

Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation

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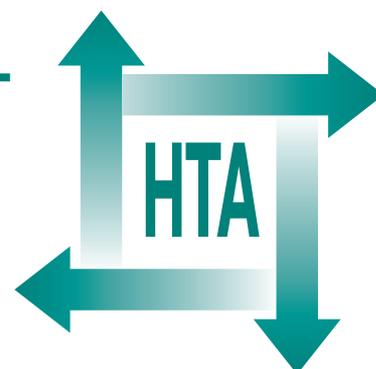
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Executive summary

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Executive summary

Objectives

The objectives of this study were 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.

Methods

Electronic literature databases and the references of identified studies were searched for relevant studies. The searches were not restricted by language or publication status. Because there were no randomised trials that have directly compared imatinib with the current standard treatment in patients with advanced GIST, this review included non-randomised controlled studies, cohort studies, and case series that reported effectiveness results of treatment with imatinib and/or other interventions in patients with advanced GIST. The effectiveness assessment was based on the comparison of results from imatinib trials and results from studies of historical control patients.

Economic evaluation was based mainly on an assessment and modification (when judged necessary) of a model submitted by Novartis. The results from a new model confirmed the findings from the modified Novartis model.

Effectiveness assessment

Two trials and eight case studies were identified from the published literature, and four ongoing trials and a case series were identified, which have reported data in abstract form only. Evidence from published uncontrolled trials involving 187 patients, and from abstracts reporting similar uncontrolled trials involving 1700 patients, indicate that approximately 50% of imatinib-treated individuals with advanced GIST experience a dramatic clinical response in terms of at least a 50% reduction in tumour mass. At present, although useful data are accumulating, it is not possible to predict which patients may respond in this way. Fifteen studies where possible GIST patients had been treated with therapies

other than imatinib or best supportive care were also identified. Because of the problems of diagnosis, in particular, an indirect comparison using these studies was not possible, therefore the results of these studies were not compared to the imatinib trials in the following section.

All imatinib-treated patients experienced adverse effects, although the adverse events were relatively mild.

Overall, imatinib was reported to be well tolerated. The most common serious events included unspecified haemorrhage and neutropenia. Skin rash, oedema and periorbital oedema were the common adverse events observed. Patients on the highest dose regimen (1000 mg per day in one trial) may experience dose-limiting drug toxicity.

A systematic review of prognostic studies confirmed that a large number of patients with advanced GIST die within a few years of diagnosis, but some patients may survive for many years. The evidence from modelling suggested that the patients in the imatinib trial were relatively comparable to all patients with recurrent or metastatic GIST in an unpublished study. (Text related to this study is academic in confidence and has been removed.)

Cost-effectiveness

Novartis submitted an economic evaluation of imatinib for unresectable and/or metastatic GIST. After a structured assessment of the Novartis model, it was found to be clearly presented and well written, the model structure and input data were transparent, and the level of simplification was reasonable in terms of the objectives and data availability. However, the original Novartis model overestimated the cost-effectiveness of imatinib because of disproportion of survival and time-to-treatment failure in the imatinib arm, and the use of a possibly biased survival curve for patients in the control arm.

The original Novartis model was modified so that the two important shortcomings were corrected. The modified Novartis model became less sensitive

to the choice of the survival curve for the control patients. According to the modified Novartis model, the estimated cost per quality-adjusted life-year (QALY) was £85,224 (range £51,515–98,889) after 2 years, £41,219 (£27,331–44,236) after 5 years and £29,789 (£21,404–33,976) after 10 years. The results from a new Birmingham model were also within the range of estimates from the modified Novartis model.

Conclusions

Evidence from uncontrolled studies indicates that the treatment with imatinib brings about clinically significant shrinkage of tumour mass in about half of patients with unresectable and/or metastatic, KIT-positive GIST. Results of modelling based on data from uncontrolled studies suggest that imatinib treatment improves survival in patients with unresectable and/or metastatic GIST. The economic evaluation modelling suggests that the cost per QALY gained ranges from £51,515 to £98,889 after 2 years, from £27,331 to £44,236 after 5 years and from £21,404 to £33,976 after 10 years. The estimates after 2 years are very uncertain because they were based on extrapolation beyond the trial data. The conclusions are based on the existing evidence, and uncontrolled trials in progress will provide additional data from more imatinib-treated patients and/or data of longer follow-up.

Recommendations for research

- More emphasis should be placed on quality of life within trials involving patients with

advanced malignancy. Adverse events should be reported so that intertrial comparisons can be made. As indicated by the increase in grade 3 adverse events with longer term use of imatinib reported in the industrial submission, long-term follow-up of adverse events is needed.

- Patients diagnosed with GIST are a heterogeneous group. Subgroup analysis of which, if any, patient types have a better or worse response to imatinib is needed. Analysis of individual patient data may be a good way of exploring these issues.
- There are many uncertainties surrounding imatinib prescription, such as the length of time for which patients should be on imatinib, the dose (i.e. is it better to step up or step down), drug resistance and the optimum time-point in the disease course to give the drug. When the present ongoing trials have had time to mature, answers to some of these uncertainties may be forthcoming and ongoing trials on adjuvant therapy in patients with primary disease may answer the question of timing of imatinib therapy. Secondary research, such as an update of this systematic review and a reassessment of the model, is highly recommended when ongoing trials reach completion.

Publication

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NHS R&D HTA Programme

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The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

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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.

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