Review protocol 17-04-2003

TECHNOLOGY ASSESSMENT REPORTS FOR THE HTA PROGRAMME

Imatinib for the treatment of patients with unresectable and/or metastatic gastro-intestinal stromal tumours

A. Final version (17-04-2003)

B. Details of the review team.

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C. Full title of research question

Imatinib (Glivec®, Gleevec®) for the treatment of patients with unresectable and/or metastatic gastro-intestinal stromal tumours.– A rapid systematic review of effectiveness and cost effectiveness.

D. Clarification of the research question and scope

This systematic review will seek to assess the clinical and cost effectiveness of imatinib in the treatment of unresectable and/or metastatic, KIT positive, gastrointestinal stromal tumours (GISTs), relative to current standard treatments.

GISTs are rare types of sarcoma arising from the connective tissue of the digestive system. Surgery is the treatment of choice, and is successful in the majority of GISTs, however options are limited if a tumour is unresectable or if metastases are present. Radiotherapy and conventional chemotherapy are reportedly of little use. Treatment of people with unresectable and /or metastatic GIST currently comprises symptom relief and best supportive care. Recent molecular research has led to an understanding that GIST tumours possess "gain-of-function" mutations, which allow the tumour cell to constitutively express the tyrosine kinase activity of the receptor coded by the KIT oncogene. This understanding has led to a shift in the definition of GIST and has also played a role in the development of new therapies such as imatinib, which is a tyrosine kinase inhibitor.

According to our scoping search it is unlikely there are published RCTs or any controlled trials that directly compare imatinib and current standard treatments for unresectable and/or metastatic GISTs. If this proves to be the case after systematic searching, we will have to make indirect comparison of imatinib and standard treatment by using evidence from cohort or case series studies. The major problem will be the inter-study comparability, particularly because the definition of GIST has shifted over recent years[1] with the result that dissimilar populations may have been subject to investigation at different times. Such indirect comparison methodology has important implications for the search strategy, inclusion criteria, and quality assessment of included studies. The scope of this review is summarised below:

Study design: Relevant RCTs, non-randomised controlled studies, cohort studies, and case series that reported effectiveness results of treatment with imatinib and/or other interventions in patients with KIT-positive GISTs.

Population: Patients diagnosed KIT positive unresectable and/or metastatic GISTs (could include primary or recurrent tumours).

Intervention: Imatinib (STI 571). Oral dosage 400 mg to 600 mg per day.

Comparators: The ideal comparator is the current standard treatment (symptom-relief and best supportive care), or placebo. If there is no data on the ideal comparators, we may have to consider data from trials that used other interventions as comparators.

Outcomes: The following outcomes will be considered whenever available: Quality of life (most preferred), mortality (overall survival), morbidity, response or partial response rate. Other surrogate outcome measures such as the results of Positron Emission Tomograpy (PET) may be considered, if an association with survival can be clearly demonstrated. Side effects and adverse events of imatinib will be assessed.

E. Report Methods

Search Strategy

Search strategies will be devised to identify studies on: the diagnosis and prognosis of GISTs; effectiveness of imatinib; and effectiveness of alternative treatments for GISTs.

Appendix D includes a draft strategy which will be adapted for each of the databases using both index and text-words where appropriate.

Diagnosis / prognosis of GISTs

MEDLINE and EMBASE will be searched using the terms for the population, combined with a 'methodological filter' to identify studies of the appropriate design.

Effectiveness of Imatinib

The following sources will be searched:

- Bibliographic databases as follows: Cochrane Library, MEDLINE, EMBASE, Science Citation Index, CancerLit, and CINAHL
- Checking citations of relevant studies
- Contact with experts
- Internet sites e.g. US National Cancer Intelligence Centre
- Invited industry submissions

Effectiveness of alternative treatments

With the exception of the industry submissions, it is anticipated that the same sources as the searches on imatinib will be interrogated. Terms for the population will be combined with 'filters' for systematic reviews and trials in the first instance.

Ongoing trials

The following sources will be searched: National Research Register, MetaRegister of Controlled Trials, NCI Clinical Trials. It is also anticipated that ongoing trial data will become available with the industrial submission.

The searches will not be restricted by language. Published and unpublished studies will be sought. Databases will be searched from inception, however, if the yield from the diagnosis / prognosis searches is unmanageable more recent references may be sought.

Inclusion criteria

The review will include relevant RCTs and non-randomised controlled studies that compared imatinib versus current standard treatment or placebo in patients with unresectable and/or metastatic GIST. If there are no controlled trials available, cohort studies and case series will be considered. According to our preliminary literature search, it is possible that there are no published studies about outcomes of current standard treatment in patients with unresectable and/or metastatic GIST. We may have to consider data from trials that used other interventions as comparators.

Including or excluding studies

Two reviewers will independently assess papers for inclusion/exclusion using the title and where available the abstract. Disagreements will be resolved by discussion. Full paper copies of relevant or possibly relevant references will be obtained for detailed examination. Inclusion/exclusion decisions will be made prior to detailed scrutiny of the results and study quality assessment. Foreign language publications will be screened using English abstracts where available. Translations will be obtained where necessary or where possible, within the resources and timeframe of the project.

Data extraction strategy

Two reviewers will independently extract data using a pre-designed data extraction form (Appendix A). Disagreements will be resolved by discussion, consulting with a third party if there is still some disagreement. Where there is missing information, the authors or industry will be contacted. Data from studies with multiple publications will be extracted and reported as a single study.

Quality assessment strategy

Quality of studies will be assessed using the York CRD criteria[2] for experimental and observational studies (Appendix B). These criteria will be tested and revised where necessary. We envisage that the following quality issues will be of paramount importance: study design, patient characteristics, (in terms of GIST diagnosis, disease severity, etc), and any possible sources of biases in patients selection, treatment provided, and outcomes measured.

Methods of analysis/synthesis

A descriptive analysis of included studies will be undertaken, and relevant evidence will be categorised and summarised in tables. If appropriate, results from individual studies will be quantitatively pooled by meta-analysis. Identified research evidence will be appropriately interpreted according to the assessment of methodological strengths and weaknesses and the possibility of potential biases.

Assessment of cost-effectiveness

A systematic review of published cost-effectiveness and cost utility studies will be undertaken. Economic evaluation studies will be assessed using the Drummond checklist. See appendix B.

If sufficient data is available, a cost effectiveness model will be developed. Data required for the economic modelling will include:

- survival data for imatinib and current standard treatment
- quality of life in patients treated with imatinib and current standard treatment
- costs of treatment with imatinib and current standard treatment

Given resource (staff and time) limitations, we are not able to collect data by primary study. Data required for the modelling will be mainly taken from published literature and the industry submission.

The searches for clinical effectiveness will be amplified to identify any existing models on treating GISTs and information on costs, cost effectiveness and quality of life from the following sources:

- Bibliographic databases; MEDLINE, EMBASE, NHS EED, DARE, HEED.
- Internet sites of national economic units

F. Handling the company submissions

The industry dossier will be used as a source of data for studies that meet the inclusion criteria. A detailed analysis of the industry model, including the strengths and weaknesses and the implications of different assumptions will be undertaken.
If we develop a model this will briefly be compared to the industry model(s).

Any 'commercial in confidence' data will be underlined in the TAR report (followed by an indication of the relevant company name e.g. in brackets) so that NICE secretariat can negotiate (before and during the Institute's consultation process) with industry the subsequent inclusion of such data in the HTA monograph publication or subsequent peer-review publications.

G. Project Management

Timetable/milestones

Event	Deadline / Date
Submission of draft protocol	1st April 2003
Submission of finalised protocol	22nd April 2003
Consultees Meeting	1st May 2003
Industry submissions to the team	21st July 2003
Submission of progress report	28th July 2003
Submission of draft assessment report to peer reviewers	8th September 2003
Submission of assessment report to NICE	10th October 2003
Appraisal Committee meeting	26th November 2003

Appendix A. Data extracted from included studies

For clinical effectiveness studies, it is anticipated that data will be extracted on the following:

- Details of the characteristics of **study population** and baseline comparability of intervention and control groups (in controlled studies).
- Details of how **diagnosis** was made and year in which the study was undertaken.
- Details of the **intervention** and **comparato**r such as: drug; doses; mode of administration; duration of treatment and follow up intervals.
- Details of the **outcomes measured** such as: identification of all outcomes which study protocols state will be measured; the specific measurement tool or data collection method; when, how and by whom the outcome data was collected; dropouts; crossovers and losses to follow-up for each outcome.
- Details of **the results**, where available, as raw numbers, plus any summary measures with standard deviations, p-value and confidence intervals where possible.

For the cost-effectiveness review it is anticipated that data will be extracted on the following:

- Details of the **study characteristics** such as form of economic analysis, comparators, perspective, time horizon, and modelling used.
- Details of the **effectiveness and cost** parameters such as: effectiveness data; health state valuations; resource use data; unit cost data; price year; discounting assumptions, productivity costs.
- Details of **the results and sensitivity analyses**.

Appendix B. Check lists for quality assessment of included studies

From the York CRD handbook[2]
(http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?
Adequate approaches to sequence generation
- Computer-generated random numbers
- Random numbers tables
Inadequate approaches to sequence generation
- Use of alternation, case record numbers, birth dates or weekdays

2. Was the treatment allocation concealed?
Adequate approaches to concealment of randomisation
- Centralised or pharmacy-controlled randomisation
- Serially-numbered identical containers
- On-site computer based system with a randomisation sequence that is not readable until allocation
- Other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients
Inadequate approaches to concealment of randomisation
- Use of alternation, case record numbers, birth dates or weekdays
- Open random numbers lists
- Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were the point estimates and measure of variability presented for the primary outcome measure?
9. Did the analyses include an intention to treat analysis?

Quality criteria for assessment of observational studies

From the York CRD handbook[2]
(http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

Cohort studies
- Is there a sufficient description of the groups and the distribution of prognostic factor
- Are the groups assembled at a similar point in their disease progression?
- Is the intervention/treatment reliably ascertained?
- Were the groups comparable on all-important confounding factors?
- Was there adequate adjustment for the effects of these confounding variables?
- Was a dose-response relationship between intervention and outcome demonstrated?
- Was outcome assessment blind to exposure status?
- Was follow-up long enough for the outcomes to occur?
- What proportion of the cohort was followed-up?
- Were dropout rates and reasons for dropout similar across intervention and unexposed groups?

Case-control studies
- Is the case definition explicit?
- Had the disease state of the cases been reliably assessed and validated?
- Were the controls randomly selected from the source of population of the cases?
- How comparable are the cases and controls with respect to potential confounding factors?
- Were interventions and other exposures assessed in the same way for cases and controls?
- How was the response rate defined?
- Were the non-response rates and reasons for non-response the same in both groups?

- Is it possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
- Was an appropriate statistical analysis used (matched or unmatched)?

Case series

- Is the study based on a representative sample selected from a relevant population?
- Are the criteria for inclusion explicit?
- Did all individuals enter the survey at a similar point in their disease progression?
- Was follow-up long enough for important events to occur?
- Were outcomes assessed using objective criteria or was blinding used?
- If comparisons of sub-series are being made, was there a sufficient description of the series and the distribution of prognostic factors?

Checklist for assessing economic evaluations

From the York CRD handbook[2]
(http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

1. Is there a well-defined question?
2. Is there comprehensive description of alternatives?
3. Are all important and relevant costs and outcomes for each alternative identified?
4. Has clinical effectiveness been established?
5. Are costs and outcomes measured accurately?
6. Are costs and outcomes valued credibly?
7. Are costs and outcomes adjusted for differential timing?
8. Is there an incremental analysis of costs and consequences?
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?
10. How far do study results include all issues of concern to users?
11. Are the results generalisable to the setting of interest in the review?

Based on Drummond's checklist

Topic Specific Quality Checks

- Was the method of GIST diagnosis reported? If so what was the method?
- Was the year of study reported?

Appendix C. Background information

Gastrointestinal stromal tumours – general description and occurrence.

GISTs are rare types of sarcoma arising from the connective tissue of the digestive system. Incidence estimates range from 4 to 40 cases per million. [1,3,4] The majority of tumours occur in the stomach (60 – 70%), with the small bowel (25 to 35%), colon and rectum (5%) and oesophagus being affected.[1] Isolated cases have been found in the appendix and tumours have also been found in the omentum, mesenteries and retroperitoneum.[1] GISTs can occur at any age, including very rare occurrences in children, however, the average age at presentation is between 50 and 70 years old.[4] GISTs range in size from a few millimetres to 40 cm in diameter. Over 95% of patients present with a solitary primary tumour, with up to 40% of these directly invading the surrounding organs.[5]

Symptoms/Diagnosis

Many patients are asymptomatic with tumours being detected incidentally. Symptoms vary depending on the size and location of the tumour, with the most common symptoms being vague abdominal discomfort or pain, a feeling of abdominal fullness, and presence of a palpable mass. Secondary symptoms such as anaemia are caused by the tumour bleeding.[5] The definite diagnosis is made from biopsy. Morphology of the tissue sample is examined for the presence of spindle cells, which indicate that there is a possibility of GIST. A raft of immunohistochemical tests are then undertaken to characterise the cell type and aid elimination of other types of tumours. Recently a positive test for the KIT protein has become adopted as the strongest indicator that a tumour with an appropriate morphology and site is in fact a GIST. This test is seen by many as the final arbiter in the diagnostic process and by some has been described as the diagnostic 'gold standard' for GIST.[6]

Prognosis

Prognosis of patients with GISTs is determined mainly by the size and mitotic activity of the tumour, but location and tumour stage at presentation may also be influential.[6,7] Prognosis for unresectable and/or metastatic GIST is poor. For example, Conlan described a 5 year survival of 0% in patients who did not have complete tumour resection in contrast to 40% in patients who underwent complete resection.[8] In metastatic disease a median survival rate of only 19 months was reported in 94 patients with metastatic GIST. [9]

Current treatment

Treatment of GIST is usually by surgical removal of the tumour. Adjuvant radiotherapy is not a standard postoperative therapy and its impact on the disease is uncertain.[7] Treatment with systemic chemotherapy (e.g. doxorubicin) has been reportedly unsuccessful. Therefore patients with tumours that are not amenable to surgery, have few treatment options.

Imatinib

MODE OF ACTION

Imatinib is a protein-tyrosine kinase inhibitor (ATC code: L01XX28) developed by Novartis Pharmaceuticals UK Ltd. Recent molecular research has found that the majority of GISTs were positive for the KIT protein, a plasma membrane receptor normally stimulated by stem cell factor (SCF) to become an active protein tyrosine kinase. The KIT gene is a proto-oncogene whose product participates in cell signalling that controls cell division and apoptosis. The KIT mutations in GIST cause the receptor to become phosphorylated in the absence of SCF and to gain constitutive protein tyrosine kinase activity. Imatinib works by inhibiting the tyrosine kinase activity of the KIT protein and so shifting the balance toward re-establishing control over apoptosis and cell division.[10,11]

SIDE EFFECTS OF IMATINIB

Side effects could include mild nausea, vomiting, diarrhoea, myalgia, muscle

cramps, fluid retention, neutropaenia, thrombocytopaenia and gastrointestinal / tumour haemorrhages.[12, 13]

LICENSING

Imatinib was approved in the USA by the FDA in February 2002 for the treatment of GIST [14] and is licensed for the treatment of adult patients with KIT (CD117) positive unresectable and/or metastatic malignant GIST. In Europe, the European Commission Committee for Proprietary Medicinal Products (CPMP), in a European Public Assessment Report (EPAR), issued a Marketing Authorisation on 24th May 2002 for imatinib to be used in the treatment of adult patients with KIT (CD117) positive unresectable and /or metastatic malignant GIST. The licence was issued on the basis of a single phase II, open-label, randomised, uncontrolled multinational study that was conducted in 147 patients (B2222).[15] The primary evidence for efficacy in these patients with unresectable and/or metastatic GIST was based on the objective response rate of tumour size. In this Phase II trial, 40% of patients had a partial response, and 41% had their disease stabilized.[13] "The Committee for Proprietary Medicinal Products (CPMP) recommended that the Marketing Authorisation should be granted under exceptional circumstances because the indications for which the medicinal product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the quality, safety and efficacy of the medicinal product".[12] In addition the EPAR states that "Given the outstanding activity observed and in view of the applicant's commitment to complete the identified programme of studies laid out as specific obligations, the results of which shall form the basis of an annual reassessment of the benefit/risk profile, the CPMP considered that an approval under exceptional circumstances could be recommended".[12]

Cost of new therapy and possible impact on the NHS

In 2002 The National Horizon Scanning Centre analysed evidence pertaining to the use of imatinib as a new and emerging technology for the treatment of GIST.[16] According to this report, if imatinib were used in patients within its licensed indication, then around 300 patients each year would be eligible for treatment with imatinib. At an estimated cost of £1,557 to £3,115 per month per patient (depending upon dose), this would result in a cost to the NHS (England and Wales) of between £5.6M to £11.2M per year. Little additional service impact was envisaged because imatinib can be used on an outpatient basis.

Problems envisaged in determining the effectiveness of Imatinib for GISTs.

- ∇ Possible uncertainty about the sensitivity and specificity of the KIT diagnostic tests for GIST. If false positives are treated with imatinib, this may have the consequence of reducing the apparent effectiveness of imatinib, because imatinib specifically targets the action of the gain of function mutation in KIT.
- ∇ Definition of GIST. Because the diagnosis/definition has shifted over recent years with the advent of molecular analysis, the groups diagnosed as GIST before these techniques were available may or may not have had GIST as judged by current criteria. This will cause difficulties with the validity of any indirect comparisons we may use in our synthesis of evidence.
- ∇ The recent shift in the definition of GIST will also have implications for development a model for economic analysis because one important component of the model will be an understanding of the natural course of the disease in the absence of treatment. Studies that have been undertaken before molecular/ KIT based diagnosis of GIST came on stream may well have included patients who were not suffering from GIST (as currently defined), making the use of these natural histories of GIST problematical. Conversely because the diagnosis of GIST through molecular techniques is so recent, < 4 years, a full understanding of the progression of KIT positive disease will not be possible.
- ∇ Comparators with limited data of effectiveness. Potentially ineffective comparators may make the intervention appear more effective than it otherwise is.

Appendix D. Draft bibliographic search strategy

Intervention:
Imatinib OR Gleevec OR Glivec OR STI571 OR STI 571 OR STI-571 OR ST1 571 OR ST1571 OR ST1-571

Population:
Gastrointestinal stromal tumo(u)r(s)
GIST(s)
CD117 positive stromal tumo(u)r(s)
CD117 antigen(s)
GI PACT
ICC tumo(u)r(s)
Gastrointestinal mesenchymal tumo(u)r(s)
C-KIT
KIT signalling
protein tyrosine kinase
proto-oncogene
Gastrointestinal smooth muscle tumo(u)r(s)
Leiomyoma(s)
Leiomyoblastoma(s)
Leiomyosarcoma(s)
Gastrointestinal autonomic nerve tumo(u)r(s)
GANT(s)
Gastrointestinal Pacemaker Cell Tumo(u)r(s)

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