

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer

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Executive summary

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Executive summary

Background

Pancreatic cancer is the eighth most common cancer in the UK and the sixth most common cause of cancer death; in 1998, 3198 men and 3364 women died from this condition. In an average health authority with a population of 500,000, there would be approximately 60 new cases of pancreatic cancer per year, based on the age and sex distribution of England and Wales. Over 75% of these patients are over 65 years of age.

The symptoms are wide ranging, but they may appear only towards the latter stage of the disease, so the vast majority of patients present with advanced disease. There are therefore rarely more than a few months between diagnosis and death, and palliative care is the best treatment that can be offered for the majority of sufferers. It is estimated that around 10–15% of patients diagnosed with pancreatic cancer currently receive palliative chemotherapy. This proportion is expected to rise and may increase to around 35% within the next few years.

5-Fluorouracil (5-FU) has been the standard chemotherapy used for pancreatic cancer in the UK over recent years, with evidence of a small survival advantage and improvement in quality of life (QoL) in a proportion of these patients. Gemcitabine is a relatively new chemotherapy drug; it inhibits DNA synthesis and is indicated for the treatment of adults with locally advanced or metastatic adenocarcinoma of the pancreas and for patients with 5-FU refractory pancreatic cancer.

Objectives

This review aimed to evaluate the clinical and cost-effectiveness of gemcitabine as first and second line therapy in the treatment of pancreatic cancer.

Methods

Systematic searches of clinical effectiveness, cost-effectiveness, and modelling in pancreatic cancer

and gemcitabine were performed. The databases searched included: MEDLINE, EMBASE, Science Citation Index, Database of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation Database and the National Research Register. Web resources and industry submissions were also consulted. All HTA and related secondary research studies were included. Primary research studies were included if the authors had attempted to measure an outcome of importance.

A qualitative review was undertaken of all identified studies conducted on patients with a diagnosis of pancreatic adenocarcinoma, using gemcitabine alone or in combination with another drug. All Phase I studies were excluded.

Cost-effectiveness analyses were performed to estimate the marginal cost and marginal effectiveness of gemcitabine in comparison with standard therapy with 5-FU. The difference in mean survival was combined with the difference in the average cost of the interventions to calculate the cost per life-year gained (LYG). Costs were direct drug costs and health service costs. No QoL data were identified. However, given the significance of QoL for patients with pancreatic cancer, an illustration was provided, using quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis, of the potential impact of QoL on the cost per LYG results.

Results

Number and quality of studies, and direction of evidence of clinical effectiveness

A review of the published literature identified seven randomised controlled trials (RCTs). However, only one was a fully published RCT comparing gemcitabine with standard chemotherapy treatment (5-FU). No RCTs of gemcitabine versus best supportive care were located. Fifty-seven other studies were identified, of which 17 examined the use of gemcitabine alone.

No high-quality RCTs of gemcitabine as a second line treatment were identified.

Summary of benefits

There is a very poor evidence base by which to assess the efficacy of gemcitabine. The validity of the only RCT that compared gemcitabine with the standard treatment of 5-FU is open to question. In the control arm of this study the drug was administered as a bolus infusion. It is unlikely that bolus 5-FU alone would be used as standard practice in the UK. In other forms of gastrointestinal cancer therapy, bolus 5-FU alone would be considered to be inferior to other 5-FU regimens in terms of response rates and efficacy. These factors, in combination with the small patient sample included in the trial, mean that its results cannot be regarded as definitive.

From the available evidence it would appear that gemcitabine as a first line therapy offers similar survival to 5-FU-based regimens, but it is impossible to demonstrate conclusively its superiority in terms of either survival or QoL.

There is insufficient evidence to determine with any degree of certainty the benefit of gemcitabine as a second line therapy.

Costs

No published UK costings of gemcitabine were identified. The cost of 5-FU is dependent on the mode of its delivery. Two regimens currently used in the UK are considered: the De Gramont regimen (5-FU 400 mg/m² by bolus injection plus 400 mg/m² 22-hour infusion, plus 200 mg/m² folinic acid 2-hour infusion for 2 days at 14-day intervals) for which an inpatient stay is generally required for its administration; and protracted venous infusion of 5-FU (300 mg/m² per day via an ambulatory pump), which allows the drug to be administered in the home setting. Although the drug cost of gemcitabine is more expensive than 5-FU this may be partly offset by lower administration costs, particularly in comparison with the De Gramont regimen. The cost of drug administration for protracted venous infusion 5-FU varies markedly according to local circumstances. For instance, the frequency of visits to the hospital for checking and flushing of the central line and pump may vary between once weekly and once every 6 weeks. This type of local variability will impact on the cost of 5-FU and, therefore, on the relative cost-effectiveness of gemcitabine.

Costs per life-year gained

Preliminary estimates of the cost of gemcitabine per LYG suggest that it may be below £20,000. However, the clinical evidence on which the

analysis is based is poor and no published UK estimates of the cost of gemcitabine have been identified. The sensitivity analysis confirms that the cost per LYG is sensitive to assumptions on cost and survival. Given these uncertainties, it would be difficult to place too much weight on the findings. Further evidence is required before any definite conclusions can be drawn about cost-effectiveness.

Cost per quality-adjusted life-year

Given the significance of QoL for patients with pancreatic cancer an illustration has been provided, using Q-TWiST analysis of the potential impact of QoL adjustments on survival and the cost per LYG. No QoL data were identified, so the results of the analysis are purely illustrative. However, the analysis does demonstrate that the addition of a QoL adjustment is likely to reduce the survival gain. This would result in a cost per quality-adjusted life-year gained that is higher than the cost per LYG.

Conclusions

Need for further research

Gemcitabine as first line therapy

Until Phase II studies with existing or new drugs, alone or in combination, demonstrate significant improved benefit in pancreatic cancer, randomised studies are likely to be directed towards toxicity, QoL and any small survival benefits that may be obtained with gemcitabine alone compared with a modern 5-FU-based protocol or a combination of the two.

The evidence for QoL benefits of gemcitabine is particularly poor. There is widespread acknowledgement of the need for a RCT to confirm the survival benefits of gemcitabine and, particularly, to enable the collation of acceptable QoL data.

Gemcitabine as second line therapy

Further high-quality randomised trial evidence is required to determine fully the value of gemcitabine as a second line treatment.

Publication

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