Clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer

The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation

AL Takeda,* J Jones, E Loveman, SC Tan and AJ Clegg

Southampton Health Technology Assessments Centre (SHTAC), University of Southampton, UK

* Corresponding author

Executive summary

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Executive summary

Background

Breast cancer is the most common cancer in the UK, accounting for one-third of all cancers in women. In 2003, the age-standardised incidence rates per 100,000 population were 120.3 for England and 120.83 for Wales. The high incidence of breast cancer in conjunction with relatively good survival rates, compared with many other cancers, has led to a relatively high prevalence. Increasing age is the strongest risk factor for breast cancer, and the disease is rare in women under the age of 40 years. Over 80% of cases occur in women over the age of 50 years, with the number of diagnoses reaching a peak in the 55–59-year age group.

Breast cancer is classified into four clinical stages. Metastatic breast cancer (Stage IV) is characterised by the spread of distant metastases to other parts of the body, such as the bones, brain, lung or liver. Approximately half of all women with breast cancer will develop metastatic disease, although the majority will have a long disease-free interval between treatment for early-stage breast cancer and the development of metastases.

Treatments for metastatic breast cancer are primarily palliative rather than curative, although high rates of response can prolong survival to some extent. Toxicity and adverse effects will therefore play an important role in treatment decisions, with quality of life being a key consideration.

Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.

The combination of gemcitabine with paclitaxel is appropriate because they have different anti-tumour activities and non-overlapping toxicity profiles.

Objectives

The aim of this systematic review and economic evaluation is to assess the clinical effectiveness and cost-effectiveness of gemcitabine, used in combination with paclitaxel, as a second-line treatment for people with metastatic breast cancer who have relapsed following treatment with anthracycline-based chemotherapy.

Methods

A systematic review of the literature was undertaken to appraise the clinical and cost-effectiveness of gemcitabine. A model was developed for the economic evaluation.

Data sources

Electronic databases were searched from inception to March 2006 and reference lists from retrieved papers were checked for additional publications not identified by the electronic searches. Clinical advisers were asked if they were aware of any additional studies.

Study selection

Studies were included if they met the following criteria:

- *Interventions*: gemcitabine in combination with paclitaxel.
- *Comparators for clinical effectiveness review*: any other licensed treatment for metastatic breast cancer.
- *Patients*: people diagnosed with metastatic breast cancer who have previously been treated with anthracycline-based therapies.
- *Types of studies*: systematic reviews of randomised controlled trials (RCTs) and RCTs of the intervention compared with other treatments for metastatic breast cancer.
- *Outcomes*: survival; time to disease progression; disease-related symptoms; health-related quality of life; and adverse effects of treatment.

The titles and abstracts of all identified studies were screened by two independent reviewers and full-text versions of relevant English-language papers were retrieved. Inclusion criteria for full-text papers were applied by one reviewer and checked by a second reviewer. Any differences in decision to include or exclude were resolved through discussion.

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Data extraction and quality assessment

Data were extracted from the included studies by one reviewer and checked by a second reviewer using a data extraction form. Any disagreements were resolved through discussion. Studies with multiple publications were data extracted on to one form, with any differences between the publications identified and explicitly referenced. The quality of included RCTs was assessed using standard criteria developed by the NHS Centre for Reviews and Dissemination.

Data synthesis

The included study reports were tabulated and synthesised in a narrative summary. Meta-analysis was not appropriate for this report, due to the limited data identified.

Economic model

A Markov state transition model was developed to estimate the cost-effectiveness of gemcitabine with paclitaxel for patients with metastatic breast cancer. The model consisted of four states (responsive, stable disease, progressive disease and death) and applied transition probabilities derived from the literature and expert opinion. The model adopted a lifetime horizon, running until the majority of the cohort was in the absorbing health state (death). Sensitivity analyses were carried out to estimate the effect of treating for a maximum of six cycles of chemotherapy.

Results

The systematic review identified only one RCT, and this has not yet been fully published. The data are only available in three conference abstracts. The methodological quality and quality of reporting of the included trial were assessed to be poor using standard criteria, but this may be due to the lack of information in the limited publications rather than being a fair reflection of the trial's quality. This RCT compared gemcitabine and paclitaxel therapy with paclitaxel monotherapy in 529 patients with metastatic breast cancer who had previously received anthracyclines, but no prior chemotherapy for metastatic breast cancer.

Survival at 1 year was statistically significantly better in the gemcitabine/paclitaxel group than the paclitaxel group. Approximately 71% of the gemcitabine/paclitaxel patients survived for 1 year, compared with 61% of the paclitaxel group. The hazard ratio showed a 26% lower chance of survival in the paclitaxel group, and time to progressive disease was also shorter in this group.

The overall response rate was higher in the gemcitabine/paclitaxel group than in the paclitaxel group. Adverse events, particularly neutropenia, were more common with gemcitabine/paclitaxel combination therapy than with paclitaxel therapy alone.

The economic model developed for this review was run for a simulation of 1000 patients, assuming that chemotherapy continued until patients' disease progressed. This base-case analysis found an incremental cost-effectiveness ratio (ICER) of £58,876 per quality-adjusted life-year (QALY) gained and £30,117 per life-year gained. In normal practice, patients are likely to receive chemotherapy for a fixed number of cycles, rather than until disease progression. As a result, the model was re-run with treatment restricted to a maximum of six cycles per patient, which yielded an ICER of £38,699 per QALY gained and £20,021 per life-year gained.

Discussion

The systematic review was restricted by the lack of published evidence for gemcitabine's licensed indication. In the absence of any fully published studies, data from three abstracts were used to form the basis of the review of clinical effectiveness. These did not generally contain sufficient data to allow a detailed review of the clinical effectiveness of gemcitabine with paclitaxel.

The economic model adopted a structure similar to that used in previous economic evaluations of chemotherapy regimes for metastatic breast cancer. Clinical trial data used to derive parameter estimates for the model were taken from published abstracts and supplementary information available on the American Society of Clinical Oncology website (http://www.asco.org/portal/site/ASCO). Although sufficient data were available to develop and populate the model, these publications were not fully peer reviewed and it was not possible to quality assess these data formally. Assumptions were necessary to convert the clinical trial data to the form required for the model and these need to be taken into account when interpreting the results from the model.

Conclusions

The review of clinical effectiveness is based on data from a single RCT which has not yet been fully published. The trial did not rate particularly ▶

well on quality assessment criteria, although this was partly a reflection of publication status and lack of published information. Only tentative conclusions can therefore be drawn from our review.

Evidence from the included RCT may indicate that treatment with gemcitabine and paclitaxel confers an improved outcome for patients in terms of survival and disease progression, but at the cost of increased toxicity. An economic model developed for this review reflects high costs per QALY for this treatment combination. The base-case analysis shows high ICERs, with costs per QALY gained close to £60,000. Adopting a more realistic treatment protocol, with chemotherapy limited to a maximum of six cycles, gives a more favourable cost-effectiveness estimate. However, this was still higher than would usually be considered to be a cost-effective treatment from the NHS's perspective.

Future research recommendations include an update of this review in 12–18 months' time, by which time the included RCT should be fully published. It would also be useful to compare gemcitabine with currently used treatments for metastatic breast cancer, including capecitabine and vinorelbine.

Publication

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