgery or chemotherapy | 1,021       | FACT-B; endocrine subscale  | No difference in overall QOL or the endocrine subscale                   |
| Asmar et al. (16)   | Exemestane \(\times 5\) y  
Tamoxifen \(\times 5\) y | Post-surgery or chemotherapy | 997         | Symptom checklist           | ↑ in vaginal dryness and bone/muscle aches with exemestane               |

Abbreviations: ATAC, Aremidex, Tamoxifen, Alone, or in Combination; FACT-B, Functional Assessment of Cancer Therapy-Breast; MENQOL, Menopause Specific Quality of Life Instrument.
Suggestions for Management of Endocrine Symptoms

QOL issues may have important implications particularly for specific women. Thus, it is important that clinicians following these women take a careful history with regard to treatment adverse effects and discuss directed symptom management with them. Some specific, if imperfect, pharmacologic treatments are available for the relief of vasomotor symptoms, including selective serotonin reuptake inhibitors, such as venlafaxine and the antihypertensive agent clonidine. Therapy for vaginal dryness and dyspareunia is problematic. Water-soluble lubricants, such as KY Jelly, can be useful, but remedies that involve local estrogen are often more effective. These can include E-string, which releases estrogen in a slow and regular fashion, or the sparing use of vaginal estrogen cream two to thrice weekly. These therapies for dyspareunia were allowed in studies, such as MA.17, and did not interfere with the observed efficacy. Whether anti-breast cancer efficacy could be superior without the use of these local estrogens is not clear. The use of local estrogens may be more problematic in patients receiving aromatase inhibitors as therapy, because the presumed mechanism of action of an aromatase inhibitor is to reduce systemic estrogen to extremely low levels, whereas tamoxifen is believed to acting by competing with estrogen in interacting with hormone receptors on tumor cells. Directed symptom-specific therapy programs, such as that described by Ganz et al., have proved even more effective in reducing a variety of symptoms (18). There are well-established treatments for osteoporosis and reduction of cardiovascular risk that apply to these as to other postmenopausal women. Exercise and weight loss may also help in general QOL as well as improving cardiovascular and bone health.

In the future, postmenopausal women with estrogen and/or progesterone receptor positive disease (perhaps as many as 70% of all postmenopausal women with breast cancer) may be receiving extended treatment with adjuvant endocrine therapy. It will be very important for clinicians to monitor these patients for compliance with that therapy and for minimization of any associated short-term and long-term toxicities and QOL changes. Future research in this area as well as careful clinical management will remain important.

Open Discussion

Dr. Carlos Arteaga: Many of these women are well below retirement age. Has anybody developed some index of work productivity outside the house? This goes to the issue of years lost to the disease.

Dr. Pritchard: When we first did the MA.5 trial with CEF and CMF, one of the data managers pointed out to me that more women on one arm than the other were having to take time off from work. There was at that time no questions in any of these quality-of-life scores that captured that. You are asking an important question, and there are items in some of the current quality-of-life instruments that address working and work productivity in a better way than they used to.

Dr. Steven Come: What is your practice in terms of the use of vaginal estrogen in patients with sexual complaints? Do you have theoretical concerns about doing that in women on AIs?

Dr. Pritchard: I ask patients about their general functioning and symptoms, including sexual functioning. Some of these women have such terrible symptoms that they really have to use something. In my practice, I recommend Estrin and some vaginal creams. I prefer Estring, because I think it is absorbed more minimally and more consistently, but the data are actually very poor. In MA.17, we allowed the use of either Estrin or local vaginal estrogen, and the trial worked in spite of that.

Dr. Come: Is there any overall epidemiologic issue with the fact that the proportion of patients in these quality-of-life studies is so small, compared with the overall study?

Dr. Pritchard: In MA.17 there was quite a large number. In the NCIC we have had a long history of doing quality-of-life studies, so our centers just do it. They don’t even complain anymore. These studies have shown us some specific areas that we should be discussing with our patients more. It may be that 90% of them don’t have these problems, but 5% may be having a big problem and we don’t always hear about it. In terms of symptoms and what therapy you choose, I get some patients who are really frightened of the AIs because they have had bad arthritis. It may not be logical; they may not be the one who is going to get the musculoskeletal effects, but they are just too scared to be on a drug that might make their functioning worse. So those are the kinds of issues where I am picking and choosing between the drugs.

Dr. James Ingle: There is a lot of evidence now about the tolerability of the AIs in this population. I think the age/ menopausal interaction that Tim Whelan identified is really interesting [J Clin Oncol, in press]. It goes along with what you would expect. You take a younger woman and radically change her estrogen levels and you are going to have more symptoms. You take a 70-year-old woman who has slowly drifted down in estrogen levels, and it is not that big a deal.

Dr. Arteaga: The effects may be tolerable, but I am also getting the message from the cardiac and sexual data that God made estrogens for a number of good reasons. There is the concept being explored by Southwest Oncology Group of combining an AI with fulvestrant. There are a lot of oncogenic inputs and in many tumors the ER may still be working as a...
transcriptional unit in the absence of any hormones, so it makes sense to test that. However, that combination is going to produce a profound hypoestrogenic state. Are these data telling us that that experiment should be done in a very well-defined population? There may be some population in which that strategy, AI plus a ER down-regulator, may be justified, because there is a molecular rationale to do it. At what point do you cross that boundary of potential benefit versus toxicity, because the combination will be pretty toxic?

Dr. Pritchard: I think we need to be studying these people, but we don’t even know that it is going to produce worse cardiac toxicity. The issue of estrogen’s effects on the heart is a bit up for grabs right now. You see a whiff of a difference in cardiac disease in several of these studies. But in MA.17 there was no difference, and there are several randomized trials of tamoxifen versus no treatment that actually show cardiac protection. Most of what we may be seeing in these studies may be tamoxifen’s cardioprotective effects versus AI. That could still be a reason to lean toward tamoxifen, but we need a lot more data on the cardiac issue. If it is a big difference, and if it really holds up, that could be a real problem because cardiac events are the competing cause of mortality and disease in this patient age group.

Dr. Ingle: Putting things in perspective, I think that this minor signal of the cardiac data is something that people are going to have to pay attention to. In the IES study, 0.5% more patients on exemestane had a myocardial infarction compared with the tamoxifen treatment group [Coombes RC, et al., presented at the 2004 San Antonio Breast Cancer Symposium]. However, in talking to women, you learn that they don’t want their cancer to come back. If they have had breast conservation therapy, they don’t want a local recurrence, because then they lose their breasts. They want to keep their breasts. So the major driver is preventing breast cancer.

Dr. Pritchard: It worries me more that 5 or 10 years from now we may see a lot of women with undertreated osteopenia and osteoporosis, because it is a condition that is undertreated in the population anyway.

References
Managing Patients on Endocrine Therapy: Focus on Quality-of-Life Issues

Timothy J. Whelan and Kathleen I. Pritchard

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