Quality-adjusted survival in a crossover trial of letrozole versus tamoxifen in postmenopausal women with advanced breast cancer

W. Irish1*, B. Sherrill1, B. Cole2, C. Gard3, G. A. Glendenning4 & H. Mouridsen4

1Research Triangle Institute, Research Triangle Park, NC; 2Dartmouth-Hitchcock Medical Center, Lebanon, NH; 3Novartis Pharmaceutical Corporation, East Hanover, NJ; 4Righospitalet, Copenhagen, Denmark

Background: Results from a phase III study of postmenopausal women with advanced breast cancer demonstrated longer time to disease progression for patients taking letrozole versus tamoxifen. This analysis compares the trade-offs between progression-free survival and toxicity.

Design: Quality-adjusted survival was calculated using Q-TWiST (quality-adjusted time without symptoms or toxicity). Survival curves were partitioned into three health states: toxicity (TOX), disease progression (PROG) and periods without toxicity or disease progression (TWiST). The utility-weighted sum of the health state durations was derived and compared.

Results: There was not a significant difference in mean duration of serious adverse events prior to progression between the letrozole (n = 453) and tamoxifen (n = 454) groups (2.2 and 2 months, respectively). For TWiST, the mean duration for letrozole was 11.5 months, versus 8.5 months for tamoxifen (P < 0.001). The mean duration of PROG was 11.5 months for letrozole and 12.7 months for tamoxifen (P = 0.047). Using utility weights of 0.5 for TOX and PROG resulted in a 2.5-month difference in quality-adjusted survival favoring letrozole (P < 0.0001).

Conclusions: The longer time to disease progression with letrozole versus tamoxifen was achieved without increased time with adverse events and resulted in more quality-adjusted survival for patients on letrozole.

Key words: letrozole, Q-TWiST, quality-adjusted survival, tamoxifen

Introduction

Clinical decision-making for advanced breast cancer patients must balance the trade-offs between treatment toxicities and expected survival. The value of a treatment depends not only on absolute survival time, but also on the quality of the life of the patient during that time.

Unlike classical survival analysis, the Q-TWiST (quality-adjusted time without symptoms or toxicity) approach quantitatively adjusts periods in which treatment toxicities or symptoms of disease progression are present to reflect the potentially reduced value for the patient. The methodology partitions the survival time of the patient into various health states, assigns utility weights to each and compares treatments based on the overall survival experience [1–6].

Previously published results from a phase III clinical trial comparing letrozole 2.5 mg with tamoxifen 20 mg in postmenopausal women with advanced breast cancer demonstrated the superiority of first-line letrozole over tamoxifen in terms of time to progression and early survival [7]. The study reported similar frequencies and types of adverse event for the two treatments. However, as is typical in reporting of clinical trial data, the duration of adverse events and whether patients experienced adverse events multiple times was not addressed. Patients were allowed to cross over to the alternate treatment after disease progression, and overall median survival was not significantly different at end of follow-up [8].

We re-analyzed the clinical trial data using the Q-TWiST approach to assess whether the impact of duration of time with and without progression, and duration and severity of toxicities resulted in differences in quality-adjusted survival.
Patients and methods

Study design

The data source was a double-blinded, multicenter, randomized, parallel-group, phase III study comparing the efficacy and safety of letrozole and tamoxifen among postmenopausal women with advanced breast cancer. Detailed methods, inclusion/exclusion criteria, and efficacy and safety results are available in a previous publication by Mouridsen et al. [7, 8].

Patients were randomized to either letrozole 2.5 mg/day or tamoxifen 20 mg/day orally as monotherapy. The intention-to-treat (ITT) population included all randomized patients who took at least one dose of the assigned treatment (n = 907). First-line treatment was given until disease progression or other reason necessitated discontinuation. If a patient was eligible for further endocrine anticancer treatment, then treatment could be switched to the alternative study medication. Blinding was maintained after treatment switch, and patients were followed for overall survival.

Physical examinations and complete tumor assessments were performed at baseline and every 3 months. Increases of 25% or more in lesions or the appearance of new lesions were considered evidence of disease progression. Disease progression was also considered to occur if a patient discontinued treatment with clinical deterioration, or death occurred due to breast cancer or unknown cause while receiving treatment or within 6 weeks of discontinuation.

Time from randomization to disease progression (TTP) was the primary efficacy end point, and overall survival was a secondary end point. Safety was assessed through routine monitoring and recording of hematological, renal and liver function. The severity of all adverse events was designated according to the National Cancer Institute Common Toxicity Criteria.

Analysis approach

Health states. Overall survival time was classified into three clinical health states. (i) Toxicity (TOX): time spent with severe or life-threatening adverse events prior to disease progression. (ii) TWiST: time without toxicity or symptoms of disease progression defined as the difference between the time spent in TOX and the time to disease progression. (iii) Progression (PROG): period following disease progression ending with death or censoring.

Estimates of the mean amount of time spent in each of the health states were determined separately for each treatment group, using the Kaplan–Meier method. Survival curves for each treatment group corresponding to toxicity duration, disease-free survival, and overall survival within the median follow-up of 32 months were plotted on the same graph.

Q-TWiST calculation

Mean Q-TWiST for each treatment arm was calculated as:

\[ Q - TWiST = (u_{TOX} \times TOX) + TWiST + (u_{PROG} \times PROG) \]

where TOX, TWiST and PROG represent the mean health state durations from Kaplan–Meier analysis; \( u_{TOX} \) and \( u_{PROG} \) denote the utility coefficients for the states TOX and PROG, respectively. For treatment comparison purposes only, TWiST is considered to have utility equal to 1, representing the best possible quality of life for a patient with advanced breast cancer.

Utility weights

Utility weights \( (u_r) \) were used to reflect quality of time in each health state, relative to TWiST. Sensitivity analyses were conducted by varying the assigned utilities for TOX and PROG in 0.25 increments across the full range of possible utility weights from 0 (representing poorest health) to 1 (representing utility equal to TWiST). Treatment comparisons were then made using the relative weights in a threshold utility analysis to determine which relative utility weightings resulted in significant treatment differences.

Statistical analyses

Differences in mean Q-TWiST between treatments were tested using a Z-test for every possible combination of utility weights. Sensitivity analyses were performed using alternate definitions of the TOX health state: (i) adverse events attributable to study drug (possible, probable or highly probable); and (ii) all adverse events regardless of severity or attribution.

Results

The ITT population consisted of 453 patients randomized to letrozole group and 454 randomized to tamoxifen with groups well-balanced in terms of demographic and background characteristics (Table 1). Most patients experienced at least one adverse event during treatment. Adverse events related to study drug were reported by 38% of patients on letrozole and 37% on tamoxifen, and types of adverse events were similar. After a median follow-up of 32 months, 52 (11%) remained on first-line letrozole and 239 (53%) had crossed over to tamoxifen. In the tamoxifen group, only 27 (6%) remained on first-line tamoxifen and 228 (50%) had switched to letrozole.

As previously reported, TTP was 9.4 months in patients taking letrozole first-line compared with 6 months in patients treated with tamoxifen (P < 0.0001). A significant improvement in survival had been seen in the group randomized to letrozole over the first 2 years of the study. However, by end of follow-up, median overall survival was not significantly different (34 months for letrozole versus 30 months for tamoxifen).

Table 2 shows mean durations of the TOX, TWiST and PROG health states and differences between treatments in Q-TWiST for the ITT population. Figure 1 displays the partitioned survival plots for letrozole and tamoxifen groups. No significant difference was detected between the letrozole (A) and tamoxifen (B) groups in time spent with toxicity (P = 0.3).

Time without evidence of progression or treatment toxicity was, however, longer in the letrozole group compared with the tamoxifen group (11.5 versus 8.5 months, respectively; P < 0.001). The mean duration of PROG was 11.5 months for letrozole and 12.7 months for tamoxifen (P = 0.047). When utility weights for the TOX and PROG health states were set equal to 0.5, there was a 2.5-month difference in

<table>
<thead>
<tr>
<th>Table 1. Baseline patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Median age (years)</td>
</tr>
<tr>
<td>Stage IV disease (%)</td>
</tr>
<tr>
<td>Karnofsky score &lt;80 (%)</td>
</tr>
<tr>
<td>Soft tissue lesions (%)</td>
</tr>
<tr>
<td>Bone metastases (%)</td>
</tr>
<tr>
<td>Prior chemotherapy (%)</td>
</tr>
</tbody>
</table>
quality-adjusted survival favoring letrozole over tamoxifen (18.4 versus 15.8 months, respectively; \( P < 0.0001 \)). Q-TWiST was significantly different between the treatments in favor of letrozole across the entire matrix of utility weights, with the differences in quality-adjusted life ranging from just under 2 months to 3 months (Figure 2).

Results were similar in sensitivity analyses with varying definitions of the TOX health state (Table 2). When attributable adverse events were considered, patients on letrozole experienced 1.3 more months with adverse events than patients on tamoxifen (\( P = 0.06 \)). However, since letrozole extended their TTP, they also experienced 1.9 months longer without symptoms or adverse events prior to disease progression (\( P = 0.02 \)). When all adverse events were included in TOX, patients on letrozole experienced 9.4 months in TOX versus 7.2 months for patients on tamoxifen (\( P < 0.001 \)). Despite the longer TOX period when low-grade adverse events are included, letrozole resulted in a significantly longer duration of time without progression or toxicity (1 month) and significantly longer quality-adjusted survival across all ranges of utility values, except where the utility for the TOX state <0.5 and utility for relapse >0.2 (Figure 3). For these extreme utility weights, there was no significant difference between treatments.

**Discussion**

Time with severe or life-threatening adverse events was not significantly different between groups, but time without progression or toxicity was significantly longer for letrozole than for tamoxifen. These results closely reflect the TTP analysis reported by Mouridsen et al. [7, 8], but offer additional information about the trade-off between toxicities and delayed

![Figure 1](image1.png)

**Figure 1.** Partitioned survival plots. For each treatment group, the overall survival time is partitioned into three periods [time with toxicity (TOX), time without symptoms or toxicity (TWiST) and time after progression (PROG)].
disease progression. The approach used here mimics the way patients and physicians evaluate treatment options through assessing both the total expected survival and the quality of health during that survival period. Regardless of how the health states were weighted, patients experienced the equivalent of 2–3 months longer quality-adjusted survival with letrozole as first-line therapy compared with tamoxifen.

The robustness of this result was confirmed in sensitivity analyses, where additional adverse events were included in the definition of toxicity. In these analyses, the longer duration of time without disease progression or toxicities with letrozole compensated for time with toxicity related to adverse events, especially when the quality of life or utility associated with toxicity is weighted similarly or greater than utility associated with progression. This weighting scheme is a reasonable proxy for patients’ anticipation of cancer treatment, especially for advanced-stage disease, i.e. for some patients, various adverse events are tolerable and accepted as the trade-off for delayed disease progression.

For this same study, Mouridsen et al. [8] report that there was a survival advantage for patients randomized to letrozole in the first 2 years of treatment, although there was no overall difference in survival by the end of follow-up. The lack of statistical difference in overall survival could be attributed to the effects of subsequent treatment after switching to alternate treatment had occurred. Indeed, if second-line therapies were used following the randomized therapy and one was more effective, this could reduce the likelihood of detecting differences in overall survival. The analysis we conducted showed a significant advantage in quality-adjusted survival when letrozole is given as first-line treatment.

There are limitations to the assignment of relative utilities as opposed to direct elicitation of quality of life scores from patients. Specifically, some drug effects may not be reportable as adverse events but could affect patient quality of life. Models to incorporate actual quality of life measures into the Q-TWiST framework are being developed, but they are complicated by the usual problem of incomplete data from longitudinal assessments [9]. One recent Q-TWiST approach used changes in quality of life scores as transition points between health states [10]. However, since patient quality of life scores were not elicited during this trial, we provide a comprehensive view of when and how one treatment strategy may be preferred by examining treatment comparisons across the whole range of possible utilities. Further analyses showed that any effects of letrozole would have to compromise quality of life by 40% during the period between toxicities and progression to reverse the treatment difference.

This analysis shows that irrespective of how patients value periods of toxicity, a treatment strategy using letrozole offers patients significantly more quality-adjusted survival than tamoxifen.

References