Guidance on the use of gemcitabine for the treatment of pancreatic cancer

Technology appraisal guidance
Published: 8 May 2001
nice.org.uk/guidance/ta25
Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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1 Guidance

1.1 Gemcitabine may be considered as a treatment option for patients with advanced or metastatic adenocarcinoma of the pancreas and a Karnofsky performance score of 50 or more, where first line chemotherapy is to be used.

1.2 Gemcitabine is not recommended for patients who are suitable for potentially curative surgery, or patients with a Karnofsky (see Appendix D) score of less than 50.

1.3 There is insufficient evidence to support the use of gemcitabine as a second line treatment in patients with pancreatic adenocarcinoma.
2 Clinical Need and Practice

2.1 Pancreatic adenocarcinoma is a common cancer with an annual incidence rate of around 12 per 100,000. In 1997 there were an estimated 5,730 people (2,740 men and 2,990 women) diagnosed with pancreatic cancer in England and Wales. Of these 75% (4,320: 1,940 men and 2,380 women) were over 65 years of age.

2.2 The annual mortality rate from pancreatic cancer is almost identical to the incidence rate (11 per 100,000) as the prognosis is extremely poor. The 1-year survival rate is generally low at around 12%, and less than 3% of patients survive to 5 years.

2.3 The symptoms of pancreatic cancer are wide-ranging, including jaundice, nausea, diarrhoea, weight loss, loss of appetite, and severe pain. The vast majority of patients present with advanced disease and symptoms significantly reduce the patients’ quality of life.

2.4 Potentially curative surgery is currently a treatment option for around 4% of the overall patient population. As the majority of cases are diagnosed at advanced stages, palliative care will often be the best that can be offered to relieve symptoms and the outcomes remain poor.

2.5 Palliative surgery and endoscopic placement of biliary drainage stents can be used to control complications of the pancreatic cancer such as jaundice and gastric outlet obstruction, thus improving quality of life.

2.6 Alternative treatment options include chemotherapy and radiotherapy. It is estimated that around 10-15% of patients diagnosed with pancreatic cancer currently receive chemotherapy.

2.7 5-fluorouracil (5-FU) has been the standard chemotherapy used in the UK over recent years, with evidence suggesting a small survival advantage and improvements in quality of life (QoL) in a proportion of patients with pancreatic cancer. 5-FU is administered using a variety of doses and schedules but the response rate rarely exceeds 20% and no consistent effect on disease-related symptoms or survival has been demonstrated.
3 The Technology

3.1 Gemcitabine (Gemzar) is a chemotherapeutic drug that exerts its action by inhibiting DNA synthesis. It is a novel nucleoside analogue with a wide spectrum of anti-tumour activity against a variety of solid tumours including pancreatic cancer.

3.2 Gemcitabine is licensed as a first line treatment of adult patients with locally advanced or metastatic adenocarcinoma of the pancreas and as a second line treatment of patients with 5-FU refractory pancreatic cancer.

3.3 Gemcitabine is generally well tolerated but may cause rashes and mild gastrointestinal side effects such as nausea. Bone marrow suppression, influenza-like symptoms, proteinuria/haematuria, peripheral oedema, bronchospasm, and in rare cases, Adult Respiratory Distress Syndrome (ARDS), and potentially irreversible renal failure have been reported.
4 Evidence

4.1 Clinical effectiveness

4.1.1 In the first line setting, five published randomised controlled trials (RCT) were identified. One trial compares gemcitabine with a bolus infusion of 5-FU and another with intra-arterial 5-FU (abstract only). In addition, three trials compare gemcitabine to metallomatrix proteinase inhibitors (two trials involve marimastat and one BAY12 9566).

4.1.2 There is thus only one fully reported single-blind RCT, reported by Burris et al, which compares gemcitabine to treatment with 5-FU as a first line treatment used on patients with a Karnofsky score of 50 or more (n=126). In this trial, patients randomised to gemcitabine had better one-year survival (18% vs 2%, p=0.0002), better median survival (5.6 vs 4.4 months, p=0.0025) and improved median progression free survival (2.3 vs 0.9 months, p=0.0002). However, in this trial the comparator, 5-FU, was given by bolus injection, not the usual current means of administration; and the results of this trial may be prone to bias due to lack of blinding of the investigators. Furthermore, the 12-month survival rate of 2% in 5-FU group is unusually low when compared with other published 5-FU studies.

4.1.3 The trial also evaluated the impact of gemcitabine on quality of life in terms of Clinical Benefit Response (CBR) and demonstrated that the administration of gemcitabine led to more clinical benefit responders compared to 5-FU (24% vs 5%, p=0.0022). However, although it has professional support CBR is not a validated tool and its ability to measure the effectiveness of palliative chemotherapy is still investigational.

4.1.4 No relevant RCTs were identified which examine the effect of gemcitabine as a second line treatment in patients with relapsed disease. One non-randomised Phase II trial, involving exclusively individuals with relapsed disease studied the effect of gemcitabine in 74 patients with metastatic pancreatic cancer that had progressed despite the administration of 5-FU. This study demonstrated a median survival of 4 months, one-year survival of 4% and CBR rate of 27%.

4.1.5 In the Burris trial, both gemcitabine and 5-FU were generally well tolerated. However laboratory toxicity was worse for gemcitabine; 26% of patients
treated with gemcitabine had Grade 3 or 4 neutropenia compared with 5% in 5-FU group (p<0.01).

4.1.6 The role of gemcitabine in the treatment of pancreatic cancer in comparison with other agents including combination regimens is being investigated in 11 ongoing RCTs and 24 Phase II trials.

4.2 Cost effectiveness

4.2.1 Two published economic evaluations of gemcitabine as first line therapy for pancreatic cancer were identified, one of which was only available in abstract form. An economic evaluation of gemcitabine, in both first and second line treatment, was included in the Eli Lilly submission. ScHARR, on behalf of NICE, has undertaken its own analysis.

4.2.2 All of the economic analyses submitted drew on the effectiveness data from the single RCT by Burris et al. For first line treatment the estimates for cost per life year gained ranged from approximately £7,200 to £18,700 dependent on the 5-FU regimen used as comparator. These figures are very sensitive to reduced estimates of survival benefit over comparators.

4.2.3 Cost effectiveness evidence therefore suggests that gemcitabine provides a reasonably cost-effective alternative in the first-line treatment of pancreatic cancer but this conclusion is based on the results from one clinical trial.
5  Implications for the NHS

5.1  Of 6,000 patients diagnosed with pancreatic cancer each year, at least 80% of them (4,800 patients) are estimated to have locally advanced or metastatic disease. Assuming that 25-35% of those will be offered chemotherapy and only half of them are treated, the total number of patients on gemcitabine would be in the range of 600 to 840 patients per year.

5.2  The incremental cost of gemcitabine treatment ranges between £1,360 and £3,550 per patient depending on the type of the 5-FU regimen. If gemcitabine were to be made available for routine NHS use, based on the estimated number of eligible patients above, the total additional cost to the NHS is estimated to be between £816,000 and £3m per annum. This includes the direct costs to the NHS such as drug costs and utilisation of health services.
6  Further Research

6.1  Further good quality studies are needed:

- to confirm the survival benefits, and the impact on QoL of gemcitabine as a first line treatment in comparison to commonly used 5-FU regimens.

- to identify the value of gemcitabine as a second line treatment in pancreatic cancer.

- to assess the cost-effectiveness of gemcitabine as a first and second line treatment in the light of any significant new effectiveness evidence.
7 Implementation

7.1 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within 3 months of this guidance being published. This means that, if a patient has pancreatic cancer and the doctor responsible for their care thinks that gemcitabine is the right treatment, it should be available for use, in line with NICE's recommendations.

7.2 Clinicians should review their current clinical practice for the management of pancreatic cancer against the guidance set out in section 1.

7.3 Relevant clinical guidelines and protocols should be reviewed in light of this guidance and revised if necessary.

7.4 To enable clinicians to audit their own compliance with this guidance it is recommended that, if not already in place, management plans are recorded for each patient with pancreatic cancer.

7.5 This information should be incorporated into local clinical audit data recording systems and consideration given (if not already in place) to the establishment of appropriate categories in electronic record systems.

7.6 Prospective clinical audit programmes should record the proportion of treatments adhering to the guidance. Such programmes are likely to be more effective in improving patient care when they form part of the organisation's formal clinical governance arrangements and where they are linked to specific post-graduate activities.
8 Review of Guidance

8.1 Information on the review of the guidance on this technology is available on the NICE website.

Andrew Dillon
Chief Executive
May 2001
Appendix A. Appraisal Committee Members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The committee are supplemented by technology specific experts as indicated in Appendix B.

Professor R. L. Akehurst
Dean, School of Health Related Research Sheffield University

Professor David Barnett (Chairman)
Professor of Clinical Pharmacology University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy St Bartholomew's and Royal London School of Medicine

Dr Sheila Bird
MRC Biostatistics Unit, Cambridge

Professor Martin Buxton
Director of Health Economics Research Group Brunel University

Professor Yvonne Carter
Professor of General Practice and Primary Care St Bartholomew's and Royal London School of Medicine

Dr Karl Claxton
Lecturer in Economics University of York

Professor Duncan Colin-Jones
Professor of Gastroenterology University of Southampton

Professor Sarah Cowley
Professor of Community Practice Development Kings College, London

Dr Nicky Cullum
Reader in Health Studies University of York

Guidance on the use of gemcitabine for the treatment of pancreatic cancer (TA25)
Mr Chris Evennett
Chief Executive Mid-Hampshire Primary Care Group

Professor Terry Feest
Clinical Director and Consultant Nephrologist Richard Bright Renal Unit and Chairman of the UK Renal Registry

Ms Jean Gaffin
Formerly Executive Director National Council for Hospice and Specialist Palliative Care Service

Mrs Sue Gallagher
Chief Executive Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
International Medical Operations Director GlaxoWellcome R&D Ltd

Mr John Goulston
Director of Finance The Royal Free Hampstead NHS Trust

Professor Philip Home
Professor of Diabetes Medicine University of Newcastle

Dr Terry John
General Practitioner The Firs, London

Dr Diane Ketley
Research into Practice Programme Leader NHS Modernisation Agency

Dr Mayur Lakhani
General Practitioner, Highgate Surgery, Leicester and Lecturer, University of Leicester

Mr M Mughal
Consultant Surgeon Chorley and South Ribble NHS Trust

Mr James Partridge
Chief Executive Changing Faces
Professor Philip Routledge
Professor of Clinical Pharmacology University of Wales

Professor Andrew Stevens (Vice-Chairman)
Professor of Public Health University of Birmingham
Appendix B. Sources of Evidence

1. The following documentation and opinion was made available to the Committee:

a. Assessment Report prepared by The School of Health and Related Research (ScHARR), University of Sheffield (A Review of the Clinical and Cost-Effectiveness of Gemcitabine for the Treatment of Pancreatic Cancer, December 2000)

b. Manufacturer/Sponsor submissions from:
   - Eli Lilly

c. Professional/Specialist Group submissions from:
   - Royal College of General Practitioners
   - Royal College of Physicians and the Royal College of Radiologists

d. Patient Group submissions from:
   - CancerBACUP

e. External expert and patient advocate submissions from:
   - Professor William Steward, Head, Department of Oncology, Leicester Royal Infirmary
   - Ms Judith Brodie, Head of Cancer Support Service, CancerBACUP
Appendix C. Guidance on the use of gemcitabine for the treatment of pancreatic cancer – Information for Patients

'Understanding NICE Guidance', a summary of this guidance for patients and carers can be found on our website.
Appendix D. Karnofsky Performance Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>The patient has no complaints and is without evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>The patient has minor signs/symptoms, but is able to carry out his or her normal activities</td>
</tr>
<tr>
<td>80</td>
<td>The patient demonstrates some signs/symptoms and requires some effort to carry out normal activities</td>
</tr>
<tr>
<td>70</td>
<td>The patient is able to care for self, but is unable to do his or her normal activities or active work</td>
</tr>
<tr>
<td>60</td>
<td>The patient is able to care for self, but requires occasional assistance</td>
</tr>
<tr>
<td>50</td>
<td>The patient requires medical care and much assistance with self care</td>
</tr>
<tr>
<td>40</td>
<td>The patient is disabled and requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>The patient is severely disabled and hospitalisation is indicated; Death is not imminent</td>
</tr>
<tr>
<td>20</td>
<td>The patient is very ill with hospitalisation and active life-support treatment necessary</td>
</tr>
<tr>
<td>10</td>
<td>The patient is moribund with fatal process proceeding rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

ECOG/WHO/RTOG to KPS (Approximate Conversion System)

<table>
<thead>
<tr>
<th>E/W/R</th>
<th>Karnofsky</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90-100%</td>
<td>Normal activity</td>
</tr>
<tr>
<td>1</td>
<td>70-80%</td>
<td>Symptoms demonstrated, but the patient remains ambulatory, and able to perform self-care</td>
</tr>
<tr>
<td>2</td>
<td>50-60%</td>
<td>Ambulatory &gt;50% of the time and requires occasional assistance</td>
</tr>
<tr>
<td>3</td>
<td>30-40%</td>
<td>Ambulatory &lt;50% of the time and requires nursing care</td>
</tr>
<tr>
<td>4</td>
<td>10-20%</td>
<td>Bedridden</td>
</tr>
<tr>
<td>5</td>
<td>0%</td>
<td>Death</td>
</tr>
</tbody>
</table>
Changes after publication

March 2014: implementation section updated to clarify that gemcitabine is recommended as an option for treating pancreatic cancer. Additional minor maintenance update also carried out.

March 2012: minor maintenance
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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