Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation

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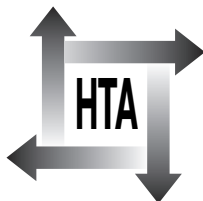
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Executive summary

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Executive summary

Background

Breast cancer is the most common cancer in women. The mainstay of treatment for early stage cancer is surgical removal of the tumour, and is often followed by adjuvant systemic therapy (chemotherapy and/or endocrine therapy) and/or radiotherapy to reduce the risk of recurrence, particularly if the tumour is large or has spread to lymph nodes. Current UK practice recommends an anthracycline-containing chemotherapy regimen. Taxanes are a class of anti-cancer drug (including docetaxel and paclitaxel) that can be used in chemotherapy, and are known to be effective against metastatic breast cancer.

Objectives

The objectives were to estimate the clinical effectiveness and cost-effectiveness of docetaxel and paclitaxel compared with non-taxane, anthracycline-containing chemotherapy regimens, for the adjuvant treatment of women with early-stage breast cancer.

Methods

A systematic review of the literature on adjuvant taxane versus anthracycline non-taxane chemotherapy for women with early breast cancer was undertaken. Literature searches were conducted between October 2005 and February 2006. A mathematical model was developed to synthesise the available data on costs, disease-free survival and health-related quality of life (HRQoL) of patients receiving taxane-containing chemotherapy versus non-taxane-containing chemotherapy. The primary outcome of interest was the cost per quality-adjusted life-year (QALY) gained. The model considered the use of taxanes within current licensed indications only.

Results

Clinical effectiveness
Eleven randomised controlled trials accepted into the clinical review had reported effectiveness data: six docetaxel trials and five paclitaxel trials. An additional seven trials had reported safety or quality of life data. Heterogeneity of interventions, comparators and populations precluded meta-analysis.

Eight of the 11 trials reported a significant improvement in disease-free survival (DFS) or time to recurrence (TTR) for taxanes over comparator regimens. For the four docetaxel trials reporting significant differences in DFS between groups, hazard ratios (HRs) varied from 0.67 to 0.83, with an absolute difference in DFS rates of 5–7%, favouring the docetaxel groups. One docetaxel trial showed no difference in DFS rates between groups and another found a non-significant difference favouring the docetaxel group. Two paclitaxel trials reported a significant improvement in DFS, and two paclitaxel trials a significant improvement in TTR, for the paclitaxel arm over the comparator arms. HRs varied from 0.63 to 0.83, with absolute differences in DFS or TTR rates between trial arms of 4–6% favouring the paclitaxel group. For the paclitaxel trial not finding a significant difference in DFS between groups, the direction of effect favoured paclitaxel.

Docetaxel was associated with more adverse events than paclitaxel, most notably febrile neutropenia. Taxanes produced cardiotoxicity, although this was not reported to be greater than for anthracycline comparator arms in all trials. Treatment-related deaths were uncommon, ranging from 0 to 0.64% across trials. Where reported, all chemotherapy regimens caused HRQoL to deteriorate during treatment. Following treatment, there were no clinically significant differences between taxane and comparator treatment groups.

There were few data available comparing licensed regimens of taxanes with chemotherapy regimens commonly used in the UK. One docetaxel trial and two paclitaxel trials used taxanes in strict accordance with current UK marketing authorisation. Four other trials used comparators that are frequently used in UK practice: two docetaxel and two paclitaxel trials.

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Cost-effectiveness

The independent economic analysis used a state transition (Markov) approach to simulate the disease outcomes of patients up to a time horizon of 35 years post-surgery for early breast cancer. The primary outcome of interest was the cost per QALY gained, associated with taxane-containing chemotherapy versus non-taxane-containing chemotherapy.

The three trials selected as the basis for the economic analysis were those which used the taxanes in accordance with current UK marketing authorisation and had also reported in full. The cost-effectiveness results suggest that the cost per QALY for taxane- compared with non-taxane-containing chemotherapy varies depending on the taxane under consideration and the specific trial used as the basis of the analysis. Docetaxel has a cost per QALY of £12,000 (£7000–39,000) compared with FAC6 based on the regimens used in the BCRIG 001 study, whereas paclitaxel has a cost per QALY of £43,000 (£16,000–dominated) and £39,000 (£12,000–dominated) compared to AC (Adriamycin/cyclophosphamide), based on the regimens used in the NSABP B28 and CALGB 9344 studies, respectively.

The estimated incremental cost-effectiveness ratio (ICER) for taxane- relative to non-taxane-containing chemotherapy is lower for docetaxel based on the BCIRG 001 study than it is for paclitaxel, based on both the NSABP B28 and CALGB 9344 studies. This is partly due to the HR for recurrence, which is lower in BCIRG 001 than in the two paclitaxel trials which have been modelled. In addition, the paclitaxel regimens have a larger number of cycles (four 3-weekly cycles of AC followed by four 3-weekly cycles of paclitaxel) than the comparator arm (four 3-weekly cycles of AC only) and therefore the period on treatment is 12 weeks longer in the intervention arm in the first year of the model. It is assumed that the quality of life of patients is lower during chemotherapy and this loss of quality of life for patients receiving a longer period of therapy on paclitaxel reduces the QALY benefits for the paclitaxel arm.

The assumption regarding the benefits in the taxane arm relative to the comparator arm, after the current follow-up period of 5 years, has a major influence on the cost-effectiveness ratio. The basecase for the ScHARR model assumes that the benefits in terms of rates of recurrence are the same in both arms after the first 5 years. Assuming that the benefits of taxanes continue for 10 years with recurrence rates the same in both arms thereafter decreases the cost per QALY by around 50% for docetaxel and by around 70% for paclitaxel.

The assumption regarding the long-term risk of recurrence after the follow-up period also has a major influence on the ICER. The basecase for the ScHARR model estimates the risk after the trial period from the risk seen during the trial period, but this may have overestimated the long-term risk and therefore underestimated the cost-effectiveness of taxanes. A sensitivity analysis was carried out to assess the extent to which the cost per QALY decreases when the long-term risk of recurrence is assumed to be at its lowest reasonable value. Decreasing the annual rate of recurrence after the trial follow-up period by 50% lowered the cost per QALY for docetaxel by around 20% and the cost per QALY for paclitaxel by around 40%.

Univariate and probabilistic sensitivity analysis suggests that these results are robust to other changes in the key model parameters.

The comparators used by the trials restrict the generalisability of the results, as they do not conform to current standard care in the UK. The comparators in these trials – FAC6 and AC4 – may be less effective than other regimens more commonly used within standard care in the UK, such as FEC6 and E4-CMF4. For this reason, an indirect comparison was undertaken to allow a comparison of taxanes against FEC6 and E4-CMF4. The indirect comparison has many limitations and can therefore only be considered an exploratory analysis showing the minimum uncertainty in the cost-effectiveness achievable with the current evidence base. This exercise does suggest that the ICERs may be higher than those estimated for taxanes compared to FAC6 and AC and that there is a high degree of uncertainty in the benefit of taxanes compared with current standard practice. This suggests that the cost-effectiveness of taxanes relative to current standard care is unproven at this time.

Discussion

The major weakness of this analysis is that there is a lack of data on the effectiveness of taxanes relative to regimens in common use in the UK and this restricts the generalisability of the trial evidence. Also, due to the rapid advance of technologies and the very wide range of ▶

potential comparator therapies, there is little RCT evidence comparing the range of regimens used in the UK from which to construct reliable indirect comparisons.

Assumptions regarding the benefits in the taxane arm after the trial follow-up period and the annual rate of recurrence in this period have the most significant influence on the ICER. Longer term follow-up is required to determine the potential impact of any long-term adverse events, such as cardiotoxicity and severe gastrointestinal toxicity. It should also be noted that the benefits of taxanes in terms of overall survival have not yet been confirmed due to the relatively short follow-up data available. The model assumes that benefits from reduced recurrence in the first 5 years will translate into overall survival benefits in the medium and long term. There is as yet no long-term evidence to support this as the maximum follow-up from the published trials is currently 69 months.

Conclusions

There is a large degree of heterogeneity in the evidence base for the effectiveness of taxane- compared with non-taxane-containing regimens in terms of the interventions, comparators and populations. Eight of the 11 trials providing effectiveness data reported a significant improvement in DFS or TTR for taxanes over comparator regimens. The remaining three trials found no significant differences between the groups in DFS/TTR. However, there were few data available comparing licensed regimens of taxanes with chemotherapy regimens commonly used in the UK.

The cost-effectiveness results suggest that docetaxel-containing chemotherapy has a cost per QALY of £12,000 (£7000–39,000) compared with non-taxane-containing chemotherapy based on the regimen used in the BCRIG 001 study, whereas paclitaxel-containing chemotherapy has a cost per QALY of £43,000 (£16,000–dominated) compared with non-taxane-containing chemotherapy based on the regimens used in the

NSABP B28 study and a cost per QALY of £39,000 (£12,000–dominated) based on the regimens used in the CALGB 9344 study. However, the comparators in these trials do not reflect the regimens currently used in the UK. The use of indirect comparison demonstrates that there is a high degree of uncertainty in the effectiveness of taxane-containing regimens relative to regimens in common use in the UK and therefore the cost-effectiveness of taxanes compared with current standard practice is considered to be unproven at this time. The cost-effectiveness of taxanes will need to be reconsidered as further data become available from ongoing trials comparing taxanes with standard UK regimens. Of particular interest will be the TACT trial, which compares four cycles of FEC followed by four cycles of docetaxel with two regimens used in the UK – eight cycles of FEC or four cycles of EMF, followed by four cycles of CMF. This trial is expected to report efficacy data in the next year or two.

Suggested research priorities

More research is needed, comparing taxanes used in line with their current UK marketing authorisation, with anthracycline-containing regimens commonly used in the UK. The ongoing TACT trial is expected to provide useful data. There are currently few data on the effectiveness of taxanes for the over-70s. Further research is required into the long-term outcomes of taxane therapy, such as whether there are any long-term adverse events that significantly impact on overall survival or quality of life and whether the increases in DFS will translate into increases in overall survival.

Publication

NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

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The research reported in this monograph was commissioned by the HTA Programme as project number 06/18/01. The contractual start date was in November 2005. The draft report began editorial review in October 2006 and was accepted for publication in December 2006. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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