Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer

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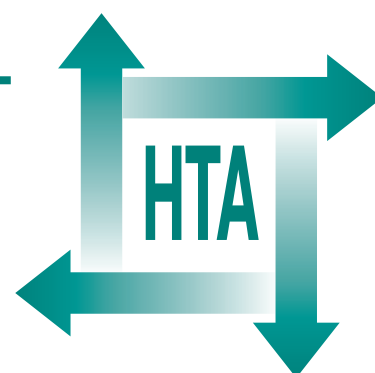[2] Centre for Health Economics, University of York, UK

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Executive summary

**Health Technology Assessment
NHS R&D HTA Programme**

Executive summary

Background

Breast cancer is the most common cancer affecting women in the UK, accounting for nearly 30% of all cancers in women. It is the second leading cause of cancer deaths in women; in 1998 there were over 13,000 deaths from breast cancer in the UK. Around 50% of women diagnosed with primary breast cancer will eventually relapse and develop metastatic or advanced disease. In addition, around 10% of patients present with metastatic disease at first diagnosis. Metastatic breast cancer is currently considered incurable and most women will die of the disease. Prognosis of patients with metastatic disease depends on age, extent of disease and oestrogen receptor status. First-line chemotherapy regimens available for advanced or metastatic breast cancer include CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and anthracycline-containing regimens. Almost all patients who have received first-line chemotherapy for their metastatic progression will relapse or progress and require subsequent treatment. For these patients requiring second- and subsequent-line therapy, the goals of treatment are to maintain a good quality of life (QoL) and to prolong survival. Current guidance from the National Institute for Clinical Excellence (NICE) recommends the taxanes (paclitaxel and docetaxel) "as an option for the treatment of advanced breast cancer where initial cytotoxic chemotherapy has failed or is inappropriate". In addition, vinorelbine, a third-generation vinca alkaloid, has demonstrated some activity in advanced breast cancer in patients with anthracycline-resistant or -refractory disease. Capecitabine has recently been licensed for use as monotherapy for patients who have failed anthracycline-containing and taxane chemotherapy and in combination with docetaxel for patients who have failed anthracycline-containing chemotherapy.

Objective

To examine the clinical effectiveness and cost-effectiveness of oral capecitabine (Xeloda®; Roche) for locally advanced and metastatic breast cancer in relation to its licensed indications.

Methods

Search strategy

Twenty-three electronic databases and other databases of ongoing research and Internet resources were searched from inception to May 2002. The bibliographies of retrieved articles and submissions received from the drug company were also examined.

Inclusion/exclusion criteria

Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full manuscript of any study judged to be relevant by either reviewer was obtained and assessed for inclusion or exclusion. Disagreements were resolved through discussion. For the assessment of capecitabine monotherapy, uncontrolled Phase II and observational studies were included which only recruited patients reported to have received previous treatment with an anthracycline and/or a taxane. For the assessment of capecitabine in combination with docetaxel, randomised controlled trials (RCTs) and uncontrolled studies were included which investigated only patients who had received previous treatment with an anthracycline. The outcomes were: survival, response, symptom relief, QoL, adverse events and costs.

Data extraction strategy

Data were extracted into an Access database by one reviewer and checked for accuracy by a second. Any disagreements were resolved by discussion.

Quality assessment strategy

The quality of each clinical study was assessed by one reviewer and checked by a second. Any disagreements were resolved by discussion. The same quality checklist was used regardless of study design to give a continuous measure of quality. The quality of the cost-effectiveness studies was assessed using a checklist updated from that developed by Drummond and colleagues in 1997. This checklist reflected the criteria for economic evaluation detailed in the methodological guidance developed by NICE. This information is presented in table form. ▶

Methods of analysis

Owing to the small number of studies included in the review and the heterogeneity between the studies, statistical pooling was inappropriate, so statistical chi-squared tests of heterogeneity were not performed. Studies were grouped according to whether capecitabine was used alone or in combination with docetaxel. For the time to event data, where reported, hazard ratios (HR) with 95% confidence intervals (CI) were presented. For the remaining outcomes (tumour response, QoL and adverse events) relative risk (RR) estimates were calculated where appropriate, with 95% CI. RR data were also presented in the form of Forest plots without pooled estimates.

Details of each published economic evaluation, with an assessment of study quality, were presented in structured tables and as a narrative summary. Economic data were presented in the form of a summary and critique of the evidence. Additional analysis was undertaken to explore cost-effectiveness more fully. This included a careful assessment of assumptions underlying the submitted economic analyses using relevant experts, the estimation of differential mean survival duration, the use of Monte Carlo simulation to generate cost-effectiveness acceptability curves and the impact of differences in health-related QoL on cost-effectiveness.

Results

Included studies

In total, 347 titles and abstracts were screened for inclusion in the review. Full paper manuscripts of 233 citations were assessed for inclusion.

Capecitabine monotherapy

Twenty-three published reports of 12 uncontrolled studies of clinical effectiveness were identified for inclusion. One economic evaluation was also identified.

Capecitabine in combination with docetaxel

Five published reports of one RCT investigating capecitabine in combination with docetaxel compared with single-agent docetaxel were identified. Two uncontrolled studies were identified which investigated an alternative, low-dose docetaxel regimen. One economic evaluation based on the RCT comparing capecitabine in combination with docetaxel to single-agent docetaxel was identified.

Quality of the clinical effectiveness data

Capecitabine monotherapy

The methodological quality of the studies investigating capecitabine monotherapy was low. All studies suffered from a number of design flaws making them vulnerable to bias, most notably the lack of a control group. In addition, it was difficult to assess the potential effects of confounding factors on treatment outcomes. Concerns about specific studies and differences between the studies in terms of dose regimens and baseline population differences mean that data from these studies should be treated with caution.

Capecitabine in combination with docetaxel

The RCT by O'Shaughnessy and colleagues was of good quality. The other two studies were uncontrolled and used an alternative treatment regimen, so only a limited discussion of their findings was included. Therefore, the assessment of clinical effectiveness is based mainly on the evidence presented in the RCT by O'Shaughnessy.

Quality of economic evaluations

Capecitabine monotherapy

The poor quality of the clinical studies has implications for the economic analysis. As the comparisons of uncontrolled studies used to demonstrate the clinical superiority of capecitabine were open to bias, the results of the economic evaluation based on these results should also be treated with caution. In addition, the choice of vinorelbine as the only comparator is questionable as there is little evidence of the cost-effectiveness of vinorelbine in this setting.

Capecitabine in combination with docetaxel

The economic evaluation of capecitabine in combination with docetaxel compared with docetaxel monotherapy was assessed using an RCT. Some aspects of the methodology of the economic analysis may be questioned, but it was felt that these would not alter the overall conclusions.

Assessment of clinical effectiveness

Capecitabine monotherapy

The assessment of clinical effectiveness of capecitabine monotherapy included 12 non-comparative studies of capecitabine. In the absence of controlled trials, these studies represent the best currently available evidence. The outcomes assessed by the studies included survival time, time to disease progression, duration of response, time to treatment failure, tumour response rates, QoL and adverse event rates. ▶

The findings of the clinical effectiveness studies appear to indicate that capecitabine monotherapy has some effects in terms of survival time (median survival, range 8.1–15.2 months), time to progression (median time to progression, range 2.8–6.2 months) and time to treatment failure. In terms of response, duration of response ranged from 5.0 to 8.3 months, and overall response rate from 15 to 28%. QoL was not adequately addressed by the included studies. Hand–foot syndrome and diarrhoea were the most commonly reported adverse events. The percentage of patients experiencing grade 3 hand–foot syndrome ranged from 5 to 22% (any grade, 35–62%) and the percentage of patients experiencing grade 3/4 diarrhoea ranged from 5 to 19% (any grade, 27–57%). In light of the quality issues relating to uncontrolled studies in general and the particular methodological flaws identified in the studies, these findings should be treated with extreme caution.

Capecitabine in combination with docetaxel
One RCT was identified which investigated a regimen of capecitabine in combination with docetaxel. The trial included 511 patients and compared capecitabine in combination with docetaxel to single-agent docetaxel. In addition, two uncontrolled studies investigated a regimen of weekly low-dose docetaxel plus capecitabine; however, these studies provided limited, poor quality evidence and used an alternative low-dose docetaxel regimen. Hence, this section of the report focused on the admittedly limited, but higher quality evidence, from the RCT. The RCT provided some evidence that capecitabine–docetaxel combination therapy was superior to single-agent docetaxel in patients previously treated with anthracyclines: statistically significant increases in survival time (median survival, HR 0.775, 95% CI 0.634 to 0.947), time to disease progression (median time to progression, HR 0.652, 95% CI 0.545 to 0.780) and time to treatment failure (median time to treatment failure, HR not reported) were reported. Overall tumour response rates (complete response plus partial response) were also significantly increased in the combination therapy group compared with the single-therapy group (overall response, RR 1.40, 95% CI 1.10 to 1.78), although there were no significant differences in complete response rates between the two groups. Measures of QoL recorded no clinically meaningful change from baseline on the global health status domain in either group during treatment. Treatment-related adverse events occurred more frequently in the combination therapy group. The incidence of severe or life-threatening (grade 3/4) hand–foot syndrome (RR 20.66, 95% CI 6.57 to 64.97), nausea (RR 3.26, 95% CI 1.21 to 8.77), diarrhoea (RR 2.37, 95% CI 1.33 to 4.23) and stomatitis were all significantly greater in patients receiving capecitabine in combination with docetaxel.

Assessment of cost-effectiveness
Capecitabine monotherapy
For capecitabine monotherapy indirectly compared with vinorelbine, based on the limited data and poor quality data available, capecitabine was a dominant case in that it was associated with lower costs and improved patient outcomes as measured by QALYs. However, the improved QALY profile is based on the extended survival seen in the comparison of single-arm studies, in which no allowance for case mix was made. This comparison is likely to be subject to bias and while sensitivity analysis consistently favoured capecitabine monotherapy, the weakness of the comparisons made and the questionable status of vinorelbine as sole comparator require that any results be treated with caution.

Capecitabine in combination with docetaxel
The assessment of cost-effectiveness of capecitabine in combination with docetaxel compared with single-agent docetaxel was based on an RCT. The results of the economic evaluation demonstrated an improved QALY score for combination therapy together with a very small reduction in costs. In the base case estimate, therefore, combination therapy was a dominant case. This is reflected in the cost-effectiveness acceptability curve which shows that for all reasonable values of decision-makers' willingness to pay for a QALY, combination therapy is likely to be cost-effective; indeed, the probability of combination therapy being cost-effective exceeds 90% at a willingness to pay for a QALY of £2000. However, QoL was assessed by applying constant utilities to disease states. This methodology fails to address the possibility that adverse events, specific to the individual treatments, may differentially affect QoL and hence produce quite different QALY gains and therefore influence the cost-effectiveness results. Nevertheless, on the available evidence, combination therapy is likely to be cost-effective compared with docetaxel monotherapy.

Conclusions

Capecitabine monotherapy
The evidence base for the assessment of the effectiveness of capecitabine monotherapy was ▶

particularly poor. All of the studies identified for inclusion in the review lacked a control group, leaving them vulnerable to biases and confounding factors.

The evidence from these uncontrolled studies appears to indicate that capecitabine has antitumour activity when used as monotherapy in patients who have received previous treatment with anthracycline-containing regimens and taxanes. The toxicity profile appeared to indicate an increased risk of patients particularly experiencing hand–foot syndrome and diarrhoea. QoL was inadequately assessed; only one study included an assessment as part of the evaluation of capecitabine monotherapy.

In terms of cost-effectiveness, based on the available data, treatment with capecitabine, compared indirectly with treatment with vinorelbine, appears to be cost-effective. No comparative trials of these treatments were reported. Given the diverse patient population, in terms of disease and treatment history, it is likely that an RCT, comparing survival from point of randomisation for both treatments in a comparative trial, could provide different information on relative survival times.

In conclusion, good quality RCTs are urgently needed to compare the effectiveness of capecitabine monotherapy with the alternative third- and subsequent-line therapies currently available, as well as with best supportive care. These data should be collected in a form that facilitates cost-effectiveness analysis. The quality of the economic assessment reflects the poor level of clinical evidence. On the available evidence, capecitabine monotherapy is cost-effective, but there remain serious doubts about whether the quality of the clinical trials invalidates this conclusion. For a more complete picture, systematic reviews of vinorelbine, best supportive care and other relevant comparators in this setting need to be undertaken.

Capecitabine in combination with docetaxel

This review suggests that there is limited evidence in the form of RCTs on which to base an assessment of the effectiveness of capecitabine in combination with docetaxel in comparison to existing and new chemotherapy agents for the second-line treatment of advanced breast cancer. Only one RCT was identified for inclusion in the review comparing capecitabine in combination with docetaxel to treatment with single-agent docetaxel.

From the evidence available from the single trial, capecitabine in combination with docetaxel appears to be more effective than single-agent docetaxel in terms of overall survival, time to disease progression, time to treatment failure and overall tumour response (complete response plus partial response). There was no statistically significant difference between the two groups in any of the QoL domains. Statistically significant differences between combination and single-agent therapy were identified in terms of reported grade 3/4 treatment-related side-effects. Treatment with capecitabine–docetaxel was associated with higher incidences of hand–foot syndrome, nausea, diarrhoea and stomatitis.

In terms of costs, combination therapy seems to be cost-effective; however, the cost-effectiveness analysis did not directly consider the impact on QoL associated with the combination and monotherapy treatments themselves.

In conclusion, further RCTs investigating capecitabine in combination with docetaxel compared to alternative second-line therapies are required. From the limited evidence it would appear that capecitabine in combination with docetaxel is more effective in terms of median survival time, time to disease progression, time to treatment failure and overall response than single-agent docetaxel. The economic analysis indicates that combination therapy is very likely to be cost-effective. However, the method of calculation of QALYs ignores the potential for differences in adverse events between treatments to alter QoL estimates.

Publication

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Technology assessment reports are completed in a limited time to inform the appraisal and guidance development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisal and guidance produced by NICE are informed by a wide range of sources.

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