RAPID REVIEWS FOR THE HTA PROGRAMME

PROTOCOL: THE EFFECTIVENESS AND COST-EFFECTIVENESS OF IMATINIB FOR FIRST LINE TREATMENT OF CHRONIC MYELOID LEUKAEMIA IN CHRONIC PHASE

A. **This protocol is provisional and subject to change**
B. **Details of review team**

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C. **Full title of research question**
What is the effectiveness and cost-effectiveness of Imatinib for first line treatment of chronic myeloid leukaemia in chronic phase compared to current standard treatments?

D. **Clarification of research question and scope**
Chronic myeloid leukaemia (CML) is a clonal disorder in which haemopoietic stem cells proliferate and eventually replace all normal bone marrow function. The median age at diagnosis is 67 years. The disease generally passes through three phases- a chronic stage in which patients usually present, and which typically last between 2 and 6 years; an accelerated stage where the number of blast cells in the blood increases and symptoms become more prominent; and blastic phase where there is little remaining normal marrow function. The median survival is between 4 and 5 years from diagnosis.

Bone marrow transplantation is the only potential cure. It is possible in those patients for whom a suitable donor is available, preferably a tissue-type identical sibling, but matched unrelated donors can be used. Survival is between 60% and 70% at 5 years for sibling donors, less for unmatched donors. Bone marrow transplantation is not usually offered to patients older than 60 because of increased risks of the procedure in older patients.

Drug treatments ameliorate symptoms and prolong overall survival. Hydroxyurea is the usual initial treatment and has relatively few side effects. Busulphan is now rarely used because of its unfavourable side effects and apparent lower efficacy. Interferon alpha has become increasingly used in the last few years as it prolongs survival between 1 and 2 years (Chronic Myeloid Leukemia Trialists Collaborative Group, 1997). However it also has significant toxic effects, which requires a dose reduction or cessation of therapy in a substantial proportion of patients. Cytosine arabinoside (Ara-C) in combination with interferon alpha increases the likelihood of remission at the expense of increased toxicity.

CML has a characteristic genetic abnormality of chromosomes 9 and 22 (known as Philadelphia Chromosome). A protein known as BCR-ABL is produced as a result of this, and the enzyme activity of the protein (tyrosine kinase) appears to be implicated in the development of CML. Imatinib has been synthesised specifically to be an antagonist of this

tyrosine kinase. It has a limited effect on other, normal, kinases. Antileukaemic activity has been demonstrated in a number of preclinical and animal models.

Imatinib has previously been evaluated for NICE as second line treatment of CML in chronic phase and as first line treatment in accelerated and blast phases (NICE Technology Appraisal Guidance No. 50). This guidance recommended the following:

"Imatinib is recommended as a treatment option for the management of Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in chronic phase in adults who are intolerant of interferon-alpha (IFN-α) therapy or in whom IFN-α is deemed to have failed to control the disease."

The guidance defines IFN-α failure as either failing to achieve a complete haematological response after 3 months of IFN-α treatment as monotherapy or in combination with hydroxyurea or as failing to achieve major cytogenetic response after 1 year of IFN-α treatment despite haematological response. IFN-α intolerance is defined as the presence of documented Grade 3 non haematological toxicity, persisting for more than 2 weeks, in a patients receiving a regimen that contains IFN-α.

Further the guidance states that "Imatinib is recommended as an option for the treatment of adults with Philadelphia-chromosome-positive CML in accelerated phase or blast crisis provided they have not received Imatinib treatment at an earlier stage."

A preliminary review of the literature reveals that one abstract has been published evaluating the effectiveness of Imatinib as first line treatment in chronic phase.

Scope: This review will encompass the efficacy of imatinib for first line therapy of CML.

Population: All adults presenting in chronic phase of CML, who have not received prior treatment.

Intervention: Imatinib

Comparisons: Hydroxyurea, IFN-α and bone marrow transplantation as first line treatment

Outcomes: Overall survival and quality of life are preferred endpoints. Surrogate outcomes such as complete and partial haematological response, complete and partial cytogenetic response will also be considered. The validity of these surrogate outcomes will also be questioned. Adverse effects (including nausea, diarrhoea, mylagia, periorbital oedema, skin rash, peripheral oedema, liver toxicity, withdrawal from treatment, myelosuppression and cytopenia) will also be identified.

Design: We will include all direct comparisons of Imatinib to other first-line treatments. If direct comparisons are not available we will summarise the evidence for imatinib and for comparative techniques separately. We will then attempt to draw indirect comparisons. We will not attempt to synthesise uncontrolled evidence or studies with no comparison group. The comparisons are likely to be as follows:

Comparison of interest	**Likely direct evidence**	**Indirect evidence**
Imatinib vs IFN	1 RCT	Not applicable
Imatinib vs HU	No evidence	HU vs IFN
Imatinib vs BMT	No evidence	BMT vs IFN

It may not be possible to rigorously assess the optimal duration of treatment given the recent introduction of the drug and short follow-up reported in the literature. We will review the evidence on quality of life and provide a summary and critique of the evidence. In addition, we will provide sensitivity analyses of these inputs in the economic evaluation.

E. **Report Methods**

Search strategy

We will update the search performed for the previous NICE assessment report on Imatinib as second line treatment for CML. The previous strategy would have identified studies assessing first-line treatment of CML. We will also conduct searches to identify evidence for the indirect comparison of BMT vs IFN. The previous NICE assessment search for comparative treatments will be updated to identify evidence for the indirect comparison of HU vs IFN.

The search will consist of searching:

- Computerised databases including Medline, Embase, the Cochrane Library, Science Citation Index, Web of Science Proceedings, BIOSIS, Cancerlit, Conference Proceedings Index and AIDS and Cancer Research Abstracts, conference abstracts from the American Society of Hematology and the American Society of Clinical Oncology (ASCO)
- ONS (Office for National Statistics) web site, the FDA web site, the National Cancer Institute's CancerNet web site, the Novartis web site http://www.gleevec.com, and data from the National Cancer Intelligence Centre.
- Bibliographies
- Contacting research groups and industry
- Trial registers in the UK (National Research Register), US and Canada

Inclusion

The articles included in the previous NICE appraisal of Imatinib will be examined by two researchers to determine relevance to this review. The abstracts and titles of the additional articles identified will be assessed by two blinded independent researchers. The full text of articles deemed relevant will be obtained and assessed by two researchers for inclusion. The following inclusion criteria will be applied:

- RCTs or controlled trials of Imatinib compared to hydroxyurea, interferon alpha or BMT for first line treatment of CML in chronic phase
- Systematic reviews comparing HU and IFN in the first line treatment of CML in chronic phase
- RCTs or comparative studies comparing BMT and IFN or HU as a first line treatment of CML in chronic phase
- Cost-effectiveness, cost-utility and cost-benefit studies- full economic evaluations

The focus of the review will be on randomised comparisons (RCTs) if these are available.

Exclusion criteria

- Case series, case reports
- Treatment in children or youth
- Animal models
- Preclinical and biological studies (including studies where the patient is not the focus)
- Studies only reporting non-clinical outcomes
- Studies where treatment is in accelerated and blast phases of CML
- Studies where treatment is other than first line for CML
- Studies not published in English

Data extraction strategy
Data will be extracted by one researcher and checked by a second researcher. Differences will be resolved by consensus.

Quality assessment strategy
The methodological quality of included systematic reviews, RCTs and controlled trials will be assessed using the criteria specified in CRD Report 4 (Centre for Reviews and Dissemination, 1996). Assessment of the methodological quality of economic evaluations will be performed using the Drummond checklist (Drummond, 1997).

Methods of analysis/synthesis
Meta-analysis will be performed if sufficient randomised evidence is located of sufficient homogeneity. If this is not the case then a description of the evidence will be presented and results tabulated.

Methods for estimating qualify of life, costs and cost-effectiveness and/or cost/QALY
Costs for treatment and savings will be taken from published work, NHS costs and industry submission where relevant. If insufficient detail is available, estimates for cost will be derived from individual Trusts or groups of Trusts. Costs will be discounted at 6% p.a. and benefits at 1.5% (sensitivity analyses 0% to 6%).

An independent economic model will be constructed and cost effectiveness and cost utility will be calculated. The model will compare different first line treatment options for chronic phase CML.

For high-risk allograft candidates (usually older or sicker) or those in whom an allograft is not an option (no donor) the following alternatives will be modelled:

Alternatives modelled	**Source of effectiveness data**
IFN	IFN vs IM trial
HU	IFN vs HU trial
IM	IFN vs IM trial

This is the most relevant comparison and will be the priority of the economic modelling.

For patients in whom an allograft is an option (donor available and lower risk candidates) the following alternatives will be modelled (time/resource permitting):

Alternatives modelled	**Source of effectiveness data**
IFN	BMT vs IFN trial
BMT	BMT vs IFN trial
IM	IFN vs IM trial (conservative estimate as is likely to bias against IM due to older population)

The model will only consider first line treatment and will not permit crossing over. It will be based on survival for a person remaining on the first line treatment until relapse or progression.

F. Handling the company submission(s)
As little published data is available regarding imatinib as first line treatment in CML, the industry submission is likely to contain a substantial amount of new information. Early contact will be made with industry. Comparison of data assessment procedures will be performed and the reason for any differences explored. A critique of the industry submission

will be performed along with a comparison with our independent economic model (in outline). Possible reasons for any discrepancies will be explored.

G. **Project Management**

a. **Timetable/milestones** –

Submission of finalised protocol:	4 November 2002
Submission of progress report:	20 January 2003
Submission of assessment report:	31 March 2003

b. **Competing Interests**
None

H. . **External reviewers**:

The Technology Assessment Report will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the TAR encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. Comments from external reviewers and the Technical lead, together with our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.