Sorafenib for the treatment of advanced hepatocellular carcinoma

M Connock,[1] J Round,[2] S Bayliss,[1] S Tubeuf,[2] W Greenheld[1] and D Moore[1]*

[1]Unit of Public Health, Epidemiology and Biostatistics, University of Birmingham, Edgbaston, Birmingham, UK
[2]Institute of Health Sciences, University of Leeds, Leeds, UK

*Corresponding author

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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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List of authors:
M Connock, J Round, S Bayliss, S Tubeuf, W Greenheld and D Moore

Contact details:
David Moore, Unit of Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham B15 2TT, UK

E-mail: d.j.moore@bham.ac.uk

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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).

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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