

Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation

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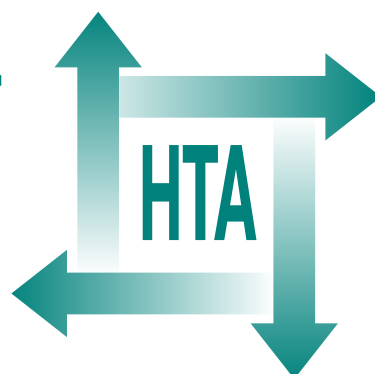
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Executive summary

Health Technology Assessment 2012; Vol. 16: No. 23
DOI: 10.3310/hta16230

**Health Technology Assessment
NIHR HTA programme
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Executive summary

Background

In November 2009, the National Institute for Health and Clinical Excellence (NICE) issued for consultation preliminary recommendations on the use of dasatinib and nilotinib for chronic myeloid leukaemia (CML) in patients whose treatment with imatinib had failed owing to resistance and/or intolerance. This consultation process was informed by a technology assessment report on the clinical effectiveness and cost-effectiveness of dasatinib and nilotinib, prepared by the Peninsula Technology Assessment Group (PenTAG) at the University of Exeter. As a result of the consultation, NICE and the Appraisal Committee identified a need for further information on second-line interventions for people who are resistant to standard-dose imatinib. An updated draft scope was issued by NICE for further consultation, focusing on the use of dasatinib, nilotinib and high-dose imatinib as second-line therapy in patients who are resistant to standard-dose imatinib.

This technology assessment report evaluates the clinical effectiveness and cost-effectiveness of dasatinib, nilotinib and high-dose imatinib, within their licensed indications, for the treatment of people with CML who are resistant to standard-dose imatinib. The present assessment report was commissioned as a supplement to the previous PenTAG assessment report (PenTAG AR), to reflect the inclusion of high-dose imatinib in the updated scope of the consultation.

Objectives

This assessment report has three objectives:

1. to update the existing systematic reviews of clinical effectiveness and cost-effectiveness undertaken in the PenTAG AR, but focusing on people with imatinib-resistant disease only and including high-dose imatinib
2. to critique economic analyses provided by manufacturers in their submissions to NICE
3. to adapt the economic analysis undertaken in the PenTAG AR to reflect the updated scope.

Methods

The three components of the work were conducted systematically following standard procedures, specified a priori in the research protocol. Studies of clinical effectiveness were summarised by narrative review with full tabulation of results.

Systematic review of clinical effectiveness studies

Potentially relevant studies were identified by searching 12 electronic bibliographic databases from inception to January 2011 (such as The Cochrane Library, MEDLINE, EMBASE and MEDLINE In-Process & Other Non-Indexed Citations) and two specialist abstract and conference proceeding resources, and by checking reference lists of articles and contacting experts. Studies were selected for inclusion through a two-stage process. Titles and abstracts were screened for inclusion to identify all of the citations that might meet the inclusion criteria. Full manuscripts of relevant citations were then retrieved and assessed by two reviewers against the following inclusion criteria:

- *Population* Patients with imatinib-resistant CML in the chronic, accelerated or blast phase.
- *Interventions* Dasatinib, nilotinib or high-dose imatinib.
- *Comparators* Dasatinib, nilotinib, high-dose imatinib, hydroxycarbamide, interferon alfa, acute leukaemia-style chemotherapy, allogeneic stem cell transplant, standard-dose imatinib or best supportive care.
- *Outcomes* Treatment response rates [including molecular, cytogenetic and haematological responses (HRs)]; time to, and duration of, response; overall survival; event-free survival; progression-free survival; adverse effects of treatment; health-related quality of life; time to treatment failure; costs and cost-effectiveness.
- *Study design* Randomised controlled trials (RCTs) and prospective controlled studies were eligible, with single-arm prospective cohort studies being eligible if no higher-level evidence existed; full economic evaluations for the review of cost-effectiveness.

Data from included studies were extracted using a standard data extraction form by one reviewer and checked by a second reviewer. The quality of included studies was appraised by one reviewer and checked by a second reviewer using quality assessment criteria specified in the PenTAG AR. For the systematic review of cost-effectiveness, quality assessment of studies was undertaken using published checklists and NICE guidance specific to the critical appraisal of economic evaluations.

Evaluation of manufacturers' submissions and the Peninsula Technology Assessment Group economic model

Characteristics of the economic evaluations in manufacturer submissions to NICE by Novartis and Bristol-Myers Squibb (BMS) and the economic evaluation conducted by PenTAG were summarised using a standard data collection template. The three economic evaluations were critically appraised by two reviewers using a standard 18-item checklist similar to that used for the quality appraisal of studies in the cost-effectiveness systematic review.

Southampton Health Technology Assessments Centre analysis

The PenTAG economic model was updated, taking into account some limitations noted in the two manufacturers' models and including the interventions dasatinib, nilotinib, and high-dose imatinib and the comparators interferon alfa, standard-dose imatinib, stem cell transplantation and hydroxycarbamide. The analysis focused on those in chronic-phase CML only.

Results

Clinical effectiveness

Eleven studies met the inclusion criteria. Four of these studies included new data published since the PenTAG AR. These were a published update of a RCT that compared high-dose imatinib against dasatinib, and three single-arm cohort studies that each assessed high-dose imatinib. The RCT had already been identified in the PenTAG AR based on earlier publications. No new studies assessing nilotinib were found. The criteria used to define imatinib failure were slightly different in each of the four studies. All participants had chronic-phase CML, except in one of the single-arm cohort studies that also included very small numbers with accelerated phase and blast crisis (three and four patients, respectively).

The RCT had a number of major limitations (also noted in the PenTAG assessment), which rendered it of limited value as a comparative study and, as such, data for the dasatinib and high-dose imatinib arms are not directly compared in this report. The methodological quality of the single-arm cohort studies was also considered suboptimal. In view of the methodological limitations of the studies included in the systematic review and the heterogeneity in their

reporting, it was considered inappropriate to attempt to combine the results of the studies in a meta-analysis. Instead, relevant new data that were not already included in the PenTAG AR are tabulated and synthesised narratively in this report.

Summary of benefits and risks: dasatinib

Only one new publication provided data on the effectiveness of dasatinib. This publication reported new or updated data for the RCT already included in the PenTAG AR. The updated data for the dasatinib arm of the RCT indicate that at 26 months' follow-up 43.6% of patients had a complete cytogenetic response. At 18 months, 90% of patients maintained a major cytogenetic response. A major molecular response was achieved in 28.7% of patients. The proportion of patients without treatment failure at 24 months was estimated at 59%. Longer follow-up was associated with additional adverse events (AEs: fluid retention, bleeding, infection, upper respiratory tract infection or inflammation), and grades 3–4 fluid retention occurred in 7% of individuals. These results should be interpreted with caution owing to the lack of a comparator and other major limitations of the study.

Summary of benefits and risks: high-dose imatinib

Four studies provided data on the effectiveness of high-dose imatinib: one high-dose imatinib arm of the RCT (described above) and three single-arm cohort studies. Data from these four cohorts suggest that, of the patients who received high-dose imatinib, 18–36% achieved a complete cytogenetic response, 33–64% achieved a major cytogenetic response and 56–82% achieved a complete haematological response. One study reported that around three-quarters of individuals maintained their major cytogenetic response at 18 months. Event-free survival of ≥ 2 years occurred in 34% of patients in one study and progression-free survival in 65–87% in two studies. Only two studies reported overall survival; they reported that 85–93% of patients would be expected to survive ≥ 2 years. Grades 3–4 haematological AEs occurred in up to 40% of patients. Non-haematological events included anorexia, diarrhoea, fatigue, muscle spasms, musculoskeletal pain, superficial oedema and rash. Grades 3–4 non-haematological AEs did not occur in more than 5% of patients. Between 0% and 20% of patients discontinued high-dose imatinib owing to AEs. These results should be interpreted with caution owing to the lack of a comparator and other study limitations.

Economic analysis

The systematic review identified one cost-effectiveness study that compared dasatinib with high-dose imatinib. The results showed that chronic-phase CML patients who are resistant to standard-dose imatinib gain 0.62 QALYs (quality-adjusted life-years) when treated with dasatinib compared with high-dose imatinib, and the incremental societal cost would be €4250 during the lifetime period or €6880 per QALY gained. It is unclear how generalisable these results are to the UK NHS, as the study was conducted in Sweden and takes a societal perspective.

The Novartis submission compared nilotinib with high-dose imatinib and also had an exploratory analysis versus stem cell transplantation/hydroxycarbamide. The results showed that nilotinib dominates high-dose imatinib (i.e. is more effective and less costly). The exploratory analysis gives an incremental cost-effectiveness ratio (ICER) of about £44,000 per QALY gained for nilotinib versus stem cell transplantation/hydroxycarbamide.

The BMS submission compared dasatinib, nilotinib and high-dose imatinib with standard-dose imatinib, stem cell transplantation, hydroxycarbamide, interferon alfa, acute leukaemia-style chemotherapy and best supportive care. The results showed that dasatinib dominates high-dose imatinib, nilotinib and stem cell transplantation.

There are two main differences between the industry models: in the BMS model, patients are treated until progression, which incurs greater costs; in the Novartis model the assumed third-line treatment is stem cell transplantation/hydroxycarbamide, which has associated high mortality and reduced overall survival. These key assumptions drive the differences between the models.

The PenTAG economic evaluation compared dasatinib and nilotinib with high-dose imatinib. Further analyses comparing these three treatments to interferon alfa were reported in an appendix. The results showed that nilotinib dominates high-dose imatinib and the ICER for nilotinib versus interferon alfa is about £44,600. The ICER for dasatinib versus nilotinib is over £277,000. Concerns relate to the fact that there is no link between overall survival and progression-free survival, as overall survival is based on major cytogenetic response but progression-free survival is not, and also the estimate for survival on interferon alfa does not fit with clinical advice.

Southampton Health Technology Assessments Centre analysis

The Southampton Health Technology Assessments Centre conducted analyses for the interventions dasatinib, nilotinib and high-dose imatinib and the comparators interferon alfa, standard-dose imatinib, stem cell transplantation and hydroxycarbamide. Owing to large uncertainties in the parameter inputs to the model, these analyses should be treated as exploratory. The results suggest that the three interventions, dasatinib, nilotinib and high-dose imatinib, have similar costs and effectiveness. Nilotinib and dasatinib are slightly more cost-effective than high-dose imatinib because of slightly lower costs and better effectiveness. Dasatinib, nilotinib and high-dose imatinib are all cost-effective when compared with hydroxycarbamide, for a willingness to pay (WTP) of about £30,000 per QALY. It is not possible to derive firm conclusions about the relative cost-effectiveness of the three interventions owing to great uncertainty around data inputs.

The uncertainty around the model results were explored using deterministic sensitivity analyses, threshold analyses and probabilistic sensitivity analyses. Deterministic sensitivity analyses showed that changes in overall survival for hydroxycarbamide and changes in treatment efficacy of the interventions had little impact on results. A probabilistic sensitivity analysis was run comparing the interventions dasatinib, nilotinib, high-dose imatinib and hydroxycarbamide. For a WTP threshold of £20,000 per QALY, hydroxycarbamide is the most cost-effective treatment. For a WTP threshold of £30,000 per QALY, nilotinib, dasatinib, hydroxycarbamide and high-dose imatinib have probabilities of being cost-effective of 60%, 28%, 12% and 0%, respectively.

Limitations

There are a number of important concerns that have a bearing on the outcome of this update report. These predominantly centre around the paucity of good-quality evidence, which provides uncertain data for the key outcomes of relevance to the scope.

Discussion and conclusions

This report is a supplement to the PenTAG AR and such the results reported herein must be considered in conjunction with the PenTAG AR.

Data suggest that dasatinib, nilotinib and high-dose imatinib appear to be efficacious in terms of obtaining cytogenetic and HRs in the imatinib-resistant population. However, there remains

an absence of evidence with which to assess the relative effectiveness of dasatinib, nilotinib and high-dose imatinib in imatinib-resistant CML, and the impact on long-term outcomes is difficult to conclude.

The uncertainties in the data mean that our exploratory cost-effectiveness analysis should be treated with caution. Although we have attempted to address the key areas of uncertainty in this update analysis, we do not feel able to make firm conclusions regarding the use of these technologies in patients with chronic-phase CML. In addition, owing to the paucity of data, we have not been able to model these technologies for accelerated phase or patients with blast-crisis-phase CML.

The implications for future research are not altered from the recommendation that PenTAG made, identifying the need for a three-way, randomised clinical trial of dasatinib, nilotinib and high-dose imatinib.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Publication

Loveman E, Cooper K, Bryant J, Colquitt JL, Frampton GK, Clegg A. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. *Health Technol Assess* 2012;**16**(23).



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The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 09/90/01. The protocol was agreed in July 2010. The assessment report began editorial review in July 2011 and was accepted for publication in July 2011. 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.

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ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

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Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Charlesworth Press.