A trial-based cost-effectiveness analysis of letrozole followed by tamoxifen versus tamoxifen followed by letrozole for postmenopausal advanced breast cancer

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Background: Third-generation aromatase inhibitors are being considered as an alternative to tamoxifen as first-line therapy for advanced breast cancer. These newer therapies are more expensive, and will gain greater acceptance if they can demonstrate cost-effectiveness.

Methods: Life table analyses are used to compare the costs and benefits [life years gained and quality-adjusted life years (QALYs) gained] of treating postmenopausal women with advanced breast cancer with first-line letrozole (with the option of second-line tamoxifen) compared with first-line tamoxifen (with the option of second-line letrozole). Patient-level data from a large clinical trial describes the effectiveness of the therapy options, clinicians estimate resource usage and utility values are obtained from the literature.

Results: The mean cost of providing first- and second-line hormonal therapy is £4765 if letrozole is the first-line therapy and £3418 if tamoxifen is provided first (a difference of £1347). However, patients receiving letrozole as first-line therapy gain an additional 0.228 life years, or 0.158 QALYs. The cost-effectiveness analysis found that first-line hormonal therapy with letrozole gains additional life years at a cost of £5917, whilst the cost per additional QALY gained is £8514.

Conclusion: The strategy of letrozole as first-line hormonal therapy not only provides an opportunity for extending and improving patient’s quality of life, but also is highly cost-effective compared with other generally accepted medical treatments.

Key words: advanced breast cancer, clinical trial, cost-effectiveness, letrozole, tamoxifen

Introduction

Tamoxifen has been the predominant first-line hormone therapy for breast cancer of all stages [1]. However, third-generation aromatase inhibitors such as letrozole and anastrozole represent a significant advantage in terms of improved efficacy and tolerability, and are now being considered an alternative to tamoxifen as first-line therapy [2].

In a high-prevalence disease such as breast cancer, aggregate treatment costs will rise quickly and those responsible for setting priorities in health care need to ensure that new therapies adopted offer greater value to the health-care system than existing therapies. An economic analysis comparing alternative combinations of first- and second-line hormonal therapies for postmenopausal women with advanced breast cancer—first-line letrozole (with the option of second-line tamoxifen) compared with first-line tamoxifen (with the option of second-line letrozole)—is presented in this paper. The analysis involves a comparison of the difference in lifetime treatment costs between the alternative therapy combinations and the difference in survival adjusted for patients’ quality of life [measured as the difference in quality-adjusted life years (QALYs) gained].

The economic analysis is based on data from a phase III double-blind, randomised clinical trial that compared letrozole 2.5 mg (n = 453) versus tamoxifen 20 mg (n = 454) as first-line therapy in postmenopausal women with advanced breast cancer [3]. Letrozole was significantly superior to tamoxifen in prolonging time to disease progression (TTP) [median 9.4 (letrozole) versus 6.0 (tamoxifen) months; hazard ratio 0.72; 95% confidence interval (CI) 0.62–0.83; P <0.0001], time to treatment failure (TTF) (9.0 versus 5.7 months; hazard ratio 0.73; 95% CI 0.64–0.84; P <0.001), with a higher overall objective response rate (32% versus 21%; P = 0.0002) and clinical benefit rate (50% versus 38%; P = 0.004). These benefits in efficacy for letrozole translated into a significant improvement in survival during the first 2 years of the trial [4]. The trial design included a prospective crossover to the alternative treatment at the time of progression. A total of 239 (52%) patients initially treated with letrozole switched over to tamoxifen at progression, while 228 (50%) patients initially
treated with tamoxifen switched over to letrozole. Following crossover, patients switching from tamoxifen to letrozole achieved longer TTP (hazard ratio 1.32; 95% CI 1.07–1.61; P = 0.0086) and TTF (hazard ratio 1.33; 95% CI 1.09–1.62; P = 0.0053), with a higher overall objective response rate (8.8% versus 6.7%; P = 0.0584) and clinical benefit rate (29.8% versus 29.8%; P < 0.0001).

Methods

The methods used to estimate the cost per additional QALY gained between the alternative therapy combinations are presented in three sections, which describe the process for estimating survival differences, the estimation of the associated costs and QALYs and the analysis of uncertainties in the baseline estimates of cost-effectiveness.

Estimation of survival difference

Ideally, differences in survival between the two treatment groups are directly informed by data from the trial with the two therapy combinations. The relevant trial discontinued follow-up after a median duration of 32 months (with a maximum observation period of 57 months), at which point 514 of the eligible 907 patients in both treatment arms had been observed to die. The final follow-up period enabled the estimation of median overall survival (OS), which showed an insignificant difference of 4 months in favour of first-line letrozole (34 months) over tamoxifen (30 months). However, economic analyses should use mean outcomes, which describe the expected treatment effect for each patient. Median OS is an inappropriate economic outcome measure because survival times are known to be skewed, such that median survival is likely to significantly underestimate expected survival.

As <60% of patients were observed to die within the final follow-up period it is difficult to estimate mean OS directly from the trial. An alternative option for the estimation of mean survival would be to model the respective treatment pathways for each of the therapy combinations. However, no data informing differential pathways between the alternative therapy combinations from the end of hormone therapy are identified, and there is no external basis for assuming alternative survival profiles.

A post hoc analysis of the trial data is undertaken to test for the impact of first-line therapy on post-hormone therapy survival. Survival times for the 736 patients who were followed up beyond the end of first- or second-line hormonal therapy are analysed using a Cox proportional hazards regression model. The hazard ratio for letrozole is 1.102 (95% CI 0.923–1.315; P = 0.282), which indicates that first-line letrozole patients have an insignificantly increased hazard of dying post-hormone therapy. The similarity of post-hormone therapy survival in the two treatment groups is also demonstrated by the survival curves presented in Figure 1.

On the basis of the insignificance of first-line therapy as an indicator of post-hormone therapy survival, mean survival for patients receiving first-line letrozole (with the option of second-line tamoxifen) or first-line tamoxifen (with the option of second-line letrozole) is estimated as the time to the end of either first- or second-line hormone therapy.

Estimation of lifetime costs and QALYs

The estimation of the survival difference between the alternative therapy combinations is the basis for the estimation of lifetime costs and QALYs. It is not feasible to simply multiply the survival period for each patient by defined cost and quality of life weights to estimate lifetime costs and QALYs, respectively, because both costs and QALYs must be discounted to reflect the notion of time preference [5].

Life table models (for each of the relevant treatment states: first-line letrozole, first-line tamoxifen, second-line letrozole and second-line tamoxifen) are developed to estimate the discounted costs and QALYs associated with each therapy combination. The life table approach calculates the proportion of patients remaining in a healthy state at regular intervals [6], to which relevant cost and utility weights can be applied at appropriate rates of discount.

The trial did not collect resource use information or utility weights, and so it is necessary to combine economic data derived from outside the trial with the clinical data collected within the trial. The estimation of the cost associated with each of the four therapy states involves the estimation of the resources used, and the assignment of relevant unit costs to the resources. The range of resource use includes drugs, patient consultations, laboratory tests and periods of hospitalisation, which are based on a series of expert interviews described in a previous study [7]. Current UK costs are applied to the estimated resources. Details of the costing process are presented in Table 1. It is assumed that all patients on first- or second-line hormonal therapy receive the same resources, other than the hormonal intervention.

The range of utility values for patients with advanced breast cancer, without progression, has been presented as 0.59–0.8 [8]. The midpoint of these estimates (0.695) is taken as the baseline estimate of the utility weight for all four of the hormonal therapy states.

Sensitivity analysis

The life table model allows the representation of uncertainty using conventional one- and multi-way sensitivity analyses (which re-estimate cost-effectiveness when one or more input parameters are altered), as well as a probabilistic approach that uses bootstrapping techniques to generate a probability distribution of the costs and QALYs associated with each therapy combination. The bootstrapping procedure samples patients from the trial with replacement to create new datasets of the same size. The mean costs, life years and QALYs calculated from each new dataset generate an alternative estimate of cost-effectiveness. Generating 2000 bootstrapped estimates of cost-effectiveness allows for the estimation of the 2.5th and the 97.5th percentiles (which are analogous to 95% confidence intervals).

Multi-way sensitivity analyses are also undertaken varying the baseline cost and utility weights for the therapy states to estimate the range of mean cost-effectiveness results. The monthly cost estimates, excluding the cost of the intervention drugs (which are known with certainty), are multiplied by 0.5 and 1.5 to represent lower and upper bounds. The range of utility values for patients with advanced breast cancer, without progression, presented above...
(0.59–0.8 [8]) represent the uncertainty in the utility weights. Each combination of cost and utility weights is analysed to estimate the lower and upper bounds of cost-effectiveness. The life table model is also analysed using equal discount rates of 6% for both costs and benefits.

The baseline analysis is conducted from the perspective of the UK National Health, with a 6% discount rate for costs, and 1.5% for benefits [5].

**Results**

Figure 2 describes the life table estimates of the proportion of patients receiving first-then second-line hormone therapy over time from the point of randomisation. The curves in Figure 3 show that patients receiving letrozole as a first-line therapy gain a progression-free survival advantage over the first 2 years, after which the survival profiles become similar due to the effect of second-line endocrine treatment.

Table 2 presents the results of the cost-effectiveness analysis. The table shows that the aggregate cost of providing first- and second-line hormonal therapy to 1000 patients (with around 50% of patients receiving second-line therapy) is £4.765 million if letrozole is the first-line therapy, and £3.418 million if tamoxifen is provided first (i.e. a difference of £1.347 million). However, the 1000 patients receiving letrozole as a first-line therapy gain an additional 228 life years, or 158 QALYs. Therefore, the baseline cost per additional life year gained is £5917, whilst the cost per additional QALY gained is £8514.

Table 2 also shows the 2.5th and 97.5th cost-effectiveness percentiles derived from the probabilistic sensitivity analysis. These results show a highly skewed distribution of cost-effectiveness, with the lower bound only marginally lower than the mean estimates. The upper bounds are just under three times the mean values, with the 97.5th interval for the cost per life year gained being £16 373, and the cost per QALY gained being £23 558.

The sensitivity analysis on the lower and upper bounds for the cost and utility weights show that the results are not sensitive to reasonably large alterations in these weights, as the cost per QALY gained varies by ≤£6000 between the best and worst case scenarios. The use of equal discount rates for costs and benefits also has only a very minor impact on the cost-effectiveness results.

**Discussion**

The results of the cost-effectiveness analysis show that, despite the improved performance of second-line letrozole following first-line tamoxifen compared with second-line tamoxifen following first-line letrozole, patients who initially receive letrozole can

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**Table 1. Costs per 3-month period for alternative first- and second-line hormonal therapy states**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Unit cost (£)</th>
<th>Proportion of patients receiving interventions in each health state</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine (per day)</td>
<td>0.68</td>
<td>0.26</td>
</tr>
<tr>
<td>Naproxen (per day)</td>
<td>0.29</td>
<td>0.2</td>
</tr>
<tr>
<td>Codeine (per day)</td>
<td>0.37</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Outpatient visits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncologist</td>
<td>106</td>
<td>0.93</td>
</tr>
<tr>
<td>General practitioner</td>
<td>24</td>
<td>0.58</td>
</tr>
<tr>
<td>Radiographer</td>
<td>14</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Laboratory tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemical</td>
<td>9</td>
<td>0.91</td>
</tr>
<tr>
<td>Blood tests</td>
<td>2.5</td>
<td>0.89</td>
</tr>
<tr>
<td>Bone scintography</td>
<td>68.63</td>
<td>0.57</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>42.46</td>
<td>0.19</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>13.66</td>
<td>0.44</td>
</tr>
<tr>
<td>Bone X-ray</td>
<td>24.58</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Hospitalisation (days)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General medicine</td>
<td>223</td>
<td>0.02 (9)</td>
</tr>
<tr>
<td>Oncology</td>
<td>334</td>
<td>0.04 (5)</td>
</tr>
<tr>
<td><strong>Mean cost per three month period (£)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen patients (1st or 2nd line)</td>
<td>(0.12 per day)</td>
<td>397</td>
</tr>
<tr>
<td>Letrozole patients (1st or 2nd line)</td>
<td>(2.97 per day)</td>
<td>657</td>
</tr>
</tbody>
</table>

expect to remain on therapy for an average of an extra 0.228 years (2.7 months), or 0.158 QALYs (1.9 months). There is only a limited extra cost to the health service required to gain such health benefits.

The estimated mean cost per QALY gained is well below the value of gaining additional QALYs demonstrated by the majority of interventions that have been accepted by the National Institute for Clinical Excellence (NICE) in the UK. Indeed, the 97.5th percentile of the cost per QALY gained (£23,558) is well below the implicitly recognised threshold of £30,000 per QALY gained [9]. The sensitivity analyses on the cost and utility weights show that the results are not sensitive to these values, nor to variations in the discount rate.

Ideally, cost per QALY estimates would be based on mean survival, but >40% of patients in both treatment arms were still alive at the end of the follow-up period, which precludes the accurate comparison of the overall survival between the two treatment arms. Exploratory analyses of differences in survival from the end of first-line therapy in patients that did not cross over, and from the end of second-line therapy for patients who did cross over, revealed no significant differences between groups (P = 0.282). There is therefore no basis for assuming alternative prognoses between the two patient populations following either first- or second-line therapy, and it is assumed that the observed differences in TTF to the end of second-line therapy represent the best estimate of the overall difference in survival between the two therapy options. The assumption of common prognoses beyond first- and second-line hormonal therapy is justified both quantitatively, by the data from the randomised controlled trial, and qualitatively, by the absence of any biological rationale for alternative prognoses.

As >90% of patients in each of the four hormone therapy states had discontinued the respective therapies, the deviation from the true mean TTF is likely to be small for all four of the TTF estimates. Moreover, the highest percentage of patients remaining in any of the four states at the end of the follow-up period was in the first-line letrozole therapy group (7.4%), which will introduce a small bias against the first-line letrozole therapy combination.

The probabilistic sensitivity analysis estimates of the 2.5th and 97.5th percentiles of cost-effectiveness show a highly skewed distribution of cost-effectiveness as expected. The bootstrapping procedure samples patient datasets from the trial data with replacement, and re-estimates the cost-effectiveness results for each sample using the life table approach. As the baseline estimate of cost-effectiveness covers the maximum follow-up period (56 months), the majority of the re-sampled datasets will cover shorter follow-up periods that will reduce the impact of the improved effectiveness of letrozole.

For postmenopausal women with estrogen receptor positive advanced breast cancer, the use of first-line letrozole, with the option of second-line tamoxifen, rather than first-line tamoxifen...
and the option of second-line letrozole, provides the opportunity for extending and improving quality of life. The cost-effectiveness analysis in this study demonstrates that first-line letrozole is very cost-effective compared with conventional treatment, with a modest increase in cost justified by significant health benefits.

Acknowledgements

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References

9. Anonymous. A QALY of 30,000 BPS is increasingly being seen as the cut-off point for a positive NICE submission. Script 2001 October; 19: 2.