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SUPPLEMENT

Single Technology Appraisals

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Health Technology Assessment

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NIHR Health Technology Assessment programme

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

Second, 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.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy makers. TARs bring together evidence on the value of specific technologies.

This supplement to the Journal series contains a collection of summaries based on Evidence Review Group reports (ERGs), produced as part of NICE's Single Technology Appraisal (STA) process. The reports are mainly based on data submissions from manufacturers and do not undergo the standard peer-review process.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

Criteria for inclusion in the HTA Journal series and Supplements

Reports are published in the journal series and supplements if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the supplement was commissioned and funded by the HTA programme on behalf of NICE. 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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Supplement introduction

Welcome to the fourth Supplement to the *Health Technology Assessment* journal series. The series is now over 10 years old and has published more than 400 titles, covering a wide range of health technologies in a diverse set of applications. In general, the series publishes each technology assessment as a separate issue within each annual volume.

The Supplements depart from that format by containing a series of shorter articles. These are all products from a 'call-off contract', which the HTA programme holds with a range of academic centres around the UK, at the universities of Aberdeen, Birmingham, Exeter, Liverpool, Sheffield, Southampton and York. These centres are retained to provide a highly responsive resource, which meets the needs of national policy makers, notably the National Institute for Health and Clinical Excellence (NICE).

Until recently, these HTA Technology Assessment Review (TAR) centres provided academic input to policy making through independent analyses of the impact and value of health technologies. As many readers will be aware, the perception that the advice NICE provides to the NHS could be made more timely has led to the development of the 'Single Technology Appraisal' process. In this approach, manufacturers of technologies, which are, in general, pharmaceuticals close to the time of launch, submit a dossier of evidence aiming to demonstrate effectiveness and cost-effectiveness. The independent academic input to NICE's process, which continues to be supported by the TAR centres around the UK under contract to the HTA programme, is to scrutinise, critique and explore this dossier of evidence.

The papers included in this Supplement report on this HTA programme funded work, and we hope that the summaries of the work carried out to inform the development of NICE guidance for these technologies will be of interest and value to readers.

Further details of each of the NICE Appraisals are available on the NICE website (www. nice.org.uk) and we welcome comments on the summaries via the HTA website (www.hta.ac.uk/correspond/).

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Cetuximab for the first-line treatment of metastatic colorectal cancer

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of cetuximab for the first-line treatment of metastatic colorectal cancer (mCRC), in accordance with the licensed indication, based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The ERG project ran between 22 January 2008 and 4 November 2008. The clinical evidence came from two unpublished randomised controlled trials (RCTs) of cetuximab plus chemotherapy versus chemotherapy alone in the first-line treatment of mCRC. A third RCT submitted later compared cetuximab with irinotecan in combination with 5-fluorouracil (5-FU) and folinic acid (FA) and cetuximab with oxaliplatin in combination with 5-FU and FA in patients with mCRC with liver metastases only. No published economic evaluations of cetuximab for first-line chemotherapy in mCRC were identified in the submission. A de novo model examined the cost-effectiveness of cetuximab in patients with mCRC that was epidermal growth factor receptor positive, *k*-ras wild type and with liver metastases. The main source of clinical effectiveness evidence came from the first two RCTs which provided follow up information for 1–2 years. Secondary information was used to estimate survival for a further 22 years. The model focused on the patients for whom the treatment had been licensed. This limited the applicability of the model to the NHS setting in which patients would be a mixture of *k*-ras wild type and mutations and also a mixture of patients with liver metastases and other

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TAR Centre(s):
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The research reported in this article of the journal supplement was commissioned and funded by the HTA programme on behalf of NICE as project number 07/91/01. The assessment report began editorial review in January 2009 and was accepted for publication in June 2009. See the HTA programme website for further project information (www.hta.ac.uk). This summary of the ERG report was compiled after the Appraisal Committee's review.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

metastases. The difference in progression-free survival for the two trials was between 0.5 to 1.2 months over a 7–10 month period. Eight months' treatment with cetuximab, given as an initial loading dose and then weekly until progression, would cost around £22,932 for an average man and £18,427 for an average woman. It is uncertain whether this constitutes good value for money. The guidance issued by NICE on 25 September 2008 stated that cetuximab was not recommended for the first-line treatment of mCRC and people currently receiving cetuximab for the first-line treatment of mCRC should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled 'Cetuximab for the first-line treatment of metastatic colorectal cancer (mCRC)'.[2]

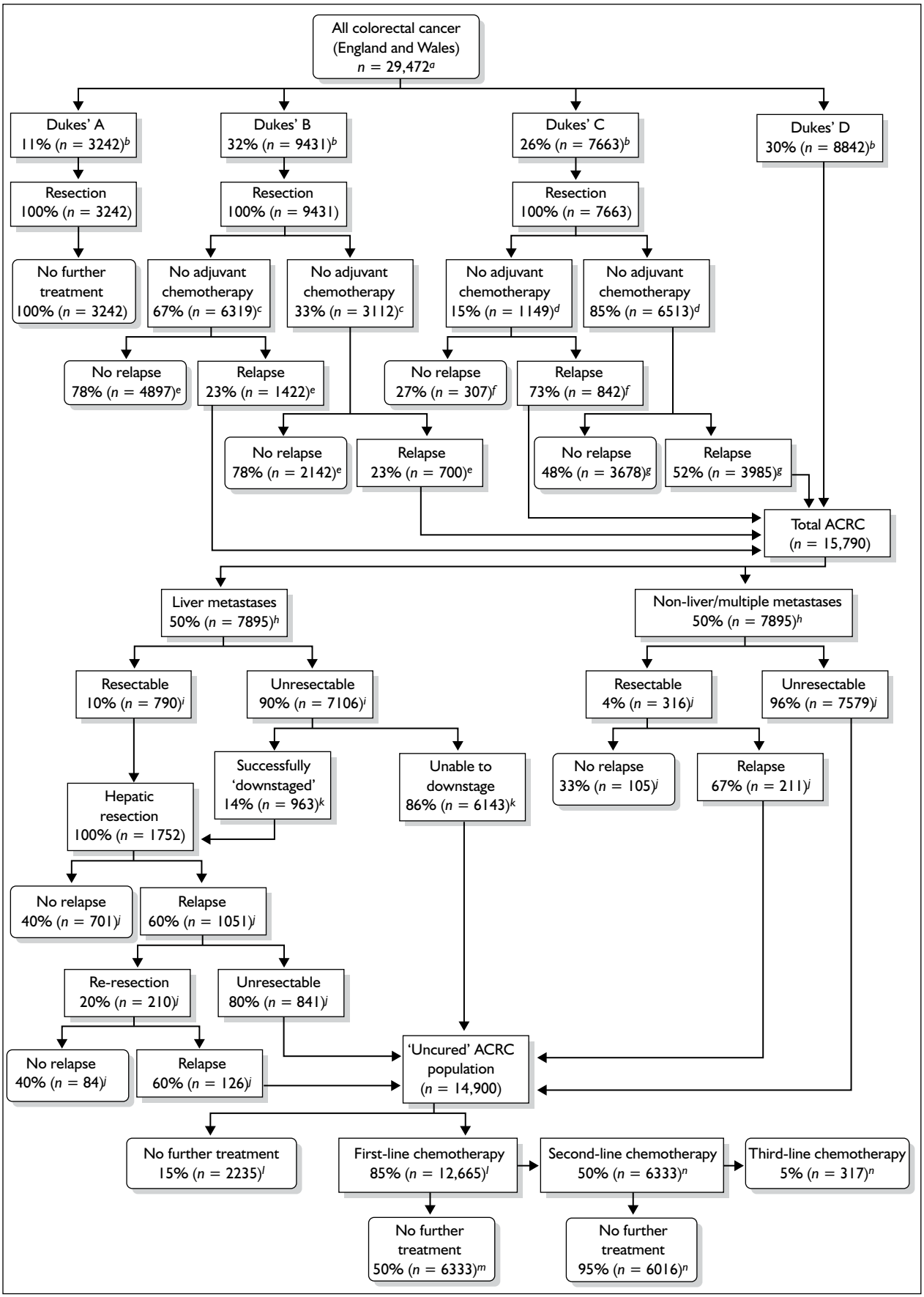
Description of the underlying health problem

Colorectal cancer is a malignant neoplasm arising from the lining (mucosa) of the large intestine (colon and rectum). Colorectal cancer is the third most common cancer in the UK, with approximately 30,000 new cases registered in England and Wales in 2002. This represents 12% of all new cancer cases in women and 14% of all new cancer cases in men. In people between the ages of 45 and 49 years, the incidence is 20 per 100,000. Amongst those over 75 years of age, the incidence is over 300 per 100,000 for men and 200 per 100,000 per year for women. The median age of patients at diagnosis is over 70 years.

In mCRC the tumour has spread beyond the confines of the locoregional lymph nodes to other parts of the body. This is described as stage IV of the American Joint Committee on Cancer tumour node metastases system, or stage D of Dukes' classification. Estimates of people presenting with mCRC range from 20% to 55% of new cases. In addition, out of patients who have undergone surgery for early stage colorectal cancer with apparently complete excision, approximately 50% will eventually develop advanced disease and distant metastases (typically presenting within 2 years of initial diagnosis). The 5-year survival rate for metastatic colorectal disease is 12%.

The management of mCRC is mainly palliative and involves a combination of specialist treatments (such as palliative surgery, chemotherapy and radiation), symptom control and psychosocial support. However, approximately 20% of patients with mCRC present with potentially resectable liver metastases. In addition, estimates suggest that for between 10% and 50% of patients, chemotherapy may render unresectable liver metastases operable. The resection of metastases can result in longer term survival for a proportion of patients. Flow of patients and approximate percentages can be seen

FIGURE 1 *(Opposite) Treatment algorithm for people with colorectal cancer in England and Wales. a, Office for National Statistics,[4] Welsh Cancer Intelligence and Surveillance Unit[5]; b, South West Cancer Intelligence Service[13]; c, Seymour M, Leeds Teaching Hospitals NHS Trust, personal communication: between 33% and 60% of people with Dukes' B cancer receive adjuvant chemotherapy (this study assumed the lower estimate); d, Seymour M, personal communication: more than 85% receive adjuvant chemotherapy; e, Seymour M, personal communication: 20–25% of patients with Dukes' B will relapse; f, estimated 40% relative risk increase of relapse for surgery alone versus chemotherapy, from pooled multicentre trial.[39] Relative risk increase applied to 5-year disease-free survival estimates from X-ACT trial;[40] g, 5-year disease-free survival estimates from X-ACT trial;[40] h, Maughan T, Velindre Hospital, Cardiff, personal communication; i, data from case series[41] suggest up to 20% may be resectable, although this is an aggressive stance; a maximum of 15% of patients are suitable; Maughan T, personal communication; j, Poston G, Royal Liverpool University Hospital, personal communication; k, data from case series[41]; l, Seymour M, personal communication: 85–90% of advanced patients receive chemotherapy[42]; m, preliminary data from FOCUS trial[42]; n, Glynne Jones R, Watford and Barnet General Hospitals, London, personal communication: only 3–5% patients would receive third-line therapy. [Note: the numbers in the text above refer to references in Hind* et al.,*[3] boxes with subscript letters c and d have error where the 33% and the 85% boxes (right-hand side of each pair) should read adjuvant chemotherapy whereas the left-hand side boxes should read no adjuvant chemotherapy (Steven N, University of Birmingham, July 2008, personal communication).] Figure reproduced with permission from Hind* et al. Health Technol Assess *2008;* ***12****(15).*



in *Figure 1*, reproduced with permission from a recent HTA report.[3]

Current guidance from NICE recommends oxaliplatin in combination with 5-fluorouracil (5-FU) and folinic acid (FA) (FOLFOX) and irinotecan in combination with 5-FU/FA (FOLFIRI) as first-line treatment options (technology appraisal 93[4]). The oral analogues of 5-FU capecitabine and tegafur with uracil are also recommended as treatment options (technology appraisal 61[5]). Bevacizumab as a first-line treatment and cetuximab as a treatment following the failure of an irinotecan-including chemotherapy regimen are not recommended as treatment options (technology appraisal 118[6]).

Scope of the evidence review group report

The purpose of the ERG report is to comment on the validity of the manufacturer's submission on the technology of interest. The scope for this submission and hence the scope for the ERG report was:

> To appraise the clinical and cost effectiveness of cetuximab within its licensed indication for the first line treatment of metastatic colorectal cancer.[7]

The relevant Commitee for Medicinal Products for Human Use (CHMP) positive opinion for cetuximab (Erbitux) was:

Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR) expressing *k*-ras (*k*-ras is the gene that encodes for KRAS, a protein that acts in cellular proliferation and transformation) wild-type mCRC:

- in combination with chemotherapy
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of cetuximab based upon the manufacturer's submission to NICE as part of the STA process. Specific steps undertaken by the ERG included:

- discussion of the nature of the problem with a clinical expert
- reanalysis of the nature of the clinical question
- rerunning searches indicated to have been carried out to inform the manufacturer's submission
- extending searches, particularly for ongoing trials
- formal critical appraisal of the systematic review of clinical effectiveness and cost-effectiveness data underpinning the manufacturer's submission
- reappraisal and checking of effectiveness and safety data from unpublished trial reports
- formal critical appraisal of the de novo economic model
- checking the consistency of the effectiveness estimates emerging from the trials with the parameters used in the economic model
- rerunning the model for a 5-year time horizon instead of the original 23-year time horizon as submitted by the manufacturer
- evaluating the evidence regarding clinical sensitivity and specificity of *k*-ras and EGFR tests
- evaluating a best-case scenario analysis of the model submitted as a response to clarifications
- evaluating a separate budget impact model submitted by the manufacturer
- evaluation of additional material from a third randomised controlled trial (RCT) and a reworked economic model between the first and second appraisal committee meetings.

The work was carried out between 22 January 2008 and 4 November 2008 (report submitted 22 July 2008). Members of the ERG team attended and advised the meetings of the NICE Appraisal Committee in which this guidance was discussed, on 3 September 2008 and 4 November 2008.

Results

Summary of submitted clinical evidence

The originally submitted clinical effectiveness consists of two unpublished RCTs of cetuximab plus chemotherapy versus chemotherapy alone in the first-line treatment of mCRC. The CRYSTAL trial enrolled 1217 patients with EGFR expressing mCRC, and the combination chemotherapy was FOLFIRI. The OPUS trial enrolled 337 patients with previously untreated EGFR expressing mCRC that was not resectable with curative intent, and the

chemotherapy used was FOLFOX4. Full follow-up was for [commercial-in-confidence data removed] months in the CRYSTAL trial when [commercial-in-confidence data removed] in both arms of the trial either had died or was lost to follow up. Full follow-up in the CRYSTAL trial, *k*-ras wild-type subgroup was given at 16 months, and there were six patients remaining in the intervention arm and three in the control arm. For the OPUS trial, full trial results for progression-free survival and overall survival were not found in the submission or the trial report, so are not presented here. For the OPUS trial *k*-ras subgroup, the equivalent numbers at 12-month follow-up were four patients in the intervention arm and two in the control arm. The difference in median progression-free survival in the CRYSTAL trial, for the *k*-ras wild-type subgroup, was 1.2 months (9.9 months versus 8.7 months) and for the OPUS trial *k*-ras wild-type subgroup was 0.5 months (7.7 months versus 7.2 months). Survival curves for these two trials are presented in *Figure 2*. A third RCT, the CELIM trial, was submitted for assessment between the first and second appraisal committee meetings.[5] This compared cetuximab with FOLFIRI and cetuximab with FOLFOX in 111 patients with mCRC with liver metastases only. Interim results only were presented.

Table 1 shows a comparison of the NICE scope, the CHMP positive opinion, the submission and the two originally submitted trials.

Summary of submitted cost-effectiveness evidence

No published economic evaluations of cetuximab for first-line chemotherapy in mCRC were identified in the submission, but additional searches by the ERG suggested that six cost-effectiveness papers may have been of relevance. A de novo model examined the cost-effectiveness of cetuximab in patients with mCRC that was EGFR positive, *k*-ras wild type and with liver metastases. The model was a time dependent state transition (Markov) model with a cycle length of 1 week and a 23-year time horizon (1200 cycles). The main source of evidence came from the two RCTs (CRYSTAL and OPUS) and used progression-free survival and mortality results. Other sources of cost and clinical model inputs were included such as Eastern Co-operative Oncology Group performance status, results of second and third-line treatment, costs of *k*-ras (but not EGFR) tests and costs of hospitalisation. Sensitivity analyses (scenario, one-way and probabilistic) were performed and reported. A reworked economic model using inputs from the CELIM trial[8] and the GERCOR trial[9] was submitted between the first and second appraisal committee meetings.

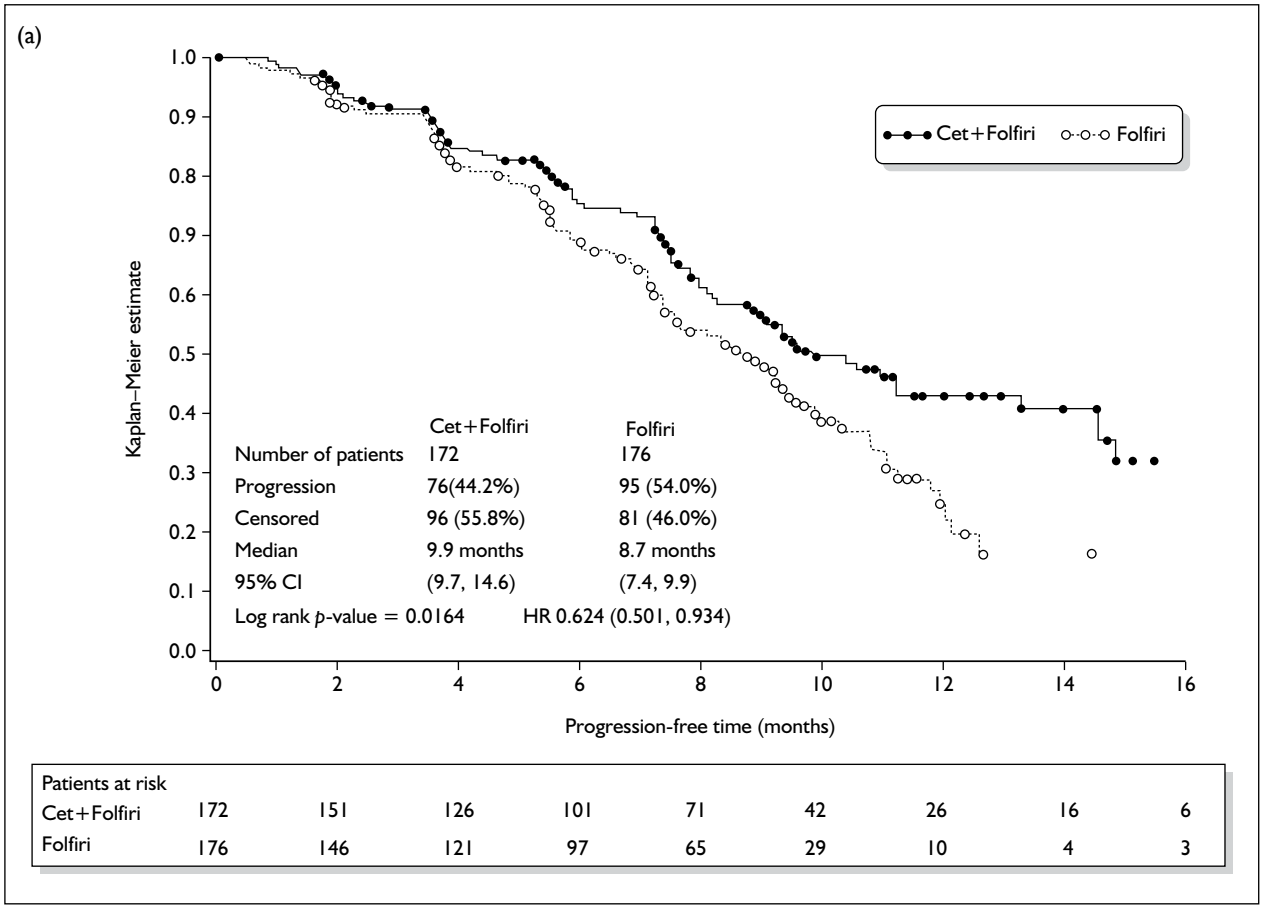
Commentary on the robustness of submitted evidence

The strength of the submitted clinical effectiveness was because it was based on two RCTs rather than

TABLE 1 *Comparison of NICE scope, CHMP positive opinion, submission and RCTs*

	NICE scope	CHMP	Submission	Trials
Patients	Untreated mCRC, first-line palliative	EGFR expressing *k*-ras wild type mCRC	Untreated EGFR expressing *k*-ras wild type mCRC	Previously untreated mCRC
Metastases	Untreated, any location	Any location	In model – metastases only in liver	Untreated, non-resectable
Intervention	Cetuximab with chemotherapy	In combination with chemotherapy	Cetuximab plus FOLFIRI or FOLFOX	Cetuximab + FOLFIRI (CRYSTAL), cetuximab + FOLFOX (OPUS)
Comparators	Oxaloplatin-including regimens, irinotecan including regimens, 5-FU/FA (including oral analogues, capecitabine and tegafur with uracil)		FOLFIRI or FOLFOX only	FOLFIRI (CRYSTAL), FOLFOX (OPUS)

EGFR, epidermal growth factor receptor; FA, folinic acid; FOLFIRI, irinotecan in combination with S-FU/FA; FOLFOX, S-FU and folinic acid (FA); FU, 5-fluorouracil; mCRC, metastatic colorectal cancer



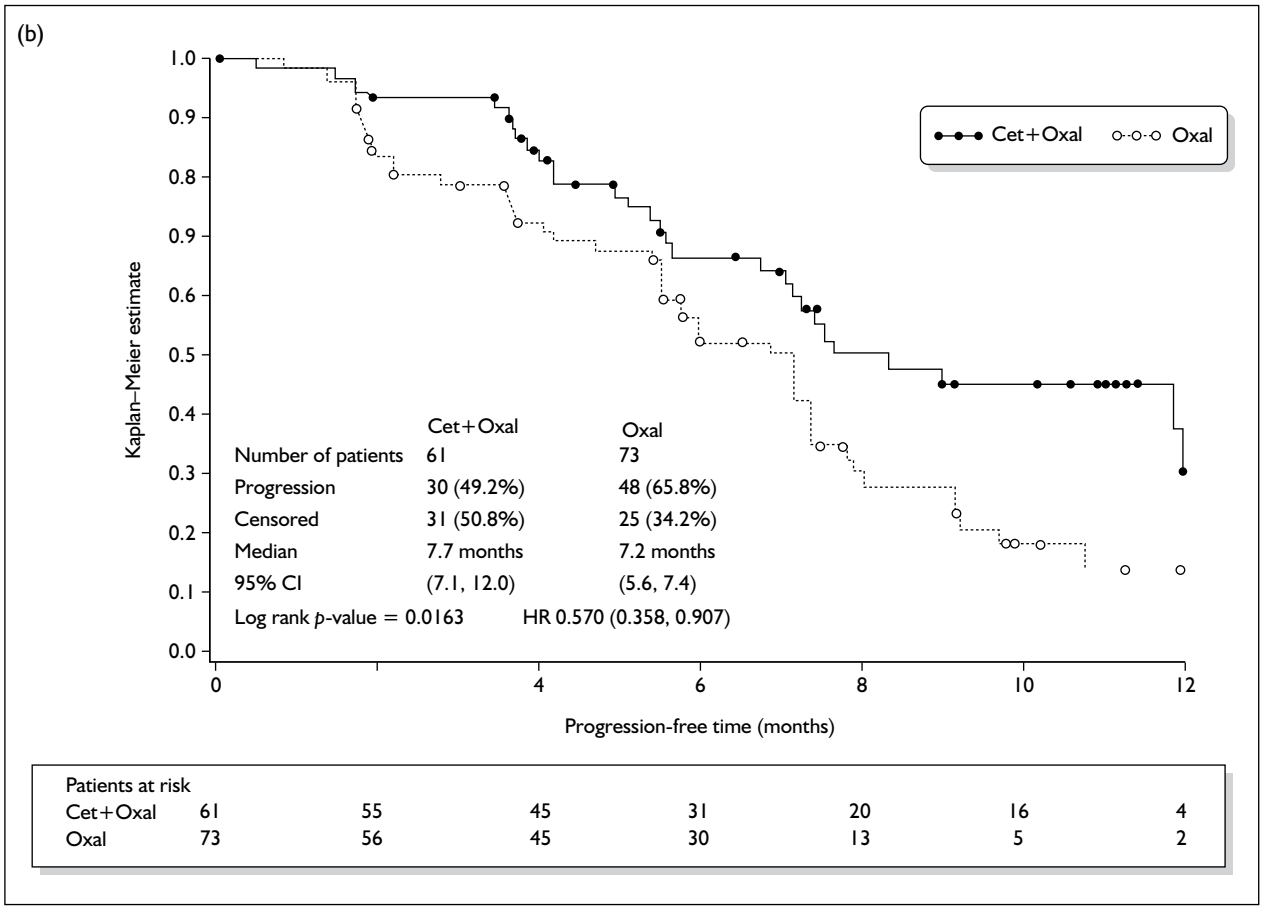


FIGURE 2 *Survival curves for the CRYSTAL and OPUS trials*

a single RCT or non-RCT evidence, and then a further two trials were introduced. The original trials were sufficiently large and follow-up was sufficiently long {[commercial-in-confidence data removed] months for CRYSTAL and 12 months for OPUS} to establish median survival times and obtain statistically significant results. However, only the *k*-ras wild-type subgroup of results was presented for clinical effectiveness. It was acknowledged in the submission that they were post hoc tests carried out for licensing purposes. In addition, a subgroup of liver metastases from the *k*-ras wild-type subgroup was also presented and it was these subgroup results that were used for the economic model. For the CRYSTAL and OPUS trials, respectively, the full intention-to-treat populations, *k*-ras wild-type subgroups and liver metastases subgroups of subgroups were 1198, 348 and 67, and 336, 134 and 38.

The CELIM and GERCOR trials were introduced at the committee stage. For the CELIM trial, the inclusion criteria stated that patients were to have non-resectable liver metastases at baseline yet randomisation was stratified by whether the liver metastases were technically resectable or not, and evaluation of resectability occurred 4 months after randomisation. This seemed contradictory. The GERCOR trial compared using FOLFIRI first the FOLFOX to FOLFOX first the FOLFIRI in mCRC.

The Markov model was appropriate for the decision problem. Having two RCTs (CRYSTAL and OPUS) as the main source of clinical effectiveness evidence was a strength in that the two trials' results were similar even though the comparator arms used different chemotherapy regimens (FOLFIRI and FOLFOX). Most of the other sources of cost and clinical model inputs were appropriate within the context of the model. Extensive and appropriate sensitivity analyses were conducted.

The model did not wholly address the problem as stated in the scope issued by NICE. Instead the model focused on the patients for whom the treatment had been licensed. This limited the applicability of the model to the NHS setting in which patients would be a mixture of *k*-ras wild type and mutations and also a mixture of patients with liver metastases and other metastases. Although the manufacturer cannot be held responsible for the differences between the licensed population and the population as set out in the NICE scope, strictly speaking the model did not answer the specified decision problem.

The model structure did not include provision for the identification of *k*-ras wild-type patients. In order to evaluate the cost-effectiveness of a treatment it is important to know the outcomes for all patients. In this case, the model assumed that all patients who were suitable for treatment were identified and treated (those who were *k*-ras wild type). It also assumed that no patients who were not suitable for treatment (those who were not *k*-ras wild type) were treated. No evidence is provided to support this key assumption. Given the importance of estimating the outcomes for those treated incorrectly (either not receiving treatment when they should receive it, or being incorrectly given treatment) in reaching a conclusion on the cost-effectiveness of the treatment, this omission from the model should be considered a serious flaw in the model design.

The reworked model had the same structure as the original, but it was difficult to determine how accurate the clinical effectiveness inputs from the CELIM and GERCOR trials were, given that neither were RCTs of cetuximab versus placebo.

Conclusions

The NICE scope did not specify the *k*-ras subgroup of patients so it is uncertain as to how the clinical effectiveness results presented matched the population specified in the decision problem. It is also uncertain as to how accurate *k*-ras testing is in clinical practice.

The effectiveness estimates for the economic model were based on 105 patients (67 CRYSTAL, 38 OPUS). It is uncertain how accurate these effectiveness estimates are, given that they were derived from small post hoc subgroup analyses of trial results.

The lifetime time horizon selected for the model was the appropriate approach to take in a decision analysis such as the one submitted by the manufacturer. However, the average age of patients developing colorectal cancer and being treated in the NHS was in the region of 10 years greater than the average age assumed in the economic model. This limited the applicability of the results to the NHS. The manufacturer's revised submission included a model that ran for 10 years to examine the impact that this would have on the results. Information from the CRYSTAL and OPUS trials was only available for a period of just over 1 year. Secondary information was used to

estimate survival over a further 22-year period. This increased greatly the uncertainty in the results although this increased uncertainty was not discussed in sufficient detail.

The difference in median progression-free survival in the CRYSTAL trial, for the *k*-ras wild-type subgroup, was 1.2 months (9.9 months versus 8.7 months) and for the OPUS trial was 0.5 months (7.7 months versus 7.2 months). Eight months' treatment with cetuximab, given as an initial loading dose and then weekly until progression, would cost around £22,932 for an average man and £18,427 for an average woman. It is uncertain whether this constitutes good value for money.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the Appraisal Consultation Document issued by NICE on 25 September 2008 states that:

1. Cetuximab is not recommended for the first-line treatment of metastatic colorectal cancer

2. People currently receiving cetuximab for the first-line treatment of metastatic colorectal cancer should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Final NICE guidance was issued in August 2009 recommending cetuximab treatment in this population subject to a number of important constraints.

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Infliximab for the treatment of acute exacerbations of ulcerative colitis

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Declared competing interests of authors: none

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis, in accordance with the licensed indication, based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The submitted clinical evidence included four randomised controlled trials (RCTs), two comparing infliximab with placebo in patients not responsive to initial treatment with intravenous corticosteroids and one comparing ciclosporin with placebo. A fourth RCT compared ciclosporin with intravenous corticosteroids as the initial treatment after hospitalisation. The manufacturer's submission concluded that infliximab provides clinical benefit to patients with acute severe, steroid-refractory ulcerative colitis and is well tolerated; it also provides additional clinical benefits over ciclosporin, particularly avoidance of colectomy. A decision tree model was built to compare infliximab with strategies involving ciclosporin, standard care and surgery. After correcting a small number of errors in the model, the revised base-case incremental cost-effectiveness ratio (ICER) for infliximab compared with standard care was £20,000. However, sensitivity analyses revealed considerable uncertainty emanating from the weight of the patient, the timeframe considered and, most importantly, the colectomy rates used. When a more appropriate mix of trials were included in the estimation of colectomy rates, the ICER for infliximab rose to £48,000.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

The guidance issued by NICE on 31 October 2008 states that infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient; for people who do not meet this criterion, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in clinical trials.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled 'Infliximab for the treatment of acute exacerbations of ulcerative colitis'.

Description of the underlying health problem

Ulcerative colitis (UC) is a chronic condition in which there is inflammation of the mucosa of the large intestine. The cause of UC is unknown. Hereditary, infectious and immunological factors have been proposed as possible causes.

The incidence of UC is approximately 10–20 per 100,000 per year with a reported prevalence of 100–200 per 100,000 in the UK. This prevalence is likely to be an underestimate as this implies an average disease duration of 10 years for a condition that is known to last for life. Based on these prevalence figures there are between 52,794 and 105,587 people in England and Wales with UC. The age of onset peaks between 20 and 40 years of age, but the disease may present at all ages. The prevalence of UC in children is about six to seven per 100,000 in the UK.

The symptoms of UC vary according to the extent and severity of the inflammation. The classic symptom of UC is bloody diarrhoea. Associated symptoms of colicky abdominal pain, urgency or tenesmus may be present. Mildly active UC is defined as less than four bowel movements daily. Moderately active UC is defined as more than four daily bowel movements, but where the patient is not systemically ill. Severe UC is defined as an attack in which the patient has more than six bowel movements daily and is systemically ill as shown by tachycardia, fever or anaemia. Fulminant disease correlates with more than 10 bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilation (expansion). Patients in this category may have inflammation extending just beyond the mucosal layer, causing impaired colonic motility and leading to toxic megacolon (toxic dilation of the colon).

Approximately 90% of all incident cases of UC are mild or moderate in severity.

In UC the severity of the symptoms fluctuate unpredictably over time with intervals of remission or reduced symptoms. Approximately 50% of patients with UC have a relapse in any year. A significant minority have frequently relapsing or chronic continuous disease. Twenty-five per cent of patients with severe UC are admitted to an inpatient setting with flares of UC that are not responding to steroids. An estimated 20–30% of patients with pancolitis (disease affecting the entire colon) will require colectomy.

Complications of UC may include haemorrhage, perforation, stricture formation, abscess formation, anorectal disease (e.g. fissures), arthritis, eye, cutaneous and liver abnormalities. Patients with long-standing dysplasia and extensive colitis have an increased risk of bowel cancer. UC has a slight excess of mortality in the first 2 years after diagnosis, but little subsequent difference from the general population. A severe attack of UC is a potentially life threatening illness.

The British Society of Gastroenterology published guidelines for the treatment of UC in 2004. The main recommendations for the

medical management of severe UC indicate that patients whose condition has not responded to maximal oral treatment with a combination of mesalazine and/or corticosteroids should be admitted for intensive intravenous therapy. When hospitalised, patients are usually given intravenous corticosteroids and, if there is no improvement during the first 3 days, surgical intervention or intravenous ciclosporin is considered. Following induction of remission, patients with UC should normally receive maintenance therapy with aminosalicylates and often also azathioprine or mercaptopurine and/or short-term ciclosporin to reduce the risk of relapse. Patients frequently receive combination therapies. Severe UC should be managed jointly by a gastroenterologist in conjunction with a colorectal surgeon within a multidisciplinary team with specialist nursing support.

Infliximab (Remicade, Schering Plough) is a chimeric monoclonal antibody that binds with high affinity to tumour necrosis factor-α, thereby neutralising its activity. It is administered by intravenous infusion and is licensed for moderately to severely active UC in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies.

Scope of the evidence review group report

The purpose of the ERG report was to comment on the validity of the manufacturer's submission on the technology of interest. The scope for this submission and hence the scope for the ERG report is shown in *Table 1*.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

Specific steps undertaken by the ERG included:

- discussion of the nature of the problem with a clinical expert
- reanalysis of the nature of the underlying clinical question
- rerunning searches indicated to have been performed to inform the manufacturer's submission
- extending searches, particularly for ongoing trials
- formal critical appraisal of systematic review underpinning the manufacturer's submission, and two related Cochrane Reviews
- reappraisal and checking of data abstraction on the four key included studies
- rerunning of mixed treatment comparison model
- checking the consistency of the direct effectiveness evidence with the estimates emerging from the mixed treatment comparison model and the parameters used in the economic model
- rerunning of the economic model supplied by the company
- correcting minor programming errors
- additional sensitivity analyses within the limits of the facilities of the submitted model.

The work was carried out between 17 April 2008 and 18 June 2008.

Members of the ERG team attended and advised the meeting of the NICE appraisal committee where this guidance was discussed on 17 July 2008.

Results

Summary of submitted clinical evidence

The manufacturer's submission reviewed systematic reviews and randomised controlled trials (RCTs) of infliximab and ciclosporin, the main alternative treatment option. The review also examined non-RCT evidence, particularly case-series of infliximab in the patient group of interest, but this did not contribute to the conclusions and is not considered further in this summary.

The main evidence identified is well known, four RCTs, two[2,3] comparing infliximab with placebo in patients not responsive to initial treatment with intravenous corticosteroids and one[4] comparing ciclosporin with placebo. A fourth RCT[5] compared ciclosporin with intravenous corticosteroids as the initial treatment after hospitalisation. The evidence on effectiveness was combined through a mixed treatment comparison model.

TABLE 1 *Submission scope*

Component of submission scope	Detail of submission scope
Appraisal objective	To appraise the clinical effectiveness and cost-effectiveness of infliximab for the treatment of acute exacerbations of severely active UC that require hospitalisation
Intervention(s)	Infliximab
Population(s)	Adults with acute exacerbations of severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies, and whose clinical management requires hospitalisation
Standard comparators	The standard comparators to be considered include: – standard clinical management which may include surgical intervention – ciclosporin
Outcomes	The outcome measures to be considered included: – health-related quality of life – survival – rates of and duration of response, relapse and remission – rates of surgical intervention – measures of disease activity – adverse effects of treatment
Economic analysis	The reference case stipulated that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year Time horizon should be long enough to allow reasonable estimation of expected costs (including adverse events if applicable) and benefits for the intervention, but should also account for the disease specific feature, particularly fluctuation and unpredictability of symptoms Costs were considered from an NHS and Personal Social Services perspective
Other considerations	Where evidence permits, the appraisal of infliximab for the acute exacerbation of severely active UC should identify patient subgroups for whom the technology is most appropriate Where evidence permits, the appraisal of infliximab for the acute exacerbation of severely active UC should consider different posology or methods of administration, treatment continuation strategies and lengths of treatment required when patients have responded to infliximab Guidance will only be issued in accordance with the Summary of Product Characteristics
Related NICE recommendations	Related ongoing technology appraisals: Infliximab for the sub-acute manifestation of ulcerative colitis. Related guidelines: none

The review and the model contribute to the two main conclusions offered in the manufacturer's submission:

- Infliximab provides clinical benefit to patients with acute severe, steroid-refractory UC and is well tolerated.
- Infliximab provides additional clinical benefits over ciclosporin, particularly avoidance of colectomy.

Summary of submitted cost-effectiveness evidence

No published economic evaluations of infliximab in acute UC were identified and so the cost-effectiveness work focused entirely on the de novo model and economic evaluation undertaken by the manufacturer. A decision tree model was built to compare infliximab with strategies involving ciclosporin, standard care and surgery. The main evidence used to estimate some of the key probabilities in the model derived from the main trials, but data on resource use and costs were available only from an expert panel. Utility data were taken from an observational cohort (the HODaR study; Health Outcomes Data Repository). The results revealed dominance in the comparison of standard care and ciclosporin. On the basis of the results, it is clear that the move from standard care to ciclosporin is highly cost-effective given that it is associated with lower costs and higher quality-adjusted life-years. Thus, the policy question then to be addressed is the subsequent move from ciclosporin to infliximab, and so the only appropriate comparator for infliximab is ciclosporin. After correcting a small number of errors in the model, the revised base-case incremental cost-effectiveness ratio (ICER) for infliximab compared with standard care was

£20,000. However, sensitivity analyses revealed considerable uncertainty emanating from the weight of the patient, the timeframe considered and, most importantly, the colectomy rates used. When a more appropriate mix of trials was included in the estimation of colectomy rates, the ICER for infliximab rose to £48,000.

Commentary on the robustness of submitted evidence

Strengths

The review of effectiveness was generally systematic in approach, building on previous work in the area.

The submission reported a de novo model-based economic evaluation that has considered the cost-effectiveness of infliximab in UC. The use of a decision tree model was appropriate, as the focus is on the acute phase of the disease. The main probability inputs were derived from trial data.

Probabilistic sensitivity analysis and one-way sensitivity analyses were performed.

Weaknesses

Although generally systematic, the review of clinical effectiveness had some errors, most notably failing to distinguish that the effect measured by one of the included RCTs[5] is qualitatively different from the other trials and should not be combined with them. There was concern that the considerable uncertainty surrounding the estimates of effectiveness arising from the very small number of RCTs, which are themselves small, was understated. Although the mixed treatment comparison model is interesting, it is debatable whether the very limited amount of data available warranted such a sophisticated approach.

The model did not consider side-effect issues or mortality events. The resource use estimates used in the model were from an expert panel. The key model inputs on colectomy rates were derived from a small number of small trials, some of which may not be directly relevant to the policy question being addressed.

Conclusions

Several areas of uncertainty were identified:

- There was considerable uncertainty about the evidence on effectiveness of infliximab and ciclosporin. Primarily this emanates from the very limited amount of RCT data, the impact of which was somewhat understated in the manufacturer submission. This was compounded by a debatable decision about 'combining' the data for an RCT with a control arm of intravenous corticosteroids with RCTs with placebo control arms and the use of a mixed treatment comparison model to generate estimates of the effect infliximab versus ciclosporin for which there is no direct evidence. This however also led to estimates of effect of infliximab and ciclosporin that differed in important respects from the original trials (*Tables 2 and 3*).
- The results consistently indicated that the move from standard care to ciclosporin is highly cost-effective. Thus, the appropriate policy question is not uncertain. The question to be addressed was: should we make a subsequent move from ciclosporin to infliximab? And so the only appropriate comparator for infliximab is ciclosporin.
- There was considerable uncertainty concerning what colectomy rates should be used.
- The weight of the patient was important – if patients tended to be 60 kg or less then the cost-effectiveness of infliximab was more attractive.
- The timeframe of the model was also important – extrapolating beyond 12 months was the approach that is consistent with the NICE methods guide. Such extrapolation indicates worsening cost-effectiveness for infliximab in general.

The key issues for consideration by the appraisal committee were thus suggested to be:

- Was the effectiveness of both infliximab and ciclosporin accurately portrayed by the manufacturer submission, particularly through the 'inclusion' of the RCT of ciclosporin by D'Haens *et al*.,[5] and through the use of the mixed treatment comparison model to summarise and estimate parameters for the economic model?
- Did the manufacturer's submitted model fully capture and convey the uncertainty arising from the problems with the effectiveness data?
- From the information available was it likely that improved estimates of effectiveness, and therefore cost-effectiveness, would arise from the ongoing trials of infliximab versus ciclosporin identified?

TABLE 2 *Colectomy 0- to 3-month results [event rates and odds ratios (ORs)] from different parts of the report*

Intervention	Jarnerot[2]	Sands[3]	Lichtiger[4]	D'Haens[5]	MTC model
Crude rates (%) [95% CI by Wilson's method]					
Infliximab	7/24 (0.29) [0.15 to 0.49]	0/3 (0.0) [0.0 to 0.56]			(0.23) [0.05 to 0.56]
Ciclosporin			3/11 (0.27) [0.10 to 0.57]	3/14 (0.21) [0.08 to 0.48]	(0.58) [0.22 to 0.88]
Placebo	14/21 (0.67) [0.45 to 0.83]	3/3 (1.0) [0.44 to 1.0]	4/9 (0.44) [0.19 to 0.73]	3/15 (0.20) [0.07 to 0.45]	(0.67) [0.46 to 0.85]
Odds ratio [95% CI]					
Infliximab vs placebo	0.21 [0.06 to 0.73][a]	0[a]			0.13 [0.03 to 0.44]
Ciclosporin vs placebo			0.47 [0.07 to 3.04][b]	1.09 [0.18 to 6.58]	0.70 [0.18 to 2.69]
Infliximab vs ciclosporin	No direct comparisons				

CI, confidence interval; MTC, mixed treatment comparison.
a Combined result from meta-analysis of Jarnerot and Sands, supplied by manufacturer in response to request for supplementary information, summary OR (fixed effects) 0.16 (0.05 to 0.53), Summary OR (random effects) 0.16 (0.04 to 0.66).
b Equivalent to relative risk of 0.61 (0.18 to 2.1).

TABLE 3 *Colectomy 3- to 12-month results [event rates and odds ratios (ORs)] from different parts of the report*

Intervention	Jarnerot[2]	Sands[3]	Lichtiger[4]	D'Haens[5]	MTC model
Crude rates (%) [95% CI by Wilson's method]					
Infliximab	3/17 (0.18) [0.06 to 0.41]				(0.27) [0 to 0.92]
Ciclosporin				3/11 (0.27) [0.10 to 0.57]	(0.18) [0.0 to 0.70]
Placebo	1/7 (0.14) [0.03 to 0.51]			3/12 (0.25) [0.09 to 0.53]	(0.14) [0.0 to 0.47]
Odds ratio [95% CI]					
Infliximab vs placebo	1.3 [0.11 to 15.0]				1.8 [0.13 to 57]
Ciclosporin vs placebo				1.1 [0.18 to 7.2]	1.1 [0.15 to 8.5]
Infliximab vs c°iclosporin	No direct comparisons				

CI, confidence interval; MTC, mixed treatment comparison.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the Final Appraisal Determination document issued by NICE on 31 October 2008 states that:

This guidance relates only to the use of infliximab within its marketing authorisation, for the treatment of acute exacerbations of severely active ulcerative colitis. It relates to an induction course of three doses of infliximab.

1.1 Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient.

1.2 In people who do not meet the criterion in 1.1, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in clinical trials.

Key references

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Sorafenib for the treatment of advanced hepatocellular carcinoma

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of sorafenib according to its licensed indication for advanced hepatocellular carcinoma (HCC). The ERG report was based on the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The licensed indication for sorafenib specifies advanced HCC patients for whom locoregional intervention and surgery are unsuitable or had been unsuccessful. The clinical evidence came from a multicentre randomised controlled trial (Sorafenib HCC Assessment Randomized Protocol; SHARP) of sorafenib plus best supportive care versus placebo plus best supportive care, with 602 participants of a predominantly European ethnicity broadly comparable to the UK population. The submitted evidence indicated that for advanced HCC patients with Child–Pugh grade A liver function and relatively good Eastern Cooperative Oncology Group performance status, sorafenib on average improves overall survival by 83 days relative to placebo, and also increases time-to-radiological disease progression. Sorafenib therapy had little or no effect on time-to-symptom progression or on quality of life as measured using a disease-specific questionnaire. Sorafenib treatment was associated with increased incidence of hypertension and of gastrointestinal and dermatological problems. However, the therapy was reasonably well tolerated

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and, in SHARP, withdrawals from treatment due to adverse events were similar in the sorafenib and placebo arms, although more temporary reductions in dose were required in the sorafenib than in the placebo group. In the base case, the manufacturer's submitted economic analysis generated a deterministic incremental cost-effectiveness ratio (ICER) of £64,754 per quality-adjusted life-year (QALY). The ERG extracted individual patient data for overall survival and disease progression, reran the economic model to check the submitted cost-effectiveness results, and performed new analyses which the ERG considered relevant to the decision problem; these analyses delivered ICERs between £76,000/QALY and £86,000/QALY. The guidance issued by NICE (7 May 2009) stated that sorafenib, within its licensed indication, is not recommended for the treatment of advanced (Barcelona-Clínic Liver Cancer stage C) HCC patients for whom surgical or locoregional therapies have failed or are not suitable, and people currently receiving sorafenib for the treatment of HCC should have the option to continue treatment until they and their clinician consider it appropriate to stop. Subsequently the manufacturer submitted a patient access scheme to the Department of Health. The base-case ICER submitted by the manufacturer for this scheme was £51,899/QALY. When the ERG reran the model with inputs considered relevant to the decision problem the ICER estimates ranged between £53,000 to £58,000/QALY and substantially higher values depending on the nature of the sensitivity analyses. NICE considered the impact of the patient access scheme and determined that it was not sufficient to alter the guidance.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of NICE. This paper presents a summary of the ERG report[2] for the STA submission[3] that considered the clinical effectiveness and cost-effectiveness of sorafenib for advanced hepatocellular carcinoma in patients for whom locoregional intervention and surgery were unsuitable or had been unsuccessful.

Description of the underlying health problem

Hepatocellular carcinoma (HCC) is a rare disease in the UK, with approximately 2340 patients diagnosed annually in England and Wales. HCC is associated with a number of underlying liver conditions and primary risk factors and these include hepatitis virus infection, alcoholism and biochemical insult from agents such as aflatoxin. Almost invariably HCC patients have compromised liver function which is currently graded according to the Child–Pugh system into grades A–C of increasing severity. Owing to the often underlying liver disease, it is difficult to disentangle patient symptoms that relate to HCC from those of the underlying condition. As in other European countries, incidence of HCC in the future is likely to increase because of the growing levels of hepatitis virus C infection in the population in previous years. Therapeutic options in HCC include liver transplant, surgical resection, loco-regional therapies such as ablation and chemo-embolisation, and systemic therapy with drugs such as doxorubicin (infused) or oral sorafenib.

The prognosis for HCC patients is poor and life expectancy after diagnosis is more likely to be months than years. Several HCC staging schemes have been developed; of these the Barcelona-Clínic Liver Cancer (BCLC) system[4] is widely used and classifies patients as stage A–D where stage A is 'early' disease, stage B is 'intermediate disease', stage C is 'advanced' disease and stage D patients are classified as having 'end stage' disease.[5,6]

Scope of the evidence review group report

The research question posed for the STA was: what is the effectiveness and cost-effectiveness of sorafenib (Nexavar®) in the treatment of advanced

HCC when surgical or locoregional therapies have failed or are unsuitable?

Sorafenib is a newly developed systemic therapy previously licensed for use in renal cancer and more recently licensed for HCC.

The clinical effectiveness data came from a multicentre randomised controlled trial (RCT) (Sorafenib HCC Assessment Randomized Protocol; SHARP) of sorafenib plus best supportive care versus placebo plus best supportive care, with 602 participants of a predominantly European ethnicity and broadly comparable to the UK population.[7] The submission was based on the premise that 'the phase III SHARP study is the largest and most relevant data source for the decision problem being addressed'. Important outcomes measured in SHARP were overall survival, time-to-symptomatic progression, time-to-disease (i.e. tumour) progression, and quality of life. Other outcomes measured included tumour and disease response rates. Two other small effectiveness studies were used for supportive evidence only; these were one RCT – the Asia-Pacific study[8] – of sorafenib versus placebo with 226 patients, and one open-label uncontrolled study[9,10] with 136 patients. The potential benefits of sorafenib treatment compared with supportive care are extended life span and increased quality-adjusted life-years (QALYs) gained, with tolerable burden of drug side effects.

The submission's estimation of resource use and costs for the cost-effectiveness analyses relied heavily on expert opinion.

Methods

The ERG reran the submission's search strategy, constructed and ran an independent search strategy broader than that in the submission, and applied less ambiguous inclusion and exclusion criteria than those in the submission in order to ascertain if relevant studies were missing from the submission.

The ERG appraised the submission's critical appraisal of the quality of the SHARP study.

The ERG checked the SHARP data in the submission against those in the published account of SHARP and also those in the full trial report that was requested from the manufacturer.

The ERG extracted individual patient data for overall survival from the SHARP trial report and performed independent survival analysis in order to test assumptions made in the submission regarding the use of the hazard ratio statistic.

The ERG extracted individual patient data for time-to-treatment progression from the SHARP trial report, checked the accuracy of this data extraction, and then performed survival analysis using extracted data to generate input parameters necessary to undertake sensitivity analysis of the submission's economic model which the ERG considered to be relevant to the decision problem.

The ERG checked the supportive evidence data presented in the submission against those in the publications of the two supportive studies (Asia-Pacific RCT[8] and open-label uncontrolled study[9,10]).

The ERG extracted data from a publication presenting results from the open-label uncontrolled supportive study which had not been included in the submission, but which the ERG considered to be relevant to the decision problem. The ERG summarised the implications of these data.

The ERG checked the published algorithm used in the submission to calculate health utilities for input to the economic model.

The ERG checked the internal validity of the submitted economic model, reran the economic model to check the submitted cost-effectiveness results and performed new sensitivity analyses which the ERG considered relevant to the decision problem.

Results

Summary of submitted clinical evidence

The submitted evidence indicated that relative to placebo, sorafenib extended overall median survival by 83 days (11.9 weeks) and also extended time-to-disease radiological (tumour) progression; two different assessments of time-to-tumour progression were submitted. Sorafenib therapy had little or no effect on time-to-symptom progression or on quality of life as measured using a disease-specific questionnaire (Functional Assessment of Cancer Therapy-Hepatobiliary; FACT-Hep). Sorafenib treatment was associated with increased

incidence of hypertension[11] and of gastrointestinal and dermatological problems.[12] However, the therapy was reasonably well tolerated and, in SHARP, withdrawals from treatment due to adverse events were similar in the sorafenib and placebo arms, although more temporary reductions in dose were required in the sorafenib than in the placebo group.

Summary of submitted cost-effectiveness evidence

In the base case, the economic model generated a deterministic incremental cost-effectiveness ratio (ICER) of £45,502 per life-year and £64,754 per QALY. Probabilistic analysis generated a 50% probability of cost-effectiveness at a willingness to pay of £45,832 per life-year and £65,244 per QALY.

In a best-case scenario, the model generated an ICER of £39,627 per life-year and £55,729 per QALY. In a best-case scenario for subgroups, ICERs of £16,794 per life-year and £24,620 per QALY were generated.

Commentary on the robustness of submitted evidence

The submitted evidence was based almost exclusively on clinical effectiveness results for patients with relatively mild impairment of liver function (Child–Pugh grade A) and with relatively good performance status [Eastern Cooperative Oncology Group (ECOG) performance status criteria]. The ERG did not identify any errors in the submission's data extraction, although there was an omission of some limited evidence relating to the effectiveness of sorafenib for Child–Pugh grade B patients. The results from SHARP demonstrated significant improvements in overall survival and in time-to-disease progression; these observations were supported by the Asia-Pacific randomised trial in a population of different ethnicity and considerably different HCC aetiology.

The best-case economic analysis submitted was inappropriate to the decision problem because the patient group (BCLC stage B 'intermediate' HCC) could not be classified as having advanced disease. In the context of uncertainty about the time-to-disease progression, the ERG undertook sensitivity analysis of the base-case scenario, which generated ICERs of £76,000 per QALY and £85,805 per QALY.

Conclusions

For HCC patients with Child–Pugh grade A liver function and relatively good ECOG performance status, sorafenib on average improves overall survival by 83 days and also increases time-to-disease progression compared with best supportive care. Available evidence does not indicate that it delays symptom progression or improves quality of life.

It is uncertain if sorafenib is equally effective for patients with poorer liver function than Child–Pugh grade A or for those of poor performance status, but the small amount of evidence available implies that it may not be.

Sensitivity analysis indicates that the ICER for patients like those in SHARP may be greater than the submitted values of £45,502 per life year and £64,754 per QALY.

Key issues for the decision problem and areas of uncertainty are:

- To what extent does the clinical effectiveness observed in SHARP apply to the broader population of patients defined by the decision problem (i.e. a broader range of liver function insufficiency)?
- By how much is time-to-disease progression improved?
- What is the quality of life for patients administered sorafenib?

Summary of NICE guidance issued as a result of the STA

The guidance appraisal consultation document issued by NICE (7 May 2009) stated that the Appraisal Committee's preliminary recommendations were:

1.1 Sorafenib, within its licensed indication, is not recommended for the treatment of advanced (Barcelona clinic liver cancer [BCLC] stage C) hepatocellular carcinoma (HCC) in patients for whom surgical or locoregional therapies have failed or are not suitable.

1.2 People currently receiving sorafenib for the treatment of HCC should have the option to continue treatment until they and their clinician consider it appropriate to stop.

Subsequent to the preliminary NICE guidance, the Department of Health (DoH) accepted a patient access scheme (PAS) proposed by the manufacturer. The detail of this scheme is confidential. The DoH were content for NICE to consider the consequences of the PAS in their deliberations. The manufacturer supplied a revised economic model and associated analyses to indicate the effect of the PAS on the cost-effectiveness of sorafenib. The ERG checked the internal validity of the submitted economic model, reran the economic model to check the submitted cost-effectiveness results and performed new analyses which the ERG considered relevant to the decision problem and the implementation of the PAS. The manufacturer's base-case analysis for the PAS gave an ICER of £51,899 per QALY. The ERG's sensitivity analysis around the base case generated ICERs of £52,641 to £58,147 per QALY and substantially higher values depending on the nature of the sensitivity analyses.

After considering analyses on the PAS the NICE Appraisal Committee's preliminary recommendations were unchanged (as of 9 September 2009).

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Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B infection

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of tenofovir disoproxil fumarate for the treatment of chronic hepatitis B, in accordance with the licensed indication, based upon the evidence submission from Gilead to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The submitted clinical evidence included two international randomised controlled trials (RCTs) comparing tenofovir with adefovir, and a mixed treatment comparison (MTC) using Bayesian methodology to compare tenofovir with other nucleos(t)ide analogues using direct and indirect RCT evidence. There were no statistically significant differences between tenofovir and adefovir in overall adverse events although, in hepatitis B 'e' antigen (HBeAg)-positive patients, there was a higher incidence of mild nausea in the tenofovir treatment group. The primary outcome, 'complete response', was a composite end point defined as histology response and hepatitis B virus DNA below 400 copies/ml. For both HBeAg-positive and HBeAg-negative patients, a significantly greater proportion had a complete response after 48 weeks with tenofovir than with adefovir. There was no statistically significant difference in histological response in either group of patients compared with adefovir. The MTC could only generate results for HBeAg positive nucleos(t)ide naive patients as there was insufficient evidence for other subgroups. The probability of achieving undetectable HBV DNA with tenofovir was found to be significantly higher than that for all other treatments considered in the analysis at the

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

0.05 level. The analysis demonstrated that there is a 98% probability that tenofovir is the most potent nucleos(t)ide in terms of this outcome. The manufacturer's submission concluded that tenofovir is a cost-effective option as first-line treatment. For HBeAg-positive patients, tenofovir followed by lamivudine has an incremental cost-effective ratio (ICER) of £9940 per quality-adjusted life-year (QALY) gained, compared with lamivudine followed by tenofovir. A more appropriate treatment strategy of tenofovir followed by tenofovir plus lamivudine has an ICER of £13,619 per QALY gained, compared with lamivudine followed by tenofovir. For HBeAg-negative patients, tenofovir followed by lamivudine has an ICER of £9811 per QALY gained, compared with best supportive care. A more clinically appropriate treatment strategy of tenofovir followed by tenofovir plus lamivudine has an ICER of £13,854 per QALY gained, compared with tenofovir followed by lamivudine. The ERG uncovered a number of errors in the submission and these ICERs approximately doubled when the analysis was corrected and reran. The guidance issued by NICE on 22 July 2009 states that tenofovir disoproxil, within its marketing authorisation is recommended as an option for the treatment of people with chronic HBe-Ag-positive or HBe-Ag-negative hepatitis B in whom antiviral treatment is indicated.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled 'Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B'.[2]

Description of the underlying health problem

Hepatitis B is an infectious disease of the liver caused by the hepatitis B virus (HBV). It is transmitted through blood-to-blood contact (e.g. through sharing of blood-contaminated needles by drug users) and sexual contact. It is also transmitted vertically from mother to infant, during or soon after birth. Infected individuals develop an acute infection, which may or may not result in symptoms. The majority of those infected during adulthood make a full recovery and acquire immunity from future infection. About only 2–10% of infected adults will develop chronic hepatitis B (CHB), defined as viraemia and hepatic inflammation that persists for more than 6 months after acute infection with HBV. In contrast, almost 100% of infected neonates and about 50% of infected young children will develop CHB if infected with HBV.

According to whether hepatitis B 'e' antigen (HBeAg) is secreted, active infection can be described as HBeAg-positive or HBeAg-negative. HBeAg is an indicator of viral replication, although some variant forms of the virus do not express HBeAg. The response to treatment and rates of progression differ between the two forms. People can be infected with the so-called HBeAg-negative form of the virus from the beginning, or the viral mutation can emerge later in the course of infection in people initially infected with the HBeAg-positive form of the virus. Chronic infection with mutant strains of HBV that do not produce the 'e' antigen (that is, HBeAg-negative) is associated with a fluctuating course and a poor prognosis.

The Department of Health estimated that about 180,000 people in the UK had CHB in 2002, but recent data from the Hepatitis B Foundation estimated that approximately 326,000 people are currently infected in the UK. There are about 7700 new cases of CHB each year. Of these, around 300 people were infected within the UK; the remainder (mainly immigrants to the UK) were infected abroad.

The progression to cirrhosis occurs at an annual rate of 2–5.5%, with a cumulative 5-year rate of

progression of 8–20% in HBeAg-positive CHB and an annual rate of 8–10% in HBeAg-negative CHB.

Scope of the evidence review group report

The ERG critically evaluated the evidence submission from Gilead on the use of tenofovir for the treatment of CHB. Tenofovir has a marketing authorisation in the UK for the treatment of chronic HBV infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

The population considered in the scope was adults with active CHB according to the licensed indication. Patient subgroups included those with HBeAg-positive and HBeAg-negative CHB; and those who are treatment (nucleoside analogue) naive or refractory to lamivudine. Patients with co-infections (e.g. HIV) were excluded in accordance with the scope. The intervention was tenofovir alone or in combination with other therapies.

Comparators included lamivudine, adefovir dipivoxil, entecavir and telbivudine.

Outcomes included HBeAg/hepatitis B surface antigen (HbsAg) seroconversion rate, virological response (HBV DNA); histological improvement (liver inflammation and fibrosis); biochemical response (e.g. ALT levels); development of viral resistance; and adverse events. Outcomes included in the scope and decision problem, but not reported in the submission include time-to-treatment failure, survival and health-related quality of life.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The ERG checked the literature searches and applied the NICE critical appraisal checklist to the included studies and checked the quality of the manufacturer's submission with the Centre for Reviews and Dissemination (CRD) quality assessment criteria for a systematic review. Searches were rerun in PubMed from August 2007 to 3 December 2008 and results screened for potentially relevant randomised controlled trials (RCTs) of tenofovir. In addition, the ERG checked and provided commentary on the manufacturer's model using standard checklists. The ERG conducted an amended base-case analysis, a one-way sensitivity analysis, a scenario analysis and a probabilistic sensitivity analysis to correct for errors in the manufacturer's economic model.

Results

Summary of submitted clinical evidence

The evidence in the manufacturer's submission comprised (i) a systematic review which included two international RCTs comparing tenofovir with adefovir,[3,4] and (ii) and a mixed treatment comparison (MTC) using Bayesian methodology to compare tenofovir with other nucleos(t)ide analogues using direct and indirect RCT evidence.

Two RCTs compared tenofovir with adefovir (one in HBeAg-positive patients, one in HBeAg-negative patients), and a third RCT compared tenofovir with tenofovir plus emtricitabine. The latter RCT was considered by the ERG to be beyond the scope of the appraisal and not considered further. The primary outcome, 'complete response', was a composite end point defined as histology response (greater than two-point Knodell necroinflammatory score without worsening in fibrosis) and HBV DNA below 400 copies/ml. For both HBeAg-positive and HBeAg-negative patients, a significantly greater proportion had a complete response after 48 weeks with tenofovir than with adefovir. There was no statistically significant difference in histological response in either group of patients compared with adefovir.

In both HBeAg-positive and HBeAg-negative patients, significantly more patients receiving tenofovir than adefovir had reductions in HBV DNA levels below 400, 300 and 169 copies/ml, and the mean reduction from baseline in plasma HBV DNA was significantly greater with tenofovir than adefovir. There were statistically significant differences between tenofovir and adefovir in ALT response (although no difference in the proportion of HBeAg-negative patients with normalised ALT levels at 48 weeks). A similar proportion of HBeAg-positive patients experienced HBeAg loss and seroconversion at week 48 in the tenofovir

and adefovir groups. No HBeAg-negative patients experienced HBsAg loss or seroconverted to anti-hepatitis B surface antibody (HBs) by week 48. Significantly more HBeAg-positive patients achieved HBsAg loss at 48 weeks with tenofovir than with adefovir. No cases of virologic HBV resistance have been identified.

There were no statistically significant differences between tenofovir and adefovir in overall adverse events in either group of patients although, in HBeAg-positive patients, there was a greater incidence of study drug-related adverse events with tenofovir. The manufacturer's submission attributes this to a higher incidence of mild nausea in the tenofovir treatment group. The most common adverse events were headache, nasopharyngitis, back pain, nausea, fatigue and abdominal pain.

An MTC was conducted on two outcomes: the probability of HBeAg seroconversion and the probability of achieving HBV DNA of less than 300 copies/ml after 1 year of treatment.

Of four subgroups considered, results could only be generated for HBeAg-positive nucleos(t)ide naive patients (13 RCTs). There was insufficient RCT evidence to construct an MTC for HBeAg-negative nucleos(t)ide naive patients, or HBeAg-positive or HBeAg-negative lamivudine refractory patients.

The probability of achieving undetectable HBV DNA with tenofovir was found to be significantly higher than that for all other comparators considered in the analysis at the 0.05 level. The analysis demonstrated that there is a 98% probability that tenofovir is the most potent nucleos(t)ide in terms of this outcome. All nucleos(t)ides were associated with a significantly higher chance of achieving undetectable HBV DNA than placebo. Tenofovir, entecavir and telbivudine were also found to be significantly superior to lamivudine at the 0.05 level.

All treatments other than telbivudine plus lamivudine in combination were found to significantly increase the probability of HBeAg seroconversion at 1 year relative to placebo at the 0.05 level. However, this analysis identified no statistically significant differences between the nucleos(t)ides for this outcome.

Summary of submitted cost-effectiveness evidence

The manufacturer's cost-effectiveness analysis adopted a Markov state transition model to estimate the incremental costs and consequences of a range of treatment strategies that include tenofovir and other antiviral drugs. Evidence on the efficacy of tenofovir, lamivudine, adefovir and entecavir (alone or in combination, when appropriate) in terms of reducing viral load and HBeAg seroconversion were taken from the MTC which also estimated baseline outcomes for best supportive care (BSC) (based on outcomes in the placebo arms of included RCTs). These outcomes are associated with reduced probability of progression to advanced liver disease and may also be associated with improved quality of life.

The model was used to simulate cohorts of patients with HBeAg-positive and HBeAg-negative CHB, at treatment initiation, separately. The model was structured to allow HBeAg-negative CHB to emerge in HBeAg-positive patients, following reactivation of disease in patients who had achieved HBeAg seroconversion. In all other respects the model was structurally similar to those adopted for previous economic evaluations, including that used in the previous NICE assessment of adefovir for the treatment of CHB.

The model adopted a lifetime horizon and was used to extrapolate lifetime costs and quality-adjusted life-years (QALYs) for patients treated with tenofovir (alone or in combination) and each of the included comparators. The analysis assumed that once patients develop resistance to their current antiviral drug, they will either switch to a new drug or add a new drug to their treatment. The model was used to evaluate single-agent and combination therapies adopted as first-, second- or third-line treatment, with BSC retained as the final treatment option for patients who have developed resistance to all antiviral agents available in each treatment strategy. Of the 211 treatment strategies evaluated (including BSC) cost-effective strategies were selected using the cost-effectiveness frontier and incremental cost-effectiveness ratios (ICERs) calculated against the next best alternative.

The manufacturer's submission concluded that tenofovir is a cost-effective option as first-line treatment. For HBeAg-positive patients, tenofovir followed by lamivudine has an ICER of £9940 per QALY gained, compared with lamivudine followed

by tenofovir. This implied switching treatments on development of resistance to first-line therapy, which is not supported by clinical guidelines as an appropriate clinical strategy. A more appropriate treatment strategy of tenofovir followed by tenofovir plus lamivudine had an ICER of £13,619 (incorrectly reported in the manufacturer's submission as £10,055 which is the ICER for tenofovir followed by tenofovir plus lamivudine, compared with lamivudine followed by tenofovir) per QALY gained, compared with lamivudine followed by tenofovir.

The manufacturer's submission reported that for HBeAg-negative patients, tenofovir followed by lamivudine had an ICER of £9811 per QALY gained, compared with BSC. A more clinically appropriate treatment strategy of tenofovir followed by tenofovir plus lamivudine had an ICER of £13,854 per QALY gained, compared with tenofovir followed by lamivudine.

In the ERG base-case analysis, amended to correct for errors in the manufacturer's model, these ICERs approximately doubled.

Commentary on the robustness of submitted evidence

Strengths

The two tenofovir RCTs were of good methodological quality and measured outcomes that are appropriate and clinically relevant, although health-related quality of life was not reported. The manufacturer's submission provided a detailed account of their procedures for the MTC, although much of this is reported in an academic-in-confidence appendix.

The economic model is structurally consistent with models adopted for previous economic evaluations. The manufacturer's submission reported that the structure of the model was discussed with clinicians with relevant expertise. The methods used to derive input data for the economic model are generally appropriate using published data that, for the MTC and pooled analysis of resistance, are clearly identified.

The model is appropriately structured to incorporate resistance to antiviral agents, and to maintain patients' history of resistance to agents within a given treatment strategy.

Weaknesses

The manufacturer's submission conducted a systematic search for clinical effectiveness and cost-effectiveness studies of tenofovir and comparator treatments for CHB. However, some of NICE's recommended databases were not searched, and the search is only current to August 2007. ERG replication of the searches (PubMed only) from August 2007 to December 2008 has not identified any additional tenofovir RCTs.

Whilst considered generally sound in terms of structure, the MTC suffers from certain limitations, including small numbers of studies/single studies in some networks, no quality assessment of the included studies and no discussion of potential clinical heterogeneity.

The ERG uncovered a number of errors in the submission. These include transcription errors (from the model into the written submission) and errors in calculations in the model. Where possible the ERG has corrected them and rerun the analyses. However, some of the errors would require substantial rewriting of the model. The ERG has attempted to identify where errors are likely to bias the outcome of the evaluation.

The reporting of pre-model analyses is poor, particularly in terms of searching for and critical appraisal of studies used to estimate parameter inputs. In many cases, very limited information is provided on studies contributing data to key input parameters in the model. There is generally little evidence of systematic searches for data to estimate parameters, and no critical appraisal of the scope, quality or appropriateness of included studies.

Conclusions

Tenofovir is one of a growing number of treatment options for patients with CHB. The manufacturer has provided a reasonably sound assessment of its clinical effectiveness based on two pivotal RCTs in HBeAg-positive and -negative nucleos(t)ide naive patients, albeit with some limitations.

Tenofovir was statistically significantly superior to adefovir for the primary composite outcome of HBV DNA response (400 copies/ml) and histological response. There were also statistically significant differences between the two drugs in

terms of secondary outcomes HBV DNA response (400 copies/ml) and ALT (HBeAg-positive patients only). However, there were no statistically significant differences for histology and HBeAg seroconversion. Tenofovir was generally well tolerated and adverse effects were generally similar to adefovir.

Clinical effectiveness data beyond 1 year are observational and should be interpreted with caution.

Tenofovir appears to have a favourable resistance profile based on limited data currently available. Whether this will be maintained with long-term treatment is yet to be established. These data will be important to guide decisions as to whether to initiate treatment with monotherapy or combination therapy. If resistance in the long-term is low, clinicians may decide to initiate treatment with tenofovir monotherapy, thus reserving other nucleos(t)ides as future treatment options if necessary. If resistance to tenofovir monotherapy is likely to be high then a clinically plausible combination of nucleos(t)ides (e.g. lamivudine and tenofovir) may be preferable in order to suppress the selection of resistant strains. However, there is currently a lack of RCT data for the clinical effectiveness of tenofovir in combination with other nucleos(t)ides.

There is a lack of head-to-head RCTs comparing tenofovir with other nucleos(t)ides, necessitating the production of an MTC. The results suggest that tenofovir has the highest probability of HBV DNA lower than 300 copies/ml response at 1 year of treatment. There were no statistically significant differences between the nucleos(t)ides in terms of HBeAg seroconversion.

The MTC is subject to certain methodological limitations, and it was not possible to conduct one for HBeAg-negative nucleos(t)ide naive patients, or lamivudine refractory patients.

The methods adopted for the economic evaluation were reasonable and generally appropriate. The model structure was consistent with previous economic evaluations. It was appropriately structured to incorporate resistance to antiviral agents and maintain a history of patients developing resistance to agents included in the treatment strategy. However, the reporting of pre-model analyses used to estimate parameter inputs was poor, with limited information on studies contributing data to key input parameters in the model, no evidence of systematic searches for data to estimate parameters and no critical appraisal of the scope, quality or appropriateness of included studies.

A number of errors were detected in the submission, including a serious error in the way in which QALY outcomes were discounted in the electronic model, which affected the deterministic (base-case and sensitivity/scenario analyses) and the probabilistic analyses. When possible, corrected analyses were presented by the ERG. Once the identified errors had been corrected and more appropriate estimates of uncertainty had been incorporated in the analysis, the ERG felt the model provided a reasonable characterisation of the cost-effectiveness of treatment strategies containing tenofovir, in the treatment of CHB.

Areas of uncertainty

There is a lack of head-to-head RCT evidence for the clinical effectiveness of tenofovir compared to other nucleos(t)ides. It was only possible to construct an MTC, taking into account direct and indirect RCT evidence, for HBeAg-positive treatment naive patients.

Key issues

Tenofovir monotherapy has a favourable resistance profile, based on currently available evidence. Long-term resistance data are awaited, and when available will guide decisions regarding whether monotherapy or combination therapy should be given. Further RCT data on the clinical effectiveness of nucleos(t)ide combination therapy are needed to support such decisions.

Summary of NICE guidance issued as a result of the STA

The NICE Appraisal Committee met on 11 February 2009 to discuss this topic. The guidance issued by NICE on 22 July 2009 states that:

Tenofovir disproxil, within its marketing authorisation is recommended as an option for the treatment of people with chronic HBe-Ag-positive or HBe-Ag-negative hepatitis B in whom antiviral treatment is indicated.

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Prasugrel for the treatment of acute coronary artery syndromes with percutaneous coronary intervention

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of prasugrel for the treatment of coronary artery syndromes with percutaneous coronary intervention, based upon the evidence submission from Eli Lilly to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The submitted clinical evidence was based on a phase III double-blind, double-dummy randomised controlled trial which compared the use of prasugrel with clopidogrel. The primary clinical outcome measure was a composite end point of death from cardiovascular causes, non-fatal myocardial infarction (MI) or non-fatal stroke at 15 months. Secondary outcomes included the primary end point at 30 days and 90 days; a composite end point of death from cardiovascular causes, non-fatal MI or urgent target vessel revascularisation; a composite end point of death from cardiovascular causes, non-fatal MI, non-fatal stroke or rehospitalisation due to a cardiac ischaemic event; and stent thrombosis. For the overall trial cohort during the 15 month follow-up period, the results of the trial demonstrated a statistically significant benefit of prasugrel compared with clopidogrel on the primary outcome. The efficacy difference between treatment groups was, in the main, due to a statistically significant lower incidence of non-fatal

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MIs in the prasugrel group than in the clopidogrel group. No statistically significant differences were found for death from cardiovascular causes or non-fatal stroke. For the fully licensed and target populations, there was a statistically significant lower incidence of non-fatal MIs in the prasugrel group than in the clopidogrel group; there was no statistically significant difference in bleeding rates. The ERG recalculated the base-case cost-effectiveness results taking changes in parameters and assumptions into account: for example, revised drug costs, mid-cycle correction, amended relative risk mortality. Subgroup and threshold analyses were also explored by the ERG. For the fully licensed population (i.e. excluding patients with prior stroke or TIA), the manufacturer reported an incremental cost-effectiveness ratio (ICER) of £159,358 per quality-adjusted life-year (QALY) gained at 12 months and an ICER of £3,220 per QALY gained at 40 years. Considering the 15-month clinical trial data available for the fully licensed and target populations and current practice in England and Wales, the evidence was considered insufficient to support the conclusion that prasugrel is clinically more effective than clopidogrel or vice versa. Assuming that there is no evidence to distinguish between prasugrel and clopidogrel in terms of clinical effectiveness in the short term for this population, equipoise between prasugrel and clopidogrel at year 1 is achieved by a 20% reduction in the acquisition cost of prasugrel (approximately £120 per patient). At the time of writing, the guidance/has not yet been published by NICE.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled 'Prasugrel for the treatment of coronary artery syndromes with percutaneous coronary intervention'.[2]

Description of the underlying health problem

Acute coronary syndromes (ACS) are life threatening conditions comprising clinical symptoms associated with acute myocardial ischaemia with or without infarction.[3] ACS represent manifestations of atherosclerosis, which is usually precipitated by acute thrombosis, induced by a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in coronary blood flow.[4]

The leading symptom that initiates the diagnostic and therapeutic cascade is chest pain, but the classification of patients is based on the presentation electrocardiogram.[4] The presence of acute chest pain and persistent ST-segment elevation indicates total occlusion of an affected coronary artery. Most of these patients will ultimately develop ST-segment elevated myocardial infarction (STEMI), resulting in necrosis of the tissue supplied by that artery. ACS with acute pain without ST-segment elevation is classified as either unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI).[4]

Options for the initial management of ACS patients include: (1) drug therapy (heparin, antiplatelet agents, beta blockers, nitrates, calcium channel blockers, thrombolytic agents and statins) or (2) drug therapy in combination with an early invasive strategy with percutaneous coronary intervention (PCI) (with or without coronary stenting) or coronary artery bypass grafting (CABG). PCI with coronary stenting is endorsed as an early invasive treatment for intermediate to high risk patients with ACS.[4,5]

Approximately 15% of the UK ACS population is treated with PCI. In 2007, within the 250,000 patients diagnosed with ACS, 77,373 PCIs were performed. Of these, 40.48% were patients with UA/NSTEMI and 13.24% were patients with STEMI. Most of the remaining patients (45.10%) had stable disease.[6]

Scope of the evidence review group report

Prasugrel is licensed in Europe to be co-administered with aspirin for the prevention of atherothrombotic events in patients with ACS undergoing primary or delayed PCI. The use of prasugrel in patients with a history of stroke or transitory ischaemic attack (TIA) is contraindicated in the Special Product Characteristics, whilst use of prasugrel in lighter (less than 60 kg) and older (75 years or more) patients is generally not recommended.

The ERG report presents the results of the evaluation of the manufacturer (Eli Lilly) evidence submission regarding the use of prasugrel with patients with ACS who are to be managed with PCI. The report includes an assessment of both the clinical effectiveness and cost-effectiveness evidence submitted by the manufacturer. The manufacturer submission described the use of prasugrel in combination with aspirin compared with clopidogrel in combination with aspirin.

The primary clinical outcome measure was a composite end point of death from cardiovascular causes, non-fatal myocardial infarction (MI) or non-fatal stroke at 15 months. Secondary outcomes included the primary end point at 30 days and 90 days; a composite end point of death from cardiovascular causes, non-fatal MI or urgent target vessel revascularisation; a composite end point of death from cardiovascular causes, non-fatal MI, non-fatal stroke or rehospitalisation due to a cardiac ischaemic event; and stent thrombosis. Safety end points included non-CABG-related thrombolysis in MI (TIMI) major bleeding, TIMI life threatening and TIMI minor bleeding. Health-related quality of life (HRQoL) was also measured.

An additional outcome measure of net clinical benefit comprising a composite end point of death from any cause, non-fatal MI, non-fatal stroke, or non-CABG-related non-fatal TIMI major bleeding was calculated.

Cost-effectiveness was measured in terms of incremental cost-effectiveness ratios (ICERs) per quality-adjusted life-year (QALY) gained.

Data for a number of different patient populations were presented:

- overall trial cohort including stroke or TIA ($n = 13,608$)
- all the ACS licensed population excluding prior stroke or TIA ($n = 13,090$)
- ACS 10-mg licensed population excluding prior stroke or TIA (target population) ($n = 10,941$)
- UA/NSTEMI licensed population excluding prior stroke or TIA ($n = 9669$)
- STEMI licensed population excluding prior stroke or TIA ($n = 3421$)
- ACS licensed population excluding prior stroke or TIA with diabetes ($n = 2947$)
- ACS licensed population excluding prior stroke or TIA without diabetes ($n = 10,143$).

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's submission to NICE as part of the STA process.

The ERG evaluated the quality of the manufacturer's clinical effectiveness review. Searches conducted by the manufacturer were assessed for completeness, and the single trial put forward as evidence of effectiveness was critically appraised using the manufacturer's responses to specific questions in the submission template. With regard to cost-effectiveness evidence, the ERG assessed the manufacturer's searches for completeness, critically appraised the submitted economic model using a standard assessment tool[7] and conducted a detailed evaluation of the model. The ERG recalculated the base-case cost-effectiveness results taking changes in parameters and assumptions into account: for example, revised drug costs, mid-cycle correction, amended relative risk mortality. Subgroup and threshold analyses were also explored by the ERG.

Results

Summary of submitted clinical evidence

The clinical effectiveness evidence was derived from a phase III double-blind, double-dummy randomised controlled trial (RCT) which compared the use of prasugrel with clopidogrel. The TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel (TRITON)–TIMI 38 was conducted in 30 countries and included 13,608 patients. For the overall trial cohort during the 15 month follow-

up period, the results of the TRITON–TIMI 38 trial demonstrated a statistically significant benefit of prasugrel compared with clopidogrel on the primary outcome (a composite end point of death from cardiovascular causes, non-fatal MI or non-fatal stroke). The efficacy difference between treatment groups was, in the main, due to a statistically significant lower incidence of non-fatal MIs in the prasugrel group than in the clopidogrel group. No statistically significant differences were found for death from cardiovascular causes or non-fatal stroke. The trial results reported a benefit for prasugrel in the overall trial cohort for the majority of secondary end points with the exception of death from any cause, where no statistical difference was identified. The results are summarised in *Table 1*. In the trial, HRQoL data were limited as this substudy comprised responses from too few patients. In the overall trial cohort, statistically significantly more bleeding events occurred in patients in the prasugrel arm than in those in the clopidogrel arm. The analysis of the pre-specified net clinical benefit outcome (death from any cause, non-fatal MI, non-fatal stroke, or non-CABG-related non-fatal TIMI major bleeding) favoured the use of prasugrel in the overall trial cohort. For the fully licensed and target populations, there was a statistically significant lower incidence of non-fatal MIs in the prasugrel group than in the clopidogrel group; there was no statistically significant difference in bleeding rates.

Summary of submitted cost-effectiveness evidence

In the absence of UK-based economic evaluations of prasugrel for patients with ACS undergoing PCI, the manufacturer conducted a de novo economic evaluation. The analysis described in the manufacturer submission used a Markov model structure with cohorts of patients modelled to experience events over the course of the TRITON–TIMI 38 study period with long-term mortality based on adjustment of population life tables

TABLE 1 *TRITON–TIMI 38: Efficacy results at 15 months (overall cohort)*

End point	Prasugrel (*n* = 6813) *n* (%)	Clopidogrel (*n* = 6795) *n* (%)	HR (95% CI)	*p*-value[a]
Primary				
Death from CV causes, non-fatal MI or nonfatal stroke	643 (9.9)	781 (12.1)	0.81 (0.73 to 0.90)	< 0.001
Death from CV causes	133 (2.1)	150 (2.4)	0.89 (0.70 to 1.12)	0.31
Non-fatal MI	475 (7.3)	620 (9.5)	0.76 (0.67 to 0.85)	< 0.001
Non-fatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71 to 1.45)	0.93
Secondary				
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78 to 1.16)	0.64
Death from CV causes, nonfatal MI or UTVR	652 (10.0)	798 (12.3)	0.81 (0.73 to 0.89)	< 0.001
Death from CV causes	133 (2.1)	150 (2.4)	0.89 (0.70 to 1.12)	0.31
Non-fatal MI	475 (7.3)	620 (9.5)	0.76 (0.67 to 0.85)	< 0.001
UTVR[b]	156 (2.5)	233 (3.7)	0.66 (0.54 to 0.81)	< 0.001
Stent thrombosis[c]	68 (1.1)	142 (2.4)	0.48 (0.36 to 0.64)	< 0.001
Death from CV causes, nonfatal MI, non-fatal stroke or rehospitalisation for ischaemia	797 (12.3)	938 (14.6)	0.84 (0.76 to 0.92)	< 0.001

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; UTVR, urgent target vessel revascularisation.

a *p*-values were calculated using the log-rank test. The analysis for the primary end point used the Gehan–Wilcoxon test for which the *p*-value was less than 0.

b Taken from published paper.[8]

c Stent thrombosis defined as definite or probable according to the Academic Research Consortium.

to reflect prognostic implications of the events modelled over the short term. The model also permitted in-hospital costs to accumulate after the end of the trial follow-up period. The model can be separated into two distinct phases: (1) the trial-based period of 15 months and (2) extrapolation beyond the trial to a lifetime horizon (40 years). The economic evaluation adopts a lifetime horizon for the consideration of in-hospital costs and benefits and the perspective is that of the UK NHS and Personal Social Services.

For the fully licensed population (i.e. excluding patients with prior stroke or TIA), the manufacturer reported an ICER of £159,358 per QALY gained at 12 months and an ICER of £3,220 per QALY gained at 40 years; the incremental QALY gain for prasugrel patients is very small (0.001 QALYs and 0.05 QALYs at 12 months and 40 years respectively). In addition to the main results, ICERs for selected subgroups were also presented at 40 years. Univariate sensitivity analysis was undertaken using a range of parameters. At 40 years, using the median UA/NSTEMI profile and halving the relative risks for all-cause mortality increases the ICER to £10,070 per QALY gained; varying the relative risk for prasugrel compared with clopidogrel in the first 3 days in an attempt to explore the preloading of clopidogrel on cost-effectiveness yielded a maximum ICER for this median patient profile of £22,727 per QALY gained.

Probabilistic sensitivity analysis was also conducted by the manufacturer using median patient profiles. At 40 years, the probabilistic sensitivity analyses illustrate that prasugrel is likely to be cost-effective compared with clopidogrel (around 75%) for what would usually be considered low levels of willingness to pay (£20,000) for an additional QALY; the ICERs were within the cost-effectiveness threshold range used by NICE.

Commentary on the robustness of submitted evidence

The manufacturer cited evidence from a large trial (TRITON–TIMI 38) to support the superior clinical effectiveness of prasugrel compared with clopidogrel for the treatment of patients with ACS managed with PCI. The trial used robust randomisation techniques and was suitably powered to show a clinical difference in the primary efficacy composite end point between the treatment groups. Appropriate pre-specified subgroup analyses and post hoc exploratory analyses were carried out.

There is only one relevant RCT (TRITON–TIMI 38) that compares prasugrel versus clopidogrel with PCI. The clinical superiority of prasugrel over clopidogrel on the primary efficacy endpoint is driven largely by a reduction in non-fatal MI, an event recorded clinically (symptomatic) and non-clinically (by biomarkers/electrocardiogram readings). If the non-clinical MIs were considered less important to patients, the resultant clinical difference in non-fatal MIs alone may not be statistically significant.

The primary efficacy composite end point used in the trial may not be appropriate as it fails to meet published recommendations. In addition, there is limited generalisability of the trial protocol to NHS patients in England and Wales due to differences in the use of clopidogrel and its current use in UK clinical practice. Moreover, the growing trend in England and Wales for PCI to be performed via radial artery access is not reflected in the trial; there is evidence that when PCI is performed radially, major bleeding rates are reduced. The HRQoL trial data were limited as the quality of life substudy recruited too few patients to allow meaningful analysis of responses.

The economic model described in the manufacturer submission made use of a large quantity of individual patient data allowing the heterogeneity of different patient groups to be assessed. The manufacturer asked a clearly defined question and attempted to identify, measure and value relevant costs and benefits in the economic evaluation.

The ERG identified six key areas where corrections and/or adjustments to the economic model were required: life table calculations to allow for competing risks; conventional approach to discounting; revised treatment costs reflecting actual usage and pack wastage; alternate utility values; amended long-term relative risks of mortality; and reduced incidence of non-fatal recurrent MIs. Taken together, these corrections and/or adjustments have increased the size of the ICER for all patient populations (*Table 2*).

The methods used to project outcomes and costs after the trial period are crucial to the acceptance or rejection of the manufacturer's ICER. The ERG advises caution in view of the various problems that are apparent with this part of the submitted model. If the ERG had been able to modify some of the model's underlying assumptions, then it is likely that the magnitude of the re-estimated ICER would be increased further.

TABLE 2 *Cost-effectiveness from submitted model[a] and with ERG modifications[a]*

Population	Model version	Horizon	Clopidogrel			Prasugrel			Incremental			ICERs	
			LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	£ per LY	£ per QALY
ACS	Submitted	1 year	0.97	0.720	£874	0.97	0.720	£1032	–0.0002	–0.0002	£158.40	clop dom	clop dom
		10 years	7.95	6.126	£3342	7.95	6.129	£3500	0.0036	0.0027	£157.67	£44,405	£57,641
		40 years	14.30	10.960	£5574	14.34	10.990	£5744	0.0392	0.0296	£170.18	£4346	£5751
	ERG	1 year	0.99	0.646	£860	0.99	0.646	£1031	–0.0001	–0.0001	£120.07	clop dom	clop dom
		10 years	8.11	5.459	£3372	8.11	5.459	£3543	–0.0002	–0.0002	£119.85	clop dom	clop dom
		40 years	14.69	9.770	£5685	14.70	9.776	£5859	0.0093	0.0060	£123.19	£13,294	£20,475
UA/NSTEMI	Submitted	1 year	0.97	0.778	£873	0.97	0.778	£1031	–0.0003	–0.0002	£158.50	clop dom	clop dom
		10 years	8.12	6.378	£3404	8.13	6.378	£3560	0.0007	0.0005	£156.84	£235,284	£340,331
		40 years	16.37	12.701	£6299	16.40	12.728	£6468	0.0349	0.0265	£168.88	£4832	£6382
	ERG	1 year	0.99	0.663	£859	0.99	0.663	£1031	–0.0002	–0.0002	£120.72	clop dom	clop dom
		10 years	8.28	5.695	£3431	8.28	5.694	£3602	–0.0014	–0.0010	£120.15	clop dom	clop dom
		40 years	16.79	11.324	£6423	16.80	11.328	£6597	0.0066	0.0042	£122.95	£18,643	£28,971
STEMI	Submitted	1 year	0.97	0.720	£859	0.97	0.720	£1019	–0.0001	–0.0001	£160.55	clop dom	clop dom
		10 years	7.88	6.074	£3300	7.88	6.077	£3461	0.0037	0.0029	£160.65	£43,258	£56,032
		40 years	13.63	10.431	£5321	13.67	10.455	£5492	0.0319	0.0241	£170.56	£5347	£7087
	ERG	1 year	0.99	0.646	£850	0.99	0.646	£1021	–0.0001	–0.0001	£118.58	clop dom	clop dom
		10 years	8.04	5.362	£3335	8.04	5.362	£3507	0.0001	0.0000	£118.86	£2,332,985	£18,536,759
		40 years	13.97	9.242	£5419	13.98	9.247	£5593	0.0077	0.0050	£121.56	£15,695	£24,161

Population	Model version	Horizon	Clopidogrel			Prasugrel			Incremental			ICERs	
			LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	£ per LY	£ per QALY
Diabetes	Submitted	1 year	0.97	0.714	£905	0.97	0.716	£1040	0.0023	0.0017	£135.79	£58,275	£79,531
		10 years	8.01	6.172	£3405	8.04	6.198	£3550	0.0335	0.0259	£144.38	£4304	£5564
		40 years	15.90	12.189	£6178	16.04	12.296	£6360	0.1412	0.1074	£182.19	£1291	£1697
	ERG	1 year	0.98	0.641	£878	0.99	0.642	£1034	0.0025	0.0016	£104.19	£41,490	£63,957
		10 years	8.16	5.539	£3417	8.19	5.559	£3581	0.0302	0.0205	£113.35	£3753	£5517
		40 years	16.34	10.896	£6289	16.42	10.952	£6473	0.0838	0.0556	£132.19	£1577	£2376
Non-diabetes	Submitted	1 year	0.97	0.718	£872	0.97	0.718	£1031	–0.0004	–0.0003	£158.46	clop dom	clop dom
		10 years	7.53	5.706	£3194	7.54	5.711	£3353	0.0066	0.0049	£158.84	£24,246	£32,551
		40 years	11.31	8.528	£4522	11.35	8.555	£4691	0.0356	0.0266	£169.04	£4751	£6365
	ERG	1 year	0.99	0.614	£859	0.99	0.613	£1030	–0.0003	–0.0002	£120.06	clop dom	clop dom
		10 years	7.70	5.003	£3228	7.70	5.002	£3399	–0.0006	–0.0004	£119.77	clop dom	clop dom
		40 years	11.62	7.555	£4604	11.63	7.560	£4778	0.0073	0.0048	£122.54	£16,725	£25,716
Target	Submitted	1 year	0.97	0.720	£873	0.97	0.720	£1032	–0.0002	–0.0002	£158.36	clop dom	clop dom
		10 years	7.91	6.094	£3328	7.91	6.097	£3485	0.0040	0.0031	£157.79	£39,469	£51,185
		40 years	13.93	10.669	£5444	13.97	10.699	£5615	0.0393	0.0297	£170.21	£4326	£5729
	ERG	1 year	0.99	0.646	£860	0.99	0.646	£1031	–0.0002	–0.0001	£120.03	clop dom	clop dom
		10 years	8.07	5.408	£3358	8.07	5.408	£3529	–0.0001	–0.0001	£119.84	clop dom	clop dom
		40 years	14.32	9.496	£5552	14.32	9.502	£5727	0.0094	0.0061	£123.18	£13,144	£20,247

ACS, acute coronary syndromes; clop dom, clopidogrel dominates prasugrel; ERG, evidence review group; ICERs, incremental cost-effectiveness ratios; LYs, life years; NSTEMI, non-ST-segment elevated myocardial infarction; QALYs, quality-adjusted life-years; STEMI, ST-segment elevated myocardial infarction; UA, unstable angina.

a Figures directly taken from model, not manufacturer submission.

Conclusions

Considering the 15-month clinical trial data available for the fully licensed (i.e. excluding prior stroke or TIA) and target populations (i.e. excluding prior stroke or TIA, and patients weighing less than 60 kg or aged 75 years or older) and current practice in England and Wales, the evidence was considered insufficient to support the conclusion that prasugrel is clinically more effective than clopidogrel or vice versa.

Assuming that there is no evidence to distinguish between prasugrel and clopidogrel in terms of clinical effectiveness in the short term for this population, equipoise between prasugrel and clopidogrel at year 1 is achieved by a 20% reduction in the acquisition cost of prasugrel (approximately £120 per patient).

The modelled net health benefits (QALYs) do not achieve positive gains for prasugrel until more than 10 years' follow-up has elapsed, except for patients with diabetes mellitus. The ERG considered that the submitted evidence from long-term projection (at 40 years) is not sufficiently robust to support the conclusion that prasugrel is more cost-effective than clopidogrel for the fully licensed population.

Given that the trial evidence appears to show that prasugrel and clopidogrel yield similar overall health benefits in the short-term, it could be argued that, at an equivalent net cost per patient, prasugrel might represent a viable alternative.

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in October 2009 states that:

1.1 Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention, only when:

- immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary **or**
- stent thrombosis has occurred during clopidogrel treatment **or**
- the patient has diabetes mellitus.

1.2 People currently receiving prasugrel for treatment of acute coronary syndromes whose circumstances do not meet the criteria in 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

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Alitretinoin for the treatment of severe chronic hand eczema

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of alitretinoin for the treatment of adults with severe chronic hand eczema refractory to topical steroid treatment in accordance with the licensed indication, based upon the evidence submission from Basilea Pharmaceuticals Ltd to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The clinical evidence came from a single placebo-controlled randomised controlled trial of daily treatment with alitretinoin for 12–24 weeks, with follow-up for a further 24 weeks, in patients with severe chronic hand eczema (CHE) unresponsive to topical steroids. A statistically significantly greater proportion of patients using alitretinoin achieved the primary end point of clear or almost clear hands by week 24 than did those with placebo. Dose-dependent headache was the most commonly reported adverse event in patients treated with alitretinoin. Serious adverse events were rare, but alitretinoin was associated with increases in both total cholesterol and triglycerides, which has implications for risks of future cardiovascular events. The manufacturer submitted a de novo decision analytic model to estimate, over a time horizon of 3 years, the cost-effectiveness of alitretinoin versus the other relevant comparators identified by NICE. In response to the points of clarification put to it by the ERG regarding the initial submission, the manufacturer provided additional evidence and a revised decision analytic model with a 'placebo' arm. In the manufacturer's original

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

submission to NICE, the base-case incremental cost-effectiveness ratios (ICERs) reported for alitretinoin were £8614 per quality-adjusted life-year (QALY) versus ciclosporin, –£469 per QALY versus psoralen + UVA (with alitretinoin dominant) and £10,612 per QALY versus azathioprine. These ICERs decreased as the time horizon was extended in sensitivity analyses. In patients with hyperkeratotic CHE and in women of child-bearing potential, the ICER remained below £20,000. When the health-related quality of life (HRQoL) values used in the model were replaced with those derived from an alternative study, these ICERs increased significantly (to £22,312 per QALY for alitretinoin versus azathioprine). In the revised model, alitretinoin was reported to have an ICER of £12,931 per QALY gained versus supportive care (placebo). However, the model underestimates the costs of treatment associated with alitretinoin. The manufacturer assumed that patients receiving alitretinoin visited the dermatologist every 4 weeks and ceased treatment as soon as they responded to it. If, in practice, patients would receive treatment for longer than this, then the manufacturer's model will have significantly underestimated the costs to the NHS. Additional analyses undertaken by the ERG produced ICERs close to £30,000 per QALY gained for alitretinoin versus supportive care. This was largely due to uncertainty surrounding the impact of alitretinoin on HRQoL. The placebo-controlled trials conducted to date have established that alitretinoin can be efficacious for the treatment of severe CHE refractory to topical steroids, but longer term follow-up of trials or the implementation of registries is required to better establish the longer term efficacy or safety of alitretinoin. NICE recommended the use of alitretinoin for patients with severe CHE and a Dermatology Life Quality Index (DLQI) score of at least 15. Treatment was recommended to be stopped as soon as an adequate response was observed, or if CHE remained severe at 12 weeks, or if response was inadequate at 24 weeks.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled 'Alitretinoin for the treatment of severe chronic hand eczema'.[2]

Description of the underlying health problem

It is estimated that between 0.5% and 0.7% of the general population suffer from severe chronic hand eczema (CHE).[3] Management of hand eczema includes avoidance of allergens and irritants, skin protection measures and use of topical corticosteroids where necessary. Patients with chronic disease may require treatment with the most potent steroid preparations available because drug penetration is impaired by significant hyperkeratosis of the hands. Approximately 50% of affected patients will be refractory to treatment with topical corticosteroids.[3] These patients suffer from painful cracks and blisters susceptible to secondary infections, itching and bleeding, which can limit manual dexterity and prevent employment. The visibility of disease, need for frequent visits to the doctor and regular application of greasy topical agents, all add to the burden of the disease. Severe CHE carries a debilitating social stigma which is associated with an impaired quality of life, comparable to that seen in patients with generalised eczema and psoriasis.[4] In addition, hand eczema has been shown to be a major cause of prolonged sick leave and has been reported to lead to job loss.[5] Patients with CHE have a poor prognosis; it is a self-perpetuating condition with a long-lasting and chronically relapsing course.[6] No licensed treatment options are available for these patients. The unlicensed options used in clinical practice include immunosuppressants, such as ciclosporin and azathioprine, and phototherapy.

Scope of the evidence review group report

Oral alitretinoin (9-*cis*-retinoic acid, Toctino®), an endogenous retinoid, is indicated for use in

adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids. The recommended dose range for alitretinoin is 10–30 mg once daily. A treatment course of alitretinoin should be started at the higher dose of 30 mg and may be given for 12–24 weeks depending on response. Discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of treatment.

The ERG report presents an assessment of the manufacturer's (Basilea Pharmaceuticals Ltd) submission to NICE on the use of alitretinoin (within the context of the licensed indication) in adults with severe chronic hand eczema refractory to topical steroid treatment and attempted to compare it with the stated comparators: psoralen + UVA (PUVA), ciclosporin and azathioprine.

Evidence for the efficacy of alitretinoin came primarily from a phase III randomised placebo-controlled double-blinded trial and an extension study.[7,8] The primary report outcome was 'clear' or 'almost clear' hands as assessed by the physician's global assessment (PGA). Other outcomes reported included signs and symptoms of the disease, as measured by the modified Total Lesion Symptom Score (mTLSS), the patient global assessment (PaGA) of disease severity, and adverse events.

The manufacturer developed a de novo decision analytic model to estimate, over a time horizon of 3 years, the cost-effectiveness of alitretinoin versus the other relevant comparators identified by NICE. In response to the points of clarification put to them by the ERG regarding the initial submission, the manufacturer provided additional evidence and a revised decision analytic model. The model estimated costs and quality-adjusted life-years (QALYs) from the perspective of the NHS and Personal Social Services (PSS), which is consistent with NICE guidelines.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

As well as a detailed critical appraisal of the manufacturer's submission, the ERG completed searches of its own to take into account some of the issues raised in its review of the manufacturer's search strategies and also modified the manufacturer's decision analytic model to examine the impact of altering some of the key assumptions.

Results

Summary of submitted clinical evidence

The main clinical effectiveness data were derived from a single placebo-controlled randomised controlled trial (RCT) of daily treatment with alitretinoin for 12–24 weeks (BAP00089), with follow-up for a further 24 weeks, in patients with severe CHE unresponsive to topical steroids. In this study, a statistically significantly greater proportion of patients using alitretinoin achieved the primary end point of clear or almost clear hands (as assessed by the PGA) by week 24 than did those with placebo: 48% with alitretinoin 30 mg ($p < 0.001$); 28% with alitretinoin 10 mg ($p < 0.005$); 16.6% with placebo. The severity of disease was also reduced when assessed by patients using the PaGA. The majority of patients who responded to alitretinoin treatment remained in remission during the 24-week follow-up period. A high PGA response rate to retreatment with alitretinoin was observed, although a similarly high response to placebo was observed among first-line 'placebo responders', and PGA results were not consistent with the PaGA evaluations. The main effectiveness data from all reported trials are presented in *Table 1*.

Dose-dependent headache was the most commonly reported adverse event in patients treated with alitretinoin, with rates of 20% in the alitretinoin 30-mg group and 11% in the 10-mg group. Serious adverse events were rare, but alitretinoin was associated with increases in both total cholesterol and triglycerides, which has implications for risks of future cardiovascular events.

No direct comparisons of alitretinoin with any of the relevant treatment comparators (PUVA, ciclosporin or azathioprine) were available. Nor were any trial data on these comparators available to permit formal indirect comparisons of alitretinoin with its comparators.

Summary of submitted cost-effectiveness evidence

The manufacturer submitted a de novo decision analytic model to estimate, over a time horizon of 3 years, the cost-effectiveness of alitretinoin versus

TABLE 1 *Primary and secondary study end points from controlled trials included in manufacturer's submission*

Trial	Treatment	Response: PGA[a] (95% CI)	Response: PaGA[a]	Symptom change: mTLSS[b] (95% CI)	Health-related quality of life: DLQI[c]	Relapse rate[d]
BAP00089	Placebo	16.6% (11.8 to 22.4)	15%	–39% (–47 to –27)		
	10 mg	27.5% (23.3 to 32.1), $p < 0.005$[e]	24%, $p < 0.02$[e]	–56% (–63 to –50), $p < 0.001$[e]		29.6% (at 6 months)
	30 mg	47.7% (42.7 to 52.6), $p < 0.001$[e]	40%, $p < 0.001$[e]	–75% (–79 to –69), $p < 0.001$[e]		37.4% (at 6 months)
BAP00091 (Cohort A)	Placebo (previously placebo)	69.2%	23.1%	–40.3%		
	Placebo (previously 10 mg)	10%				
	Placebo (previously 30 mg)	8.3%				
	10 mg	47.6%	75.5%	–78.8%, $p = 0.02$[f]		
	30 mg	79.6%	38.1%	–67.4%, $p < 0.001$[f]		
BAP00091 (Cohort B)	30 mg	46.2%	42.4%	–49.7%		
BAP00003	Placebo	27%	12%	–25% (–42 to –14)	–2	26%
	10 mg	39%, $p =$ ns[e]	29%, $p = 0.014$[e]	–59% (–73 to –42), $p = 0.03$[e]	–2	25%
	20 mg	41%, $p =$ ns[e]	34%, $p = 0.002$[e]	–52% (–73 to –42), $p = 0.002$[e]	–3	26%
	40 mg	53%, $p < 0.001$[e]	43%, $p < 0.001$[e]	–59% (–80 to –44), $p < 0.001$[e]	–3	32.5%
BAP00200	10 mg	12.5% (1.6, to 38.3)				
	30 mg	62.5% (35.4 to 84.8)				

CI, confidence interval; DLQI, Dermatology Life Quality Index; mTLSS, modified Total Lesion Symptom Score; ns, not stated; PaGA, patient global assessment; PGA, physician's global assessment.
a Percentage with clear/almost clear hands.
b Median change in mTLSS score from baseline.
c Median within-patient change from baseline to week 12.
d Percentage with mTLSS score 75% of baseline value.
e Compared with placebo.
f Compared with placebo (previously 30 mg).

the other relevant comparators identified by NICE. In response to the points of clarification put to it by the ERG regarding the initial submission, the manufacturer provided additional evidence and a revised decision analytic model.

In the manufacturer's original submission to NICE, the base-case incremental cost-effectiveness ratios (ICERs) reported for alitretinoin were £8614 per QALY versus ciclosporin, –£469 per QALY versus PUVA (with alitretinoin dominant) and £10,612 per QALY versus azathioprine. These ICERs decreased as the time horizon was extended in sensitivity analyses. In patients with hyperkeratotic CHE and in women of child-bearing potential, the ICER remained below £20,000. When the health-related quality of life (HRQoL) values used in the model were replaced with those derived from an alternative study, these ICERs increased significantly (to £22,312 per QALY for alitretinoin versus azathioprine). In the revised model, which compared alitretinoin only to placebo, the ICER was reported to be £12,931.

Commentary on the robustness of submitted evidence

Strengths

The manufacturer's submission incorporated a full systematic review of the literature of the effects of alitretinoin in severe CHE refractory to topical steroid treatment. The main findings are derived from a single generally well-conducted placebo-controlled RCT and an associated follow-up trial of retreatment.

The submission also included a review of the literature of the cost-effectiveness of alitretinoin in severe CHE. As no existing economic evaluations were identified, the manufacturer undertook a de novo economic evaluation in order to compare alitretinoin with comparators identified by NICE, consisting of ciclosporin, PUVA and azathioprine. The model estimated costs and QALYs from the perspective of the NHS and PSS, which is consistent with NICE guidelines.

Weaknesses

At present, there is a relatively limited quantity of evidence available on the clinical effects of alitretinoin. Although the RCTs presented were adequately designed and conducted, the ERG noted high numbers of withdrawals from the main efficacy trial, a lack of clear evidence for the reported subgroup effects and unexplained inconsistencies between PGA and PaGA scores in the retreatment trial.

Limitations in the submitted evidence primarily impacted on the generalisability of the manufacturer's conclusions to clinical practice. The main observed effects of alitretinoin were relative to placebo with additional emollients where required. Therefore it remains unknown to what extent alitretinoin is effective relative to emollients and topical corticosteroids combined (the current first-line treatment choice).

For inclusion in the main RCT (BAP00089), diagnosis as 'severe' on the PGA outcome measure was a pre-requisite. In clinical practice, it seems likely that a proportion of patients considered for treatment with alitretinoin would fall into the less severe PGA 'moderate' state. There is some evidence from the phase II trial BAP00003 that a 'PGA moderate' CHE population would respond to alitretinoin treatment, but there is no evidence for the effects of the 30 mg dose in this population.

The cost-effectiveness section of the submission had major shortcomings. The efficacy estimates for treatments other than alitretinoin were based on expert clinical opinion only. While the use of expert opinion may be justified where trial data do not exist to inform the relevant parameters, it should be elicited in a methodologically rigorous manner. The ERG remains unconvinced that this elicitation process generated reliable estimates of the efficacy of each of the comparator treatments. The estimates of HRQoL were derived in a two-stage prediction model that incorporated an algorithm developed for patients with psoriasis. Direct evidence of the impact of alitretinoin on HRQoL was only available from the phase II trial, which did not include the recommended 30 mg starting dose of alitretinoin and showed no difference between alitretinoin (10 mg, 20 mg and 40 mg) and placebo.

Serious issues remain around the implementation of the model in EXCEL. Inspection of the VBA (Visual Basic for Applications) code indicated that a number of the assumptions given in the written submission were not implemented correctly. In particular, the first 4 weeks of every subsequent treatment cycle were omitted. The definition of relapse used in the model did not correspond to that used in the relevant clinical trials. As a consequence the estimated costs and health outcomes presented by the manufacturer may be regarded as unreliable. The ERG attempted to amend the model to provide more appropriate estimates of the ICERs, but in some cases this was not feasible.

Furthermore, the model originally submitted to NICE did not include a 'supportive care' (or 'placebo') arm and the treatment effects for alitretinoin were not placebo adjusted; as such, the model did not address whether alitretinoin was a cost-effective alternative to supportive care. Consequently, the ERG does not regard the ICERs generated by the manufacturer's original model as providing a reliable indication of the cost-effectiveness of alitretinoin compared with each of the comparators considered.

Areas of uncertainty

Crucially, there is no evidence on the efficacy and safety of alitretinoin beyond around 48 weeks. Given the chronic recurring nature of CHE, longer term follow-up is required to detect potentially rare adverse events and possibly to characterise the cardiovascular risks posed by the observed increase in cholesterol levels associated with alitretinoin treatment.

There was also no direct or indirect evidence presented for the clinical effects of alitretinoin relative to the comparators specified in the scope

for the treatment of CHE (PUVA, ciclosporin and azathioprine). No additional evidence was identified by the ERG.

A change in threshold for the definition of 'relapse' from 75% to 50% of baseline mTLSS substantially reduced the time to relapse observed in the 30-mg alitretinoin group. If clinicians were to consider retreatment for less severe 'relapses', this would have clinical and cost implications in terms of the reduced time between treatment periods.

As the relief of symptoms and consequent improvement in HRQoL are the aims of treatment for chronic hand eczema, the ERG believes that the economic evaluation of alitretinoin should be based on good evidence of the improvement in HRQoL offered by alitretinoin. However, the estimates used in the submission are subject to a great deal of uncertainty due to the two-stage prediction employed and the paucity of direct observations in the population of interest.

The ERG modified the manufacturer's model to examine the impact of altering some of the key assumptions. However, as the manufacturer did not undertake a probabilistic sensitivity analysis, the combined impact of uncertainty in the inputs to the economic model on the overall decision uncertainty could not be evaluated.

Conclusions

In response to a request from the ERG, the manufacturer provided a revised model with a 'placebo' arm, and the comparison of alitretinoin with placebo made in this revised model is of greater merit given the more reliable efficacy data in the comparator arm. In this analysis, alitretinoin was reported to have an ICER of £12,931 per QALY gained versus supportive care (placebo). However, the omission of adverse events from this revised model, in combination with a number of other factors, means that the model underestimates the costs of treatment associated with alitretinoin.

TABLE 2 *Results of additional analyses comparing the impact of two alternative health-related quality of life estimates provided by the manufacturer*

	BAP0003 utility data			Augustin utility data		
Treatment	**Cost**	**QALYs**	**ICER (per QALY)**	**Cost**	**QALYs**	**ICER (per QALY)**
Analysis 1: Base-case reanalysis						
Supportive care	£481.40	1.79		£481.40	2.05	
Alitretinoin (30 mg)	£3369.21	2.01	£13,431.67	£3369.21	2.16	£27,996.89
Analysis 2: Patients relapse into PGA moderate and severe						
Supportive care	£481.60	1.78		£481.60	2.05	
Alitretinoin (30 mg)	£3509.33	1.99	£14,525.65	£3509.33	2.15	£29,864.39
Analysis 3a: Potentially child-bearing women only						
Supportive care	£481.40	1.79		£481.40	2.05	
Alitretinoin (30 mg)	£3548.95	2.01	£14,267.64	£3548.95	2.16	£29,739.38
Analysis 3b: Men only						
Supportive care	£481.40	1.79		£481.40	2.05	
Alitretinoin (30 mg)	£3337.49	2.01	£13,284.14	£3337.49	2.16	£27,689.38
Analysis 4: Reinstate adverse events for alitretinoin only						
Supportive care	£481.40	1.79		£481.40	2.05	
Alitretinoin (30 mg)	£3370.37	2.00	£14,072.21	£3370.37	2.15	£29,199.56

ICER, incremental cost-effectiveness ratio; PGA, physician's global assessment; QALYs, quality-adjusted life-years.

The manufacturer assumed that patients receiving alitretinoin visited the dermatologist every 4 weeks and ceased treatment as soon as they responded to it, even if this was after only 4 or 8 weeks of treatment. If, in practice, patients would receive treatment for longer than this, then the manufacturer's model will have significantly underestimated the costs to the NHS.

Additional analyses undertaken by the ERG produced ICERs close to £30,000 per QALY gained for alitretinoin versus supportive care. This was largely due to uncertainty surrounding the impact of alitretinoin on HRQoL. Utilising the alternative HRQoL estimates identified by the manufacturer resulted in a two-fold increase in the ICER (see *Table 2* for a comparison of the different estimates). There remains considerable uncertainty as to the true ICER of alitretinoin versus the relevant treatment comparators.

Implications for research

Given the limited duration of the available evidence, longer term follow-up of trials or the implementation of registries may be required to better establish the longer term efficacy and safety of alitretinoin. The placebo-controlled trials conducted to date have established that alitretinoin can be efficacious for the treatment of severe CHE refractory to topical steroids. However, future studies should include a relevant HRQoL measure (such as the Dermatology Life Quality Index and the European Quality of Life – 5 Dimensions) alongside measures of therapeutic response and may want to establish the efficacy of alitretinoin relative to current first-line treatment (emollients plus topical steroids) and other treatments that are used in this indication (PUVA, azathioprine, ciclosporin).

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE states that:

NICE recommended Alitretinoin as a possible treatment for people with severe chronic hand eczema if:

- their eczema has not improved with treatments called potent topical corticosteroids **and**
- standard assessments (PGA and DLQI) show that their eczema is severe and is affecting their quality of life.

Alitretinoin treatment should be stopped:

- as soon as the eczema has clearly improved **or**
- if the eczema remains severe after 12 weeks **or**
- if the eczema has not clearly improved after 24 weeks.

Treatment with alitretinoin should be started and monitored only by doctors who:

- are skin specialists (dermatologists) **or**
- have experience in both treating people with severe chronic hand eczema and using drugs like alitretinoin.

When assessing how a person's eczema affects their quality of life, healthcare professionals should take into account any disabilities or difficulties in communicating which might mean that the standard assessments do not provide accurate information.

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Pemetrexed for the first-line treatment of locally advanced or metastatic non-small cell lung cancer

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of pemetrexed for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), in accordance with the licensed indication, based upon the evidence submission from Eli Lilly Ltd to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The majority of the efficacy evidence described in the manufacturer's submission is derived from a phase III open-label randomised controlled trial (RCT) known as the JMDB trial. The trial achieved its primary objective to demonstrate non-inferiority of pemetrexed/cisplatin to gemcitabine/cisplatin for overall survival in all patients with NSCLC. Because no other studies were found comparing pemetrexed/cisplatin with any other relevant comparator, additional efficacy evidence was presented from two phase III RCTs comparing gemcitabine/cisplatin with gemcitabine/carboplatin and docetaxel/cisplatin. The manufacturer's submission reported from its indirect comparisons' analysis that median overall survival and progression-free survival and tumour response rates were more favourable for pemetrexed/cisplatin than for any other comparator. The manufacturer did not identify any published cost-effectiveness analyses of pemetrexed for the first-line treatment of patients with NSCLC. Therefore economic evidence was derived solely from a de novo economic model developed by the manufacturer. A Markov model was developed

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

to evaluate the cost-effectiveness of pemetrexed/cisplatin compared to gemcitabine/cisplatin, docetaxel/cisplatin and gemcitabine/carboplatin. The clinical data used in the economic evaluation were primarily generated from the JMDB trial, with additional data from the two further trials used in the indirect comparisons analysis. The ERG identified a series of problems with this economic model. As a result, three different versions of the model were submitted to NICE and considered by the ERG. The ICERs estimated by this final version of the model ranged from £8056 to £33,065 per QALY, depending on the comparator, the population and the application of a continuation rule. The ERG considered that the model required extensive modification and redesign, and should be subjected to thorough validation against the JMDB trial results. A full quality audit was also required as it was likely that further model inconsistencies may be present that had not yet been identified. The manufacturer subsequently included evidence in the form of three cost effectiveness analyses (two models and an 'in-trial' analysis), stating that a thorough validation process had been followed according to the NICE request. The very short time available to the ERG to consider the new evidence precluded a comprehensive assessment. Instead, the ERG chose to present a simple exploratory analysis combining its own survival projections with key cost estimates obtained from the JMDB trial individual patient data. Compared to gemcitabine, this resulted in ICERs ranging from £17,162 to £30,142 per QALY, depending on the patient population, the maximum number of cycles of chemotherapy and whether a cycle based efficacy adjustment was applied or not. The guidance issued by NICE in September 2009 states that pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic NSCLC only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of pemetrexed for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC).[2]

Description of the underlying health problem

According to Cancer Research UK,[3] over 38,000 people were diagnosed with lung cancer in the UK in 2005. Survival from lung cancer is poor with around a quarter of patients (25% men, 26% women) surviving for 1 year after diagnosis, falling to 7% for 5 years after diagnosis, and the disease was responsible for approximately 34,000 deaths in 2006. Reasons for this poor prognosis include the late identification of the disease and low active anticancer treatment rates.

The main subtypes of NSCLC are squamous cell carcinoma, adenocarcinoma and large-cell carcinoma. According to a recent audit of England and Wales,[4] 33% of patients had squamous NSCLC, 25% had adenocarcinoma, 4% had large-cell carcinoma with the remaining 36% defined as NSCLC 'not-otherwise specified' (NSCLC-NOS).

Scope of the evidence review group report

The ERG report presents the results of the assessment of the manufacturer's (Eli Lilly Ltd) evidence submission regarding the use of pemetrexed with cisplatin compared to platinum-based chemotherapy for the first-line treatment of locally advanced or metastatic NSCLC. The report includes an assessment of both the clinical effectiveness and cost-effectiveness evidence submitted by the manufacturer. The primary clinical outcome measure was overall survival with secondary outcomes of progression-free survival (PFS), response to therapy and tolerability. The cost-effectiveness data were presented as incremental cost-effectiveness ratios (ICERs).

Pemetrexed (Alimta®) is a multitargeted anticancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication. It was approved by the European Commission for the first-line treatment of NSCLC (other than predominantly squamous cell histology) in combination with cisplatin on 8 April 2008. In this group of patients, it is indicated for patients with locally advanced or metastatic NSCLC.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's submission to NICE as part of the STA process. The ERG evaluated the quality of the manufacturer's clinical effectiveness review. Searches conducted by the manufacturer were assessed for completeness, and the single trial put forward as evidence of effectiveness[5] was critically appraised. With regard to cost-effectiveness evidence, the ERG assessed the manufacturer's searches for completeness, critically appraised the submitted economic model using a standard assessment tool (Drummond and Jefferson[6]) and conducted an evaluation of the model.

Results

Summary of submitted clinical evidence

The majority of the efficacy evidence described in the manufacturer's submission is derived from a phase III open-label randomised controlled trial (RCT) known as the JMDB trial[5] and is presented in *Table 1*. The trial achieved its primary objective to demonstrate non-inferiority of pemetrexed/cisplatin to gemcitabine/cisplatin for overall survival in all patients with NSCLC [median 10.3 months for both trial arms, adjusted hazard ratio (HR) = 0.94; 95% confidence interval (CI) 0.84 to 1.05]. As pemetrexed is only indicated for the first-line treatment of patients with non-squamous NSCLC, a subgroup analysis of patients with non-squamous NSCLC was presented that reported superiority of pemetrexed/cisplatin on the primary outcome of overall survival compared with gemcitabine/cisplatin (median 11.0 and 10.1 months, respectively, adjusted HR = 0.84; 95% CI 0.74 to 0.96). In the population of patients with non-squamous NSCLC, median PFS was not reported to be statistically superior and, while tumour response rates were reported to be higher for pemetrexed/cisplatin, significance tests were not reported.

The manufacturer also defined a more specific target population of patients with adenocarcinoma or large-cell carcinoma. In this target population, median overall survival was also significantly superior in the pemetrexed/cisplatin group (median 11.8 and 10.4 months, respectively, adjusted HR = 0.81; 95% CI 0.70 to 0.94). It should be noted that defining the target population in clinical practice would require more specific testing than is currently standard practice in the UK (as treatment is currently based on whether patients have squamous or non-squamous NSCLC). A study of preoperative histological classification of lung cancer[7] cited by the manufacturer suggests that diagnosing adenocarcinoma may be particularly challenging.

Because no other studies were found comparing pemetrexed/cisplatin with any other relevant comparator, additional efficacy evidence was presented from two phase III RCTs comparing gemcitabine/cisplatin with gemcitabine/carboplatin[8] and docetaxel/cisplatin[9] (*Table 2*). The manufacturer's submission reported from its indirect comparisons' analysis that median overall survival and PFS and tumour response rates were more favourable for pemetrexed/cisplatin than for any other comparator.

With the exception of nausea, pemetrexed/cisplatin appeared to be more tolerable than gemcitabine/cisplatin in terms of grade 3/4 toxicities. No safety issues related to pemetrexed/cisplatin arose beyond those already previously documented. No significant differences were reported for tolerability regarding the different cisplatin regimens (pemetrexed/cisplatin, gemcitabine/cisplatin and docetaxel/cisplatin). Gemcitabine/carboplatin reported less non-haematologic toxicity in terms of nausea and vomiting, and more haematoxicity in terms of an increased incidence of thrombocytopenia than gemcitabine/cisplatin.

Summary of submitted cost-effectiveness evidence

The manufacturer did not identify any published cost-effectiveness analyses of pemetrexed for the first-line treatment of patients with NSCLC. Therefore economic evidence was derived solely

TABLE I *Key efficacy findings in the JMDB trial[5] (intention-to-treat analysis)*

Patient group	Median (months) (95% CI) or response rate (%)		Adjusted HR (95% CI)	*p*-value (superiority)
	Pemetrexed/Cisplatin	Gemcitabine/Cisplatin		
Overall survival				
All randomised patients including squamous NSCLC (*n* = 1725)	10.3 (9.8 to 11.2)	10.3 (9.6 to 10.9)	0.94 (0.84 to 1.05)	*p* < 0.001[a] *p* = 0.259[b]
Patients with non-squamous histology (*n* = 1252)	11.0 (10.1 to 12.5)	10.1 (9.3 to 10.9)	0.84 (0.74 to 0.96)	*p* = 0.011[b]
Target patients: adenocarcinoma or large-cell carcinoma (*n* = 1000)	11.8 (10.4 to 13.2)	10.4 (9.6 to 11.2)	0.81 (0.70 to 0.94)	*p* = 0.005[b]
Patients with adenocarcinoma (*n* = 847)	12.6 (10.7 to 13.4)	10.9 (10.1 to 11.9)	0.84 (0.71 to 0.99)	*p* = 0.033[b]
Patients with large-cell carcinoma (*n* = 153)	10.4 (8.6 to 14.1)	6.7 (5.5 to 9.0)	0.67 (0.48 to 0.96)	*p* = 0.027[b]
Patients with NSCLC-NOS (*n* = 252)	8.6 (6.8 to 10.2)	9.2 (8.1 to 10.6)	1.08 (0.81 to 1.45)	*p* = 0.586[b]
Progression-free survival				
All randomised patients including squamous NSCLC (*n* = 1725)	4.8 (4.6 to 5.3)	5.1 (4.6 to 5.5)	1.04 (0.94 to 1.15)	Not reported
Patients with non-squamous histology (*n* = 1252)	5.3 (4.7 to 5.5)	5.0 (4.6 to 5.4)	0.95 (0.84 to 1.06)	Not reported
Target patients: adenocarcinoma or large-cell carcinoma (*n* = 1000)	5.3 (4.8 to 5.7)	4.7 (4.4 to 5.4)	0.90 (0.79 to 1.02)	Not reported
Patients with adenocarcinoma (*n* = 847)	5.5 (4.9 to 5.7)	5.0 (4.5 to 5.5)	0.90 (0.78 to 1.03)	Not reported
Patients with large-cell carcinoma (*n* = 153)	4.4 (3.0 to 5.8)	4.2 (3.5 to 4.7)	0.89 (0.65 to 1.24)	Not reported
Patients with NSCLC-NOS (*n* = 252)	4.5 (4.0 to 5.5)	5.6 (4.7 to 5.9)	1.28 (0.99 to 1.67)	Not reported
Tumour response rate				
All randomised patients including squamous NSCLC (*n* = 1725)	27.15	24.68	Not applicable	Not reported
Patients with non-squamous histology (*n* = 1252)	28.64	22.24	Not applicable	Not reported
Target patients: adenocarcinoma or large-cell carcinoma (*n* = 1000)	Not reported	Not reported	Not applicable	Not reported
Patients with adenocarcinoma (*n* = 847)	28.90	21.65	Not applicable	Not reported
Patients with large-cell carcinoma (*n* = 153)	27.63	27.27	Not applicable	Not reported
Patients with NSCLC-NOS (*n* = 252)	Not reported	Not reported	Not applicable	Not reported

CI, confidence interval; HR, hazard ratio; NSCLC-NOS, non-small cell lung cancer-not otherwise specified.
a Non-inferiority.
b Superiority.

TABLE 2 *Summary of the unadjusted trial results for all patients with squamous or non-squamous non-small cell lung cancer*

Study	Treatment arm	Median (range) OS (months)	Median (range) PFS (months)	Median response rate
JMDB trial	Pemetrexed/cisplatin (*n* = 862)	10.3 (9.8 to 11.2)	4.8 (4.6 to 5.3)	27%
(ITT population)[5]	Gemcitabine/cisplatin (*n* = 863)	10.3 (9.6 to 10.9)	5.1 (4.6 to 5.5)	25%
Zatloukal 2003[8]	Gemcitabine/cisplatin (*n* = 87)	8.8 (6.7 to 10.5)	5.9 (4.3 to 6.7)	41%
	Gemcitabine/carboplatin (*n* = 89)	8.0 (6.9 to 11.4)	4.8 (4.0 to 5.6)	29%
Schiller 2002[9]	Gemcitabine/cisplatin (*n* = 301)	8.1 (7.2 to 9.4)	4.2 (3.7 to 4.8)	22%
	Docetaxel/cisplatin (*n* = 304)	7.4 (6.6 to 8.8)	3.7 (2.9 to 4.2)	17%

ITT, intention to treat; OS, overall survival; PFS, progression-free survival

from a de novo economic model developed by the manufacturer.

A Markov model was developed to evaluate the cost-effectiveness of pemetrexed/cisplatin compared with gemcitabine/cisplatin, docetaxel/cisplatin and gemcitabine/carboplatin. The clinical data used in the economic evaluation were primarily generated from the JMDB trial,[5] with additional data from the two further trials used in the indirect comparisons analysis.[8,9] Although the economic evaluation was trial-based, the modelling component enabled the extrapolation of health effects beyond the period of 30 months of the trial, adopting a lifetime horizon (taken as 6 years) for the consideration of costs and benefits. The perspective of the model was that of the UK NHS and Personal Social Services.

The ERG identified a series of problems with this economic model. As a result, three different versions of the model were submitted to NICE and considered by the ERG. The ICERs estimated by this final version of the model ranged from £8056 to £33,065, depending on the comparator, the population and the application of a continuation rule.

Commentary on the robustness of submitted evidence

The JMDB trial was a randomised controlled head-to-head clinical trial that was well-designed, used robust randomisation techniques and was suitably powered to demonstrate the primary non-inferiority objective of the trial for the total population of patients with squamous and non-squamous NSCLC. Subgroup analyses of patients with non-squamous NSCLC and the manufacturer's own defined target population were conducted. The subgroups appeared to be clinically appropriate and confidence in the robustness of the findings was increased by the fact that these two subgroups were both pre-specified and relatively large in size.

Evidence from the indirect comparisons should be treated with caution as other comparators defined in the original scope and decision problem (vinorelbine and paclitaxel in combination with cisplatin or carboplatin and docetaxel/carboplatin) were excluded from the indirect comparisons analysis. In addition, the statistical approach employed to generate the findings is not considered to be the most optimal, as calculations were based on median survival times and individual trial arm level data from within trials were compared, thus ignoring the benefits of randomisation. Finally, data was only available for all patients with NSCLC (i.e. squamous or non-squamous NSCLC) in all but the JMDB trial. Thus, the HRs for each subgroup in the JMDB trial were used to estimate HRs for subgroups of patients given gemcitabine/carboplatin or docetaxel/cisplatin in the comparator trials. However, it was impossible to confirm from the data reported by the published papers of these trials whether the relative effects found in the JMDB trial would be consistent across subgroups for these patients.

Examination of the final version of the economic model submitted to NICE and considered by the ERG showed that, although minor modifications had been made to correct some of the problems identified by the ERG with earlier versions, the model still failed to adequately address the crucial problems at the heart of the model. These were beyond the remit of the ERG to address, and included:

- The chosen model design was not obviously suitable for modelling the disease and treatments described in the published clinical trial, imposing as it does serious constraints

on the possibility of representing the observed patterns of response to treatment and progression of disease.
- The implementation of the model was marked by examples of basic errors with marked consequences.
- There is little evidence of a systematic approach by the manufacturer to identifying and eliminating errors in the development of the model, or of attempting to replicate the prime source of information for the model, i.e. the JMDB trial itself.
- The restriction of comparators to those that are relatively high cost is likely to give a misleading impression of the true cost-effectiveness of pemetrexed regimen. Furthermore, gemcitabine will be off patent in the UK from March 2009 and may soon become available in generic form at a lower price. This was not considered in the manufacturer's model.
- The methods used for adjusting treatment effects (positive and negative) when a scenario is used with fewer treatment cycles than in the trial evidence are not obviously robust and defensible and may tend to overestimate the outcome benefits to be expected from use of pemetrexed/cisplatin, while underestimating the additional cost.

Thus, the ERG believed that the model requires extensive modification and redesign, subjected to thorough validation against the JMDB trial results. A full quality audit was also required as it is likely that further model inconsistencies may be present that have not yet been identified.

Conclusions

Given that the JMDB trial subgroup analyses were predefined and a large number of patients were included, confidence in the robustness of the subgroup results was increased. These findings provide important evidence warranting further exploration that pemetrexed/cisplatin may be superior to gemcitabine/cisplatin in terms of prolonging overall survival in patients with non-squamous NSCLC, particularly in those with adenocarcinoma or large-cell carcinoma.

Identifying patients in the manufacturer's target population requires more specific histological testing than is standard across all UK centres at present. In the JMDB trial, patients with adenocarcinoma represented half of all patients. The known proportion of patients with adenocarcinoma in the UK is not presented in the manufacturer's submission which reports only recent audit data suggesting a quarter of patients with NSCLC have adenocarcinoma.[4] Thus, the accurate diagnosis for this significant group of patients may be a particular challenge.

As no other regimens recommended by NICE were compared in head-to-head clinical trials with pemetrexed/cisplatin, the manufacturer undertook an indirect comparisons' analysis. This suggested pemetrexed/cisplatin to be the most efficacious regimen when also compared with gemcitabine/carboplatin, the most common regimen in the UK, or docetaxel/cisplatin. However, because not all relevant comparators were included in the indirect comparisons' analysis and because of the statistical method employed to undertake this analysis, these findings should be treated with caution.

The ERG found a number of substantial problems with the economic model. Most seriously, there were underlying structural problems and logic errors which had still not been addressed in the third version of the model submitted by the manufacturer. Consequently, the model was unable to replicate the response rates arising in the JMDB trial and it was impossible to provide reliable ICERs. Thus, even in its modified form, the economic model was not able to provide estimates upon which to base a decision regarding the cost-effectiveness of pemetrexed/cisplatin.

Summary of NICE guidance issued as a result of the STA

Given the above conclusions, NICE guidance was only issued after considering additional evidence subsequently submitted by the manufacturer (two models and an 'in-trial' analysis) and a critique of this evidence by the ERG. The very short time available to the ERG to consider the new evidence precluded a comprehensive assessment. The ERG believed that some issues of face validity had not been appropriately addressed and thus the ERG presented a simple exploratory analysis combining its own survival projections with key cost estimates obtained from individual patient data provided by the manufacturer from the JMDB trial. Compared to gemcitabine, this resulted in ICERs ranging from £17,162 to £30,142 per QALY, depending on the patient population, the maximum number of cycles of chemotherapy and whether a cycle based efficacy adjustment was applied or not. Thus the guidance issued by NICE in September

2009 states that pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic NSCLC only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma. People who are currently being treated with pemetrexed for NSCLC but who do not meet this criterion should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

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Topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of topotecan in combination with cisplatin for the treatment of recurrent and stage IVB carcinoma of the cervix, in accordance with the licensed indication, based upon the evidence submission from the manufacturer to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The outcomes measured were overall survival, progression-free survival, response rates, adverse effects of treatment, health-related quality of life (HRQoL) and quality-adjusted life-years (QALYs) gained. The manufacturer stated that topotecan plus cisplatin is the only combination regimen to date to have demonstrated a statistically significant survival advantage compared to cisplatin monotherapy in the licensed population. The clinical evidence came from three clinical trials comparing topotecan plus cisplatin with cisplatin monotherapy (GOG-0179), topotecan plus cisplatin with paclitaxel plus cisplatin (GOG-0169), and four cisplatin-based combination therapies: topotecan plus cisplatin, paclitaxel plus cisplatin, gemcitabine plus cisplatin, and vinorelbine plus cisplatin (GOG-0204). Results from GOG-0179 showed greater median overall survival with topotecan plus cisplatin than with cisplatin monotherapy: 9.4 months versus 6.5 months. Similar results were also reported for median progression-free survival. Response rates also showed an advantage with topotecan plus cisplatin compared with cisplatin monotherapy. The response rates in patients receiving cisplatin monotherapy were very low, but

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

the potential reasons for this were not discussed in the manufacturer's submission. Patients receiving topotecan plus cisplatin experienced a greater number of adverse events and the ERG was concerned with some of the assumptions related to HRQoL. In the base-case direct comparison, the incremental cost-effectiveness ratio (ICER) of topotecan plus cisplatin versus cisplatin monotherapy was £17,974 per QALY in the main licensed population, £10,928 per QALY in the cisplatin-naive population (including stage IVB patients) and £32,463 per QALY in sustained cisplatin-free interval patients. In response to the point for clarification raised by the ERG, the manufacturer submitted a revised indirect comparison incorporating HRQoL and a longer time horizon. Where the hazard ratio derived from GOG-0169 was employed, paclitaxel plus cisplatin was dominated by topotecan plus cisplatin, but, where the hazard ratio from GOG-0204 was adopted, paclitaxel plus cisplatin was found to have an ICER of £13,260 per QALY versus topotecan plus cisplatin. At present there is a paucity of evidence available on the clinical effects of topotecan plus cisplatin and the effects of palliative treatment in general for women with advanced and recurrent carcinoma of the cervix. Further trials, or the implementation of registries, are required to establish the efficacy and safety of topotecan plus cisplatin. The guidance issued by NICE on 28 October 2009 as a result of the STA states that topotecan in combination with cisplatin is recommended as a treatment option for women with recurrent or stage IVB cervical cancer, only if they have not previously received cisplatin. Women who have previously received cisplatin and are currently being treated with topotecan in combination with cisplatin for the treatment of cervical cancer should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled 'Topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix'.[2]

Description of the underlying health problem

Cervical cancer is the second most common malignant neoplastic disease among women worldwide, with a standardised incidence rate of 8.4 per 100,000 females in the UK.

Most patients in the UK are diagnosed with early disease and surgery may be curative. In more advanced non-metastatic disease, radiotherapy may be administered as a potentially curative treatment. For recurrent or metastatic disease, treatment is, in most cases, palliative. Stage IVB cervical cancer is the most advanced form of the disease, in which the cancer has spread to more distant organs.[3] The median survival for stage IVB cervical cancer is very low, at approximately 9–10 months, with 30% survival at 1 year and 2–5% survival at 2 years (Paul Symonds, personal communication to GlaxoSmithKline UK, 2009).

Cisplatin has long been considered the most effective platinum-based chemotherapy for the treatment of recurrent or advanced cervical cancer,[4–8] either alone or in combination with other chemotherapies. Although the use of combination therapies, particularly paclitaxel in combination with either cisplatin or carboplatin or topotecan in combination with cisplatin, has increased, only topotecan in combination with cisplatin has been explicitly licensed for this indication; recommended for restricted use within NHS Scotland and NHS Wales for the treatment of cisplatin-naive patients only.

Scope of the evidence review group report

The ERG report appraised the clinical effectiveness and cost-effectiveness of topotecan in combination with cisplatin (within its licensed indications – see *Figure 1*) for the treatment of recurrent and

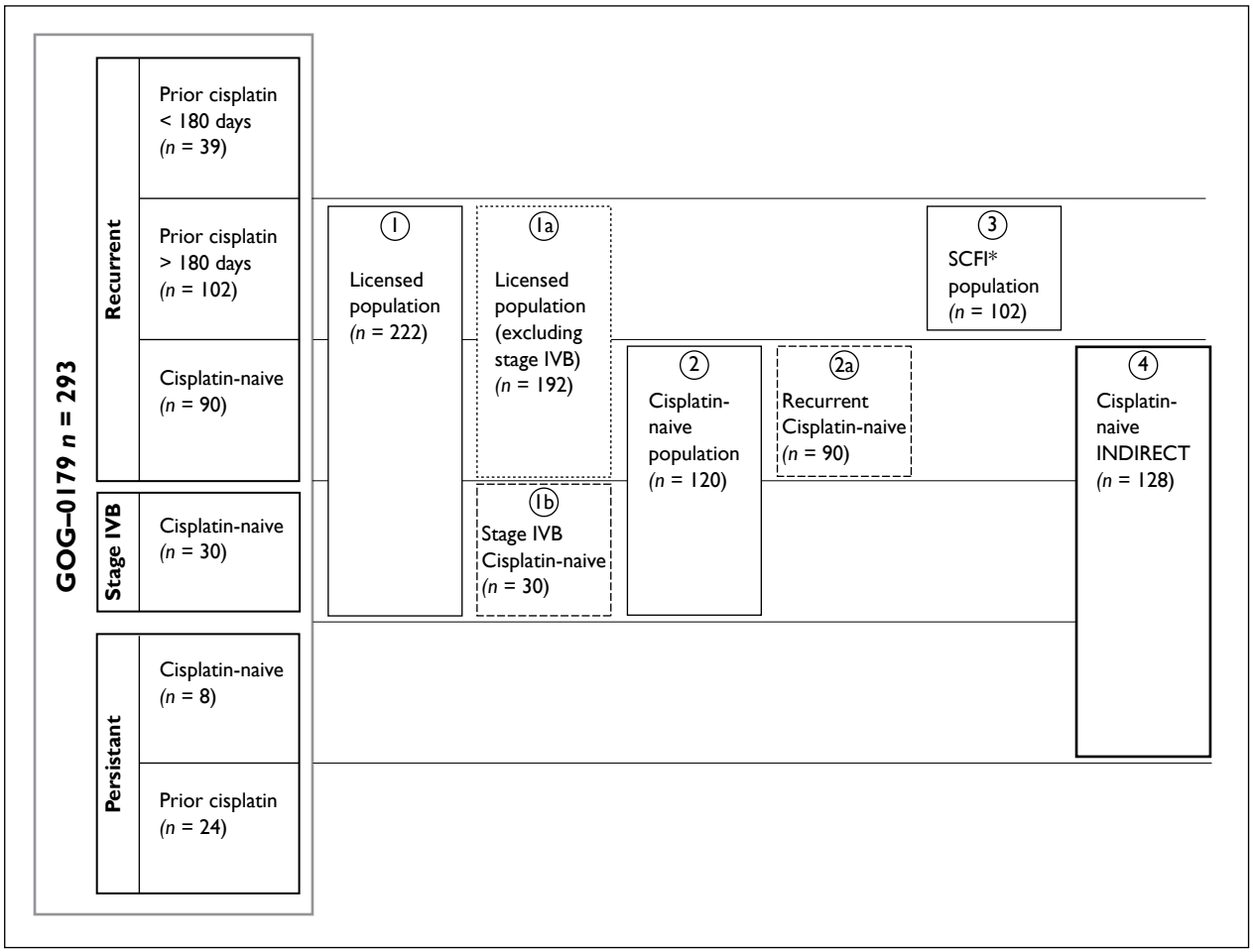

FIGURE 1 *Schematic of study population and subgroups analysed in the manufacturer's submission 1. Licensed population, consisting of: 1a. licensed population excluding IVB patients; 1b. stage IVB patients (by definition cisplatin-naive, as they are newly presenting). 2. Cisplatin-naive population, consisting of: 2a. cisplatin-naive recurrent population excluding stage IVB patients; b. stage IVB patients. 3. Patients with a sustained cisplatin-free interval (SCFI; prior cisplatin > 180 days). 4. A further subgroup was analysed specifically for an indirect comparison of topotecan plus cisplatin versus paclitaxel plus cisplatin. The cisplatin-naive (for indirect analysis) population contains all cisplatin-naive patients in GOG-0179 for comparison with patients in a second study (GOG-0169).*

stage IVB carcinoma of the cervix. The outcomes measured were overall survival, progression-free survival, response rates, adverse effects of treatment, health-related quality of life (HRQoL) and quality-adjusted life-years (QALYs). The manufacturer stated that topotecan plus cisplatin is the only combination regimen to date to have demonstrated a statistically significant survival advantage compared to cisplatin monotherapy in the licensed population.

The manufacturer recommended that topotecan is administered in combination with cisplatin; 0.75 mg/m^2 per day of topotecan, administered as 30-minute intravenous infusion on days 1, 2 and 3, with one dose of 50 mg/m^2 per day of cisplatin administered on day 1 following topotecan. Treatment is repeated every 21 days for six cycles or until disease progression.

The manufacturer's submission focused on direct evidence from a phase III randomised controlled clinical trial (GOG-0179) comparing topotecan plus cisplatin with cisplatin monotherapy, and indirect clinical evidence from a phase III trial (GOG-0169) comparing topotecan plus cisplatin with paclitaxel plus cisplatin. A second direct comparison trial (GOG-0204) was mentioned, which compared four cisplatin-based combination therapies: topotecan plus cisplatin, paclitaxel plus cisplatin, gemcitabine plus cisplatin, and vinorelbine plus cisplatin. GOG-0179 included patients outside the licensed population, and the manufacturer undertook subgroup analyses to reflect the different subgroups within the licensed population, namely: licensed population including or excluding stage IVB patients, cisplatin-naive patients, and patients with sustained cisplatin-free interval (SCFI) longer than 180 days.

The manufacturer submitted two separate cost-effectiveness comparisons: a trial-based direct comparison between topotecan plus cisplatin and cisplatin monotherapy based on patient-level data from GOG-0179 and evaluated using the statistical package SAS®, considered by the manufacturer to be the primary analysis within their submission; and a Microsoft EXCEL model-based indirect comparison between topotecan plus cisplatin and paclitaxel plus cisplatin, considered to be a secondary analysis.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's submission to NICE as part of the STA process.

The ERG replicated the manufacturer's amended search strategy, and attempted to reproduce its patient-level analysis. The ERG was unable to comprehensively validate the patient-level analysis because of the manufacturer's failure to provide a fully executable SAS®-based model, and instead focused on the EXCEL-based analysis. The ERG made a number of revisions to the manufacturer's model, including altering the assumptions related to utility values, the costs of administering treatment, and the number of vials of topotecan utilised.

Results

Summary of submitted clinical evidence

The GOG-0179 trial reported greater median overall survival with topotecan plus cisplatin than with cisplatin monotherapy: 9.4 months versus 6.5 months. The unadjusted hazard ratio (HR) of 0.76 [95% confidence interval (CI) 0.59 to 0.98, $p = 0.033$] translates into a 24% reduction in mortality with combination therapy. Similar results were also reported for median progression-free survival in GOG-0179: 4.6 months (topotecan plus cisplatin) versus 2.9 months (cisplatin), HR 0.76 (95% CI 0.60 to 0.97, $p = 0.027$).

Response rates also showed an advantage with topotecan plus cisplatin (24%) compared with cisplatin monotherapy (12%) ($p = 0.0073$). The response rates in patients receiving cisplatin monotherapy were very low, but the potential reasons for this were not discussed in the manufacturer's submission.

The safety profile of topotecan plus cisplatin was reported to be predictable and manageable, and there was reportedly no evidence to suggest that HRQoL was significantly reduced in patients receiving combination therapy. However, patients receiving topotecan plus cisplatin experienced a greater number of adverse events and the ERG is concerned with some of the assumptions related to HRQoL.

Subgroup analyses were undertaken and showed favourable results towards topotecan plus cisplatin (*Table 1*), but the results should be interpreted with caution as the number of patients in quite a few of the subgroups was small and some of the analyses were performed post hoc.

For overall survival, the indirect comparison between GOG-0179 and GOG-0169 showed non-significant results in favour of topotecan plus cisplatin compared with paclitaxel plus cisplatin: HR 0.72 (95% CI 0.46 to 1.15).

The GOG-0204 trial was closed early as all experimental arms were unlikely to demonstrate a significant advantage compared with paclitaxel plus cisplatin. In response to a point for clarification raised by the ERG, the manufacturer conducted direct and indirect comparisons including data from GOG-0204. The direct comparison favoured paclitaxel plus cisplatin (HR 1.27, 95% CI 0.96 to 1.69), while the pooled data using direct and indirect evidence from GOG-0169, GOG-0179 and GOG-0204 favoured topotecan plus cisplatin (HR 0.98, 95% CI 0.73 to 1.23), but neither result was statistically significant.

Summary of submitted cost-effectiveness evidence

In the base-case direct comparison, the incremental cost-effectiveness ratio (ICER) of topotecan plus cisplatin versus cisplatin monotherapy was £17,974 per QALY in the main licensed population, £10,928 per QALY in the cisplatin-naive population (including stage IVB patients) and £32,463 per QALY in SCFI patients.

Results for the indirect comparison were presented only for a cisplatin-naive population, and outcomes were expressed in terms of life-years gained only. In the base-case indirect comparison, paclitaxel plus cisplatin was dominated by topotecan plus

TABLE 1 *Overall survival in main direct comparison and indirect comparison of GOG-0179 versus GOG-0169*

	Licence population		**Cisplatin-naive population**		**Sustained cisplatin-free interval population**		**Cisplatin-naive (for indirect analysis) population**	
	Cisplatin (*n* = 115)	**Topotecan plus cisplatin (*n* = 107)**	**Cisplatin (*n* = 62)**	**Topotecan plus cisplatin (*n* = 58)**	**Cisplatin (*n* = 53)**	**Topotecan plus cisplatin (*n* = 49)**	**Cisplatin (*n* = 64)**	**Topotecan plus cisplatin (*n* = 64)**
Overall survival time (months)								
Mean	9.9	12.9	11.1	15.1	7.9	9.5	11.1	14.4
Median	7.3	11.9	8.5	14.5	6.3	9.9	8.5	12.5
95% CI for median survival time	6.0 to 9.5	9.4 to 13.7	6.4 to 11.1	11.5 to 17.5	4.9 to 9.5	7.0 to 12.6	6.5 to 11.3	9.2 to 17.4
Log rank *p*-value	0.0041		0.0098		0.1912		0.0206	
Hazard ratio (95% CI)	0.652 (0.485 to 0.875)		0.587 (0.389 to 0.884)		0.75 (0.492 to 1.155)		0.633 (0.428 to 0.935)	
Minimum	0.3	0.4	1.3	0.4	0.3	0.6	1.3	0.4
Maximum	39.0	34.4	34.0	31.0	17.2	27.1	38.9	34.4
Observed events	100 (87.0%)	81 (75.7%)	55 (89.0%)	40 (69.0%)	45 (84.9%)	41 (83.7%)	57(89.1%)	46 (71.9%)
Censored events	15 (13.0%)	26 (24.3%)	7 (11.0%)	18 (31.0%)	8 (15.1%)	8 (16.3%)	7 (10.9%)	18 (28.1%)

CI, confidence interval.

cisplatin, which in turn had a cost per life-year gained of £19,964 versus cisplatin monotherapy; where the HR used to calculate overall survival with paclitaxel plus cisplatin was taken from GOG-0204 (rather than derived from GOG-0169, as in the base case), paclitaxel plus cisplatin was found to have a cost per life-year gained of £982 versus topotecan plus cisplatin.

In response to the point for clarification raised by the ERG, the manufacturer submitted a revised indirect comparison incorporating HRQoL and a longer time horizon. Similar to the previous analysis, where the HR derived from GOG-0169 was employed, paclitaxel plus cisplatin was dominated by topotecan plus cisplatin, but, where the HR from GOG-0204 was adopted, paclitaxel plus cisplatin was found to have an ICER of £13,260 per QALY versus topotecan plus cisplatin.

The ERG made a number of revisions to this model to explore alternative assumptions to those employed by the manufacturer. Where the number of vials used was assumed to be minimised (or maximised) because of alternative assumptions about possible wastage, the ERG found topotecan plus cisplatin to have an ICER versus cisplatin monotherapy of £26,778 (£34,327) per QALY in the cisplatin-naive patient population and £58,872 (£73,833) per QALY in the full licensed population from GOG-0179. These ICERs were considered to be potentially conservative as no account was taken of the potential impact of dose reductions because of adverse events on the acquisition costs of the interventions. In order to consider the potential impact of dose reduction, the ERG employed a 'hybrid' approach combining estimates from the manufacturer's patient level and the ERG's revised model analyses. Where wastage of vials was assumed to be minimised, the ICER of topotecan plus cisplatin versus cisplatin monotherapy fell to £19,815 in the cisplatin-naive population and £53,868 in the licensed population. While assuming maximum wastage of topotecan, the ICER of topotecan plus cisplatin versus cisplatin monotherapy rose to £27,362 in the cisplatin-naive population and £68,826 in the licensed population.

Topotecan plus cisplatin, paclitaxel plus cisplatin, and cisplatin monotherapy were compared in a fully incremental analysis; topotecan plus cisplatin was found to extendedly dominate paclitaxel plus cisplatin in most scenarios where the GOG-0169 HR was adopted, but was dominated by paclitaxel plus cisplatin in all scenarios where the GOG-0204 HR was adopted.

Commentary on the robustness of submitted evidence

The main strength of the direct comparison was the potential for the results to have a very high internal validity due to the use of patient-level data from a recent, relevant and seemingly well-conducted trial (GOG-0179). This was considered to be a potential strength only because the manufacturer did not provide in a timely manner the necessary code and data sets for the ERG to validate fully the programming of this comparison.

A further strength of the direct comparison was the presentation of results for the main licensed population and a series of subgroups within that, highlighting the population gaining most benefit from treatment, and allowing variability in the cost-effectiveness estimates to be considered. However, the limitations of subgroup analyses should be borne in mind.

The main strengths of the indirect comparison were the relatively high degree of transparency within the submitted EXCEL model and the high degree of consistency between the electronic model and the submitted report.

The lack of transparency regarding the literature search and rationale for exclusion of potentially relevant trials was a limitation, and this was not satisfactorily addressed in the manufacturer's response document.

For the direct comparison, the results from GOG-0204 were not formally included in the submission. For the indirect comparison, it was not clear that a comprehensive network of evidence was investigated. Potentially relevant studies were excluded by the manufacturer on the basis that the comparators were not licensed for use in this population; however, the comparator selected for the indirect comparison (i.e. paclitaxel plus cisplatin) was not licensed – this contradiction was not satisfactorily explained.

The analyses submitted for the cost-effectiveness evidence were incomplete and required considerable clarification. The lack of transparency regarding the programming of the direct comparison was a significant weakness; the coding was incompletely submitted in a non-executable form and with evidence of errors. There were also concerns surrounding the methods used, which may potentially overestimate the incremental QALY gains associated with topotecan plus cisplatin. The primary analysis based on GOG-

0179 suffers from a lack of external validity as it makes no comparison between topotecan plus cisplatin and other relevant treatment comparators other than cisplatin monotherapy.

The indirect comparison initially submitted neglected to consider HRQoL, reporting life-years gained instead of QALYs, although this was rectified following a request from the ERG. The results were only presented for a single population (cisplatin-naive patients, including patients with persistent disease) and the model was not probabilistic, so that uncertainty surrounding the cost-effectiveness results could not be appropriately quantified.

Both comparisons also failed to properly justify a number of assumptions over costs, including the cost of administering treatments, the number of vials of topotecan needed per cycle and the costs of adverse events, all of these were considered for revision by the ERG.

Conclusions

At present there is a paucity of evidence available on the clinical effects of topotecan plus cisplatin and the effects of palliative treatment in general (including various off-license drugs regularly used in UK clinical practice) for women with advanced and recurrent carcinoma of the cervix.

Further trials, or the implementation of registries, are required to establish the efficacy and safety of topotecan plus cisplatin. Such research should assess all aspects of quality of life, including the impact of treatment toxicities, scheduling and convenience to the patient. It is also important to untangle further which patients will benefit the most from treatments and the factors that potentially moderate these benefits. Further research to provide appropriate utility values for patients with cervical cancer, reflecting both the stage and course of disease (e.g. impact of disease progression) as well as the specific impact of individual therapies, would be beneficial.

Key issues

For the direct comparison submitted by the manufacturer, there was a paucity of clinical effectiveness evidence available, and the manufacturer made limited use of the results from GOG-0204. The ERG questioned the handling and reporting of quality of life data and whether the results were representative of the whole patient experience. For the economic evaluation, key issues relate to the appropriateness of the mapped utility values adopted, the reasonableness of the costing assumptions, the external validity of an analysis with only a single comparator, and (perhaps most importantly) the validity and transparency of the SAS analysis.

In terms of the indirect comparison, a potentially relevant network of indirect evidence has not been fully explored, although the ERG acknowledges that the quality of such evidence would be limited. The inclusion of direct evidence from GOG-0204 (further results will shortly be available) and evidence from a forthcoming Cochrane Review would increase the network of evidence and enable further assessment of the clinical effectiveness and cost-effectiveness of treatments used in current UK practice.

Key issues in relation to the indirect comparison were the appropriateness of the utility values, the reasonableness of the costing assumptions, and the appropriate source of the HR used to estimate survival for paclitaxel plus cisplatin – deriving this HR from GOG-0169 favours topotecan plus cisplatin, while deriving it from GOG-0204 favours paclitaxel plus cisplatin.

Areas of uncertainty

There is uncertainty surrounding the population(s) that will benefit most from treatment with topotecan plus cisplatin. The number of patients who have received chemoradiation is likely to increase in the future, thus the number of cisplatin-naive patients will diminish. This raises the question of the applicability of the results to current and future clinical practice.

The economic submissions are subject to significant uncertainty over the utility values and cost assumptions adopted by the manufacturer, and this uncertainty feeds into the results of the subsequent analyses.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the final appraisal consultation document issued by NICE on 28 October 2009 states that:

Topotecan in combination with cisplatin, is recommended as a treatment option for women with recurrent or stage IVB cervical cancer only if they have not previously received cisplatin.

Women who have previously received cisplatin and are currently being treated with topotecan in combination with cisplatin for the treatment of cervical cancer should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

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Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of trabectedin for the treatment of advanced metastatic soft tissue sarcoma, in accordance with the licensed indication, based on the evidence submission from the manufacturer to NICE as part of the single technology appraisal (STA) process. The outcomes stated in the manufacturer's definition of the decision problem were overall survival (OS), progression-free survival (PFS), response rates, adverse effects of treatment, health-related quality of life, and cost per quality-adjusted life-year (QALY) gained. The clinical evidence was derived from one randomised controlled trial (RCT), in which the licensed dose of trabectedin was compared with a different dose of trabectedin, and three phase II studies. In the RCT, the median OS was 13.9 months for the licensed dose of trabectedin, which was not significantly different from that for the comparator dose of trabectedin, which was 11.8 months. From the phase II uncontrolled trials, median OS was reported as 9.2 or 12.8 months. The RCT reported significantly superior PFS for the licensed dose of trabectedin (median 3.3 months) over the comparator trabectedin dose (median 2.3 months). One phase II uncontrolled trial reported median PFS as 1.9 months in the licensed dose of trabectedin. The RCT reported PFS rates at 6 months were 35.5% for the licensed dose of trabectedin, and 27.5% for the comparator dose of trabectedin. From the phase II uncontrolled trials, PFS rates at 6 months were 24.4% or 29%. For the RCT, deaths attributed to trabectedin occurred in 3.1% of the licensed dose, and 2.3% of the comparator group. The most common severe adverse events were neutropenia,

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although with a low rate of febrile neutropenia, thrombocytopenia, and aspartate aminotransferase and alanine aminotransferase elevation, although these were reported to be non-cumulative and reversible. Following dialogue iterations with the ERG team, the manufacturer revised the model twice. However, despite revisions, errors/inconsistencies were found in the latest version of the model and were corrected by the ERG (only for the base case). In the latest manufacturer's submission, the cost per QALY gained of trabectedin compared with best supportive care (BSC) was estimated to be £56,985 for the base case using effectiveness from the STS (Soft Tissue Sarcomas)-201 trial for trabectedin and a pool analysis of the European Organisation for Research and Treatment of Cancer data set for BSC. This analysis was constrained to patients with L–sarcomas only. When the joint uncertainty between parameters was considered, the cost-effectiveness acceptability curve showed that trabectedin has a very low probability of being cost-effective at a threshold of £30,000 per QALY gained compared with BSC for any scenario. The guidance has yet to be issued by NICE.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled 'Trabectedin for the treatment of advanced metastatic soft tissue sarcoma: a single technology appraisal'.[2]

Description of the underlying health problem

Trabectedin is licensed for patients with advanced metastatic soft tissue sarcoma having failed anthracycline and ifosfamide or for whom these agents are unsuitable.

Soft tissue sarcomas (STS) constitute a heterogeneous group of malignancies arising in soft tissues of the body including muscle, fat and blood vessels. The most frequent types are leiomyosarcoma and liposarcoma, which account for approximately 40–50% of all STS. There is an estimated annual incidence of 2000 STS in England and Wales (including gastrointestinal stromal tumour, which is excluded from this report).[3] Approximately 50% of patients present with, or develop, advanced or metastatic disease.

Scope of the evidence review group report

The principal research question was to appraise the clinical effectiveness and cost-effectiveness of trabectedin within its licensed indication for the treatment of advanced metastatic soft tissue sarcoma. Trabectedin is licensed for use in patients with advanced metastatic STS who have failed anthracycline and ifosfamide, either in combination as first-line therapy or in sequence as first- and second-line therapy. No other chemotherapies are currently licensed in the UK for STS at this point in therapy. The comparator was best supportive care. Relevant outcomes were overall survival (OS), progression-free survival (PFS), response rates (including stabilisation), adverse effects of treatment, health-related quality of life, and cost per quality-adjusted life-year (QALY) gained.

The manufacturer submitted a state transition model developed in EXCEL, with individuals followed up to 5 years (until death). The base case in the manufacturer's submission assumed that patients treated with trabectedin enter the model in the progression-free state (PFS) while patients in the best supportive care (BSC) arm enter the model in the progressive disease (PD) state. The base case was limited to patients with leukaemia (L)-sarcomas. Additional analyses requested by the ERG adjust the base case to account for differences in the starting health state. In addition, the manufacturer presented three additional scenarios. The first scenario used the pooled effectiveness of trabectedin from three

uncontrolled phase II studies which was not limited to patients with L-sarcomas. In the second and third scenarios, the manufacturer assumed that a proportion of patients in BSC would receive further chemotherapies (either 33% or 100% of patients).

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The ERG repeated, although could not replicate exactly, the searches undertaken by the manufacturer. The ERG does not believe that any relevant clinical or cost-effectiveness studies have been missed.

Following dialogue iterations with the ERG team, the manufacturer revised the model twice. However, despite revisions, errors/inconsistencies were found in the latest version of the model and were corrected by the ERG (only for the base case). These errors were identified by a review of the model structure and internal logic and the responsiveness of the results to changes in parameters values.

Results

Summary of submitted clinical evidence

Owing to the lack of any comparative trials comparing trabectedin and BSC, the main evidence in the manufacturer's submission was derived from one phase II randomised trial, in which the licensed dose of trabectedin was compared with a different dose of trabectedin. In the randomised controlled trial (RCT), median OS was 13.9 months [95% confidence interval (CI) 12.5 to 18.6] for the licensed dose of trabectedin (24-hour regimen every 3 weeks), which was not significantly different ($p = 0.1985$) from that for the comparator dose of trabectedin (weekly 3-hour regimen) which was 11.8 months (95% CI 9.9 to 14.9). From the phase II uncontrolled trials, median OS was reported as 9.2[4] or 12.8 months.[5] Historical control data, presented by the manufacturer's submission as equivalent to BSC, had median OS of 5.9–6.6 months.[6] The RCT reported significantly ($p = 0.04$) superior PFS for the licensed dose of trabectedin (median 3.3 months) over the comparator trabectedin dose (median 2.3 months). One phase II uncontrolled trial reported median PFS as 1.9 months in the licensed dose of trabectedin.[5] The RCT reported PFS rates at 6 months were 35.5% (95% CI 27.1 to 43.9) for the licensed dose of trabectedin, and 27.5% (95% CI 19.4 to 35.5) for the comparator dose of trabectedin. From the phase II uncontrolled trials, PFS rates at 6 months were 24.4%[7] or 29%.[4] Historical control data, presented by the manufacturer's submission as equivalent to BSC, reported PFS rates at 6 months of 14% for patients treated with ifosfamide or dacarbazine after failure of anthracycline or 8% for patients from pooled studies on 'inactive' regimens.

For the RCT, deaths attributed to trabectedin occurred in 3.1% of the licensed dose, and 2.3% of the comparator group. Safety data for the licensed dose of trabectedin from the included RCT and three phase II studies' reported rates of grade 3/4 haematological events varied: neutropenia 34–61%; febrile neutropenia 0.8–7.0%; thrombocytopenia 12–19%; and anaemia 8–22%. Across the four included studies, rates of grade 3/4 non-haematological events varied: aspartate aminotransferase (AST) elevation 26–48%; alanine aminotransferase (ALT) elevation 20–57%; nausea 4–7%; vomiting 2–9%; and asthenia/fatigue 0–15%.

Summary of submitted cost-effectiveness evidence

In the latest manufacturer's submission, the cost per QALY gained of trabectedin compared with BSC was estimated to be £56,985 for the base case using effectiveness from the STS-201 trial for trabectedin and a pool analysis of the European Organisation for Research and Treatment of Cancer data set for BSC. This analysis was constrained to patients with L-sarcomas only.

The ERG was concerned that patients in the trabectedin arm began in a different health state than those in the BSC arm, and that those on trabectedin were assumed to have a higher starting utility. An exploratory analysis by the manufacturers in amending this assumption raised the cost per QALY gained for trabectedin compared with BSC to £61,064.

In addition to the base case, the manufacturer presented three additional scenarios. The first used the pooled effectiveness of trabectedin from three uncontrolled phase II studies which was not limited to patients with L-sarcomas; this produced

a cost per QALY gained of £50,017. In the second and third scenarios, the manufacturer assumed that a proportion of patients in BSC would receive further chemotherapies (either 33% or 100% of patients). The cost per QALY gained for these two scenarios was estimated to be £62,044 and £80,279 respectively. None of these three scenarios amended the model to take into consideration the different starting utilities between the trabectedin and BSC arms.

When the joint uncertainty between parameters was considered, the cost-effectiveness acceptability curve showed that trabectedin has a very low probability of being cost-effective at a threshold of £30,000 per QALY gained compared with BSC for any scenario.

Commentary on the robustness of submitted evidence

Limited data were available. The main evidence in the manufacturer's submission was derived from one phase II randomised trial, in which the licensed dose of trabectedin was compared with a different dose of trabectedin. The population in this trial was limited to L-sarcomas. Supplementary data were presented from three uncontrolled phase II trials of the licensed dose of trabectedin. Owing to the lack of a relevant comparator group in the included trabectedin trials, the manufacturer's submission reported data from a database of other studies that are suggested to equate to BSC. The manufacturer acknowledged there were limitations with these controls, which, in addition to being historical comparisons, were from studies with populations comprising types of STS not restricted to L-sarcomas, and Eastern Cooperative Oncology Group (ECOG) performance status not confined to 0–1. This would bias against these controls for effectiveness data. There were some data available for ifosfamide studies restricted to a population similar to the trabectedin trials. Data presented in the clinical effectiveness section did not have OS calculated appropriately in all cases, and for OS and PFS data, further chemotherapy was given to some patients, thus making treatment not just BSC.

Iterations were needed to amend errors found by the ERG, which included errors in the treatment cost and additional analyses to explore the likely impact of the different starting health states. The ERG, however, still had concerns regarding the structure of the model and its ability to capture the cost-effectiveness of trabectedin for adults with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide. Firstly, the ERG had concerns about the potential non-comparability between patients included in studies to derive the effectiveness for trabectedin and BSC despite the adjustment of the Weibull curves for age, gender, histopathology and World Health Organization performance score. Secondly, the base case focuses on patients with L-sarcomas only and may not be generalisable to patients with other forms of STS. Thirdly, despite the attempt to adjust for the differences in the starting health state, uncertainties still exist on the likely impact of such model structure. Fourthly, while no utility values are available for patients with STS, there are uncertainties about the appropriateness of using utility values for patients with lung cancer as a proxy for STS. Fifthly, the probabilistic sensitivity analyses did not capture all the uncertainty within the decision, for example, the model assumed no correlation between time to disease progression and OS, nor correlation between the utility estimates for health states or the number of 1-mg and 0.25-mg vials used. Finally, the proportion of patients treated did not vary according to the proportion of patients in PFS. It is unclear how incorporating these correlations would change the mean cost per QALY, although it is likely that the range in the results generated from the PSA would increase.

Conclusions

Although the ERG does not believe relevant studies of trabectedin have been missed, the manufacturer's submission contained only one phase II RCT comparing trabectedin at the licensed dose compared with trabectedin at a lower dose, with population L-sarcoma patients with ECOG performance status of 0–1. Further evidence was presented from phase II uncontrolled trials of trabectedin. Data for BSC were taken from historical controls from a database of other studies. The manufacturer acknowledges that there are limitations with these controls. There was a rate of deaths due to toxicity of 3.1% for the licensed dose of trabectedin in the RCT. The most common severe adverse events were neutropenia, although with a low rate of febrile neutropenia, thrombocytopenia, and AST and ALT elevation, although these were reported to be non-cumulative and reversible.

Despite iterations with the ERG, the ability of the model to capture the cost-effectiveness of trabectedin for adults with advanced STS after

failure of anthracyclines and ifosfamide is unclear. Uncertainties exist about the potential non-comparability between patients in the trabectedin and BSC arm, the likely impact of the differences in the starting health state and the use of utility values for lung cancer as a proxy for STS patients. It is also unclear how results for the base case would be generalisable to patients with other forms of STS.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance issued by NICE in February 2010[8] states that:

Trabectedin is recommended as a treatment option for people with advanced soft tissue sarcoma if: treatment with anthracyclines and ifosfamide has failed, or they are intolerant of **or** have contraindications for treatment with anthracyclines and ifosfamide; **and** the acquisition cost of trabectedin for treatment needed after the fifth cycle is met by the manufacturer. This last clause reflects the patient access scheme submitted by the manufacturer, with the manufacturer offering the acquisition cost of the drug after the fifth cycle, this led to a considerable reduction of the ICER, from £61,000 to about £34,000.

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Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of azacitidine (aza) compared with conventional care regimes (CCR) for higher risk patients with myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML), based on the evidence submission from the manufacturer to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The patient outcomes governing relative effectiveness and cost-effectiveness were defined as overall survival, time to progression (TTP) to AML, adverse events and health-related quality of life (HRQoL). The clinical evidence was derived from an open-label randomised controlled trial referred to as study AZA-001. It compared aza with CCR in 358 patients with higher risk MDS, CMML and AML 20–30% blasts. The outcomes reported in AZA-001 included overall survival, TTP to AML and adverse events. No HRQoL results were reported; however, outcomes likely to impact on HRQoL were provided. The results showed that: the median overall survival was 24.5 months on aza, compared with 15.0 months in the CCR group ($p = 0.0001$); the response rates were low (complete remission 17% aza versus 8% CCR); the median time to transformation to AML was greater in the aza group (17.8 versus 11.5 months; $p < 0.0001$); and of patients who were red blood cell (RBC) transfusion-dependent at baseline, 45% of those on aza became RBC transfusion-independent

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

during the treatment period, compared with 11.8% in the CCR group ($p < 0.0001$). The ERG reran the submission's search strategies after some modifications incorporating minor improvements. The ERG analysed the submitted economic model (model 1) and identified a number of inconsistencies and errors within the model. The manufacturer submitted a revised model for analysis by the ERG. Using the issues identified in the earlier analysis, the ERG conducted those repairs to the revised model that were feasible within time constraints. The ERG ran this version in probabilistic sensitivity analyses to generate cost-effectiveness acceptability frontiers. The results of these exploratory analyses indicated that: for standard-dose chemotherapy (SDC)-treated patients, of six treatment options available, best supportive care (BSC) was likely the most cost-effective option up to a threshold of £51,000/quality-adjusted life-year (QALY) [beyond £51,000/QALY, aza + low-dose chemotherapy (LDC) became cost-effective]; for LDC-treated patients, of four options available, BSC was again the most cost-effective option up to a willingness-to-pay threshold of £51,000/QALY (aza + LDC became cost-effective after £51,000/QALY); for BSC-treated patients, aza + BSC became cost-effective relative to BSC at a threshold of about £52,000/QALY. The ERG considers these results exploratory and considers that they should be viewed with caution. The AZA-001 study showed that, compared with CCR, those MDS patients receiving aza had prolonged median survival, had delayed progression to AML, had reduced dependence on transfusions and had a small improvement in response rate. Given the general paucity of economic modelling work in MDS and the limitations of the submitted industry model there is an evident need for an independent cost-effectiveness analysis of aza in MDS. At the time of writing, the guidance appraisal consultation document issued by NICE on 4 March 2010 states that azacitidine is not recommended as a treatment option for people not eligible for haemopoietic stem cell transplantation with the the following conditions: intermediate-2 and high-risk MDS according to the International Prognostic Scoring System, CMML with 10-29% marrow blasts without myeloproliferative disorder, or with AML with 20-30% blasts and multilineage dysplasia, according to World Health Organization classification.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report[2] for the STA entitled 'Azacitidine (aza) for the treatment of myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML)'.

Description of the underlying health problem

The following is taken from the NICE scope for this STA.

The MDSs are a diverse group of haematological disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. Red blood cells (RBCs), white blood cells and platelets may all be affected by MDS, resulting in life threatening disease, with anaemia and increased risk of bleeding and infections. MDS affects patients' quality of life owing to debilitating symptoms such as fatigue and dyspnoea, treatment regimens involving hospitalisation with intravenous drug infusions and blood transfusions, and complications such as severe infections.

Myelodysplastic syndromes are subdivided using the International Prognostic Scoring System (IPSS), and the French–American–British (FAB) and World Health Organization (WHO) classification systems. Based on the proportion of leukaemic cells (or 'blasts'), the presence of chromosome 7 abnormalities and the presence of blood cytopenia, the IPSS classifies outcome as either low-risk, intermediate-I risk, intermediate-II risk or high-risk. It is estimated that higher risk MDS subgroups

(intermediate-II and high-risk) form approximately 22% and 7% of the MDS population, respectively. The FAB system divides MDS into five subgroups, including CMML, which is characterised by high numbers of white blood cells in the blood and bone marrow. The WHO system, which divides MDS into eight subgroups, does not class CMML as a type of MDS, but rather within a new category of myelodysplastic–myeloproliferative overlap syndromes.

Myelodysplastic syndromes are associated with an increased risk of transformation to AML. AML is a progressive form of MDS characterised by rapidly growing cancer of the blood and bone marrow. Around 30% of patients with MDS will progress to AML.

There were 1993 people newly diagnosed with MDS in England in 2004, with over 90% of patients aged over 60 years at the time of diagnosis. Median survival of patients with MDS is around 20 months, but can be less than 6 months for high-risk subgroups. Establishing the presence of chromosome 7 abnormalities is important as this is associated with rapid progression to AML.

The mainstay of treatment for MDS is best supportive care (BSC) (transfusions, growth factors, antibiotics) to control the symptoms of bone marrow failure, and low-dose standard chemotherapy for some patients. Stem cell transplant is not an option for the majority of patients as the patient's age and/or comorbidities usually precludes this treatment option.

Scope of the ERG report

The scope for this STA was to address the clinical effectiveness and cost-effectiveness of aza relative to CCR, particularly BSC, low-dose chemotherapy (LDC) and standard-dose chemotherapy (SDC) in patients with higher risk MDS, CMML and AML with 20–30% blasts. The patient outcomes governing relative effectiveness and cost-effectiveness were defined as: overall survival, time-to-progression (TTP) to AML, adverse events and health-related quality of life (HRQoL).

The marketing authorisation indicates the dose and route of aza to be 75 mg/m^2 subcutaneously daily for 7 days followed by a rest period of 21 days (28-day treatment cycle). It is recommended that patients be treated for a minimum of six cycles, continuing for as long as the patient continues to benefit or until disease progression. The unit cost of aza is £321/100 mg.

The key source of evidence on clinical effectiveness was an open-label randomised controlled trial (RCT) by Fenaux *et al*.[4] referred to as study AZA-001. It compared aza with CCR in 358 patients with higher risk MDS, CMML and AML 20–30% blasts. The outcomes reported in AZA-001 included overall survival, TTP to AML and adverse events. No HRQoL results were reported; however, outcomes likely to impact on HRQoL were provided (e.g. freedom from transfusion and rates of infection requiring intravenous antibiotics).

The manufacturer submitted a de novo economic model that was used to estimate the cost per quality-adjusted life-year (QALY) gained from aza in comparison with BSC, LDC and SDC. HRQoL utilities were obtained by mapping with a published algorithm to convert European Organisation for Research and Treatment of Cancer scores in Study CALBG 9221 into European Quality of Life-5 Dimensions values. Resource utilisation was based on expert opinion gathered from consultant haematologists in the UK, and costs were obtained from standard sources.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process. This work was undertaken in 8 weeks, beginning from 7 June 2009.

Because of the central importance of the AZA-001 study, it was formally fully appraised by the ERG, taking advantage of responses to requests for clarification from the manufacturer.

The ERG reran the submission's search strategies after some modifications incorporating minor improvements.

The ERG analysed the submitted economic model (model 1) and identified a number of inconsistencies and errors within the model. The manufacturer submitted a revised model for analysis by the ERG. Using the issues identified in the earlier analysis, the ERG conducted those repairs to the revised model that were feasible within time constraints.

The submitted models estimated overall survival using log-logistic (baseline) and Weibull distribution fits. When estimating uncertainty the models assumed a one-to-one and approximately linear relationship in these parameters. The ERG considered that this likely underestimated variation in these parameters and therefore incorporated the actual correlation between parameters where made available.

The ERG ran an ERG-repaired version of the second submitted model encompassing both the original two-way comparisons proposed by the manufacturer and additionally probabilistic sensitivity analyses that, in ERG judgement, might more accurately reflect the full range of clinical options available for the patient population. Other changes were made to the model, but a detailed account cannot be provided here.

The ERG extracted overall survival data for all the patient subgroups examined in the manufacturer's economic model and prepared Kaplan–Meier plots to indicate the inherent uncertainty in the observed data.

The ERG explored curve fits to the observed overall survival for patient subgroups using a greater range of distributions than those provided in the manufacturer's submission.

The ERG tested the face validity of the curve fits for overall survival submitted by the manufacturer by extrapolating to the base-case time horizon (25 years) rather than to the 7.7 years shown in the manufacturer's submission. The ERG also compared extrapolations of alternative curve fits.

The ERG extracted data relating to survival in the AML state and attempted to replicate the values provided in the manufacturer's submission.

The ERG extracted observed data for TTP to AML and compared observed TTP with the modelled TTP used in the manufacturer's economic model.

Results

Summary of submitted clinical evidence

The key source of evidence on clinical effectiveness was the AZA-001 open-label RCT[4] comparing aza with CCR in 358 patients with higher risk MDS, CMML and AML 20–30% blasts.

The AZA-001 study showed that:

- The median overall survival was 24.5 months on aza, compared with 15.0 months in the CCR group ($p = 0.0001$).
- The response rates were low (complete remission 17% aza versus 8% CCR).
- The median time to transformation to AML was greater in the aza group (17.8 versus 11.5 months; $p < 0.0001$).
- Of patients who were RBC transfusion-dependent at baseline, 45% of those on aza became RBC transfusion-independent during the treatment period, compared with 11.8% in the CCR group ($p < 0.0001$).

Summary of submitted cost-effectiveness evidence

The first model submitted by the manufacturer provided the following base-case incremental cost-effectiveness ratio (ICER) values for investigator pre-selected subgroups:

aza + BSC versus BSC = £63,295/QALY

aza + LDC versus LDC = £58,837/QALY

aza + SDC versus SDC = £44,523/QALY

The ERG concluded that this model was internally incomplete and was not fully executable, and apprised the manufacturer of a large number of errors and inconsistencies that resulted in submission of a second model that was accompanied by the base-case ICER values shown below:

aza + BSC versus BSC = £51,139/QALY

aza + LDC versus LDC = £47,178/QALY

aza + SDC versus SDC = £34,207/QALY

Commentary on the robustness of submitted evidence

Concerning clinical effectiveness, the AZA-001 study was open to bias, particularly from lack of blinding and uncertainty about losses to follow-up. In addition there was no direct evidence on impact on HRQoL. There is no evidence for differences in effects between investigator pre-selected treatment groups.

With regard to cost-effectiveness, the ERG had serious concerns regarding the validity of survival inputs into the model. However, the overwhelming observation concerned the errors in the submitted model which were sufficiently severe and numerous that the credibility of the estimates of cost-effectiveness provided in the manufacturer's submission was completely undermined.

Deficiencies identified in the first submitted model included serious coding errors preventing control of model assumptions. When these were corrected, the model was not functional and did not produce results under its base-case assumptions. Other issues included: the non-discounting of all cost data; minor deficiencies in the discounting of utility data; a lack of functionality to reproduce selected analyses in the manufacturer's submission; a large amount of redundant material within the model; and incorrect or inappropriate characterisation of uncertainty in cost, utility and survival estimates.

The manufacturer was apprised of the ERG's concerns regarding the model and submitted a second 'modified' model.

Although functionality was partially restored and discounting was improved in the second model, the ERG considered that several serious concerns remained unaddressed, the most important of these being: failure of the model to reflect treatment options available in clinical practice; mischaracterisation of the uncertainty in survival analyses; lack of face validity regarding base-case inputs for overall survival; and questionable reliability regarding the TTP to AML.

In view of these concerns, the ERG had little confidence in the deterministic or probabilistic analyses submitted.

The ERG fixed the deficiencies remaining in the model as much as was possible within the remit of the STA and ran this version in probabilistic sensitivity analyses to generate cost-effectiveness acceptability frontiers. The ERG considered these analyses better reflected the treatment options likely to hold in clinical practice than did the two-way comparisons undertaken in the manufacturer's analyses for those who would otherwise receive chemotherapy options (SDC, LDC). The results of these exploratory analyses indicated that:

- For SDC-treated patients, of six treatment options available, BSC was likely the most cost-effective option up to a threshold of £51,000/QALY. Beyond £51,000/QALY, aza + LDC became cost-effective.
- For LDC-treated patients, of four options available, BSC was again the most cost-effective option up to a willingness-to-pay threshold of £51,000/QALY (aza + LDC became cost-effective after £51,000/QALY).
- For BSC-treated patients, aza + BSC became cost-effective relative to BSC at a threshold of about £52,000/QALY.

The ERG considers these results exploratory and considers that they should be viewed with caution because of concerns regarding various biases relating to the TTP to AML, the uncertainty associated with the parameters describing fitted curves for overall survival from the trial, the effect of age-related non-MDS/AML mortality, and the impact of revised Health Resource Group figures.

Conclusions

The AZA-001 study showed that, compared with CCR, those MDS patients receiving aza had prolonged median survival (by about 9 months), had delayed progression to AML, had reduced dependence on transfusions and had a small improvement in response rate. As an open-label design, this study was at risk of bias and there was concern regarding losses to follow-up; these considerations may indicate some overestimation in the survival benefit of aza.

Aza reduces the requirement for transfusion and for intravenous antibiotic administration, and the claim has been made that 'azacitidine results in a marked improvement in patient well-being'. There is no direct research evidence about well-being of the patient population of interest in this STA, and research on quality of life for MDS patients is clearly required.

The economic models submitted for assessment were flawed and the cost-effectiveness of aza versus CCR was unlikely to be reliably estimated using the manufacturer's submitted models. Exploratory analyses using an improved version of the manufacturer's model indicated that in various scenarios aza was unlikely to become cost-effective relative to competing treatment strategies at a willingness to pay of less than £51,000/QALY.

Given the general paucity of economic modelling work in MDS and the limitations of the submitted industry model there is an evident need for an independent cost-effectiveness analysis of aza in MDS.

Note

Because of the extensive inconsistencies and errors within the model first submitted by the manufacturer the ERG presented a relatively brief initial report to NICE indicating that due to model inadequacies no reliance could be placed on the submitted cost effectiveness estimates. The report also encompassed a critical appraisal of the single RCT used in the manufacturer's submission. This report was sent to NICE in line with contractual time lines. Subsequently ERG received a second economic model submitted by the manufacturer. This second model was appraised by the ERG and an addendum to the original ERG report was then submitted to NICE in time for the first committee meeting. This addendum contained a substantial critique of the survival analyses underpinning the second economic submission together with an appraisal of the economic model which unfortunately retained several deficiencies.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance appraisal consultation document[5] issued by NICE on 4 March 2010 states that:

1.1 Azacitidine is not recommended as a treatment option for people who have the following conditions and are not eligible for haemopoietic stem cell transplantation: intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System (IPSS); chronic myelomonocytic leukemia with 10-29% marrow blasts without myeloproliferative disorder or acute myeloid leukemia with 20-30% blasts and multilieage dysplasia, according to the World Health Organization classification.

1.2 People with conditions stated in 1.1 who are currently receiving azacitidine for myelodysplastic syndromes, chronic myelomonocytic leukemia or acute myeloid leukemia should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Key references

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4. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, *et al*. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009;**10**:223–32.

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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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