

Clinical effectiveness and cost-effectiveness of imatinib dose escalation for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours that have progressed on treatment at a dose of 400 mg/day: a systematic review and economic evaluation

J Hislop,^{1*} Z Quayyum,² A Elders,¹ C Fraser,¹
D Jenkinson,¹ G Mowatt,¹ P Sharma,¹ L Vale^{1,2}
and R Petty³

¹Health Services Research Unit, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

²Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

³Division of Applied Medicine, School of Medicine and Dentistry, University of Aberdeen and Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, UK

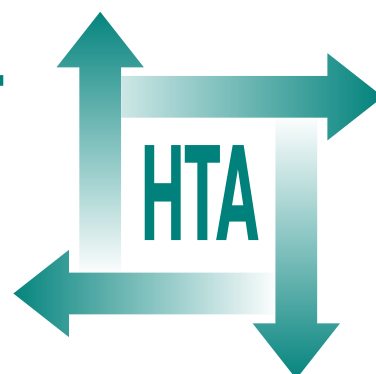
*Corresponding author



Executive summary

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Executive summary

Background

Fewer than 1% of all cancers in the gastrointestinal (GI) tract are gastrointestinal stromal tumours (GISTs). The median age of patients at diagnosis is between 50 and 60 years, and diagnosis typically depends upon morphological and clinical features being consistent with positive KIT/CD117 protein expression. Surgical resection is potentially curative but some patients will have unresectable and/or metastatic disease. Conventional chemotherapy and radiotherapy are ineffective in the management of unresectable and/or metastatic GIST and symptom control through best supportive care (BSC) was the main treatment available until imatinib (Glivec[®], Novartis Pharmaceuticals UK) at a dose of 400 mg/day was recommended in the 2004 guidance of the National Institute for Health and Clinical Excellence (NICE), as first-line management for those with KIT (CD117)-positive unresectable and/or metastatic GIST. Dose escalation upon disease progression after initially responding at the 400 mg/day dose was not recommended, although other recent guidelines have recommended dose escalation to a maximum dose of 800 mg/day, particularly for those patients with unresectable and/or metastatic GIST who also have specific exon mutations in the *KIT* gene. Since the 2004 guidance, sunitinib malate (Sutent[®], Pfizer UK), another tyrosine kinase inhibitor, has been licensed for the treatment of people with unresectable and/or metastatic GIST. NICE guidance recommends sunitinib as a treatment option for people with unresectable and/or metastatic malignant GISTs if imatinib treatment has failed because of resistance or intolerance, and the drug cost of sunitinib for the first treatment cycle is met by the manufacturer.

Objectives

The aim was to assess the effectiveness and cost-effectiveness of imatinib at escalated doses of 600 and 800 mg/day following progression of disease at a dose of 400 mg/day, compared with sunitinib, or the provision of BSC only for patients with unresectable and/or metastatic GISTs. Particular subgroups of interest were patients with specific *KIT* mutations.

Methods

Electronic searches were undertaken to identify published and ongoing randomised controlled trials (RCTs), non-randomised comparative studies and case series. Participants were adult patients with unresectable and/or metastatic GISTs whose disease had progressed on an imatinib dose of 400 mg/day. The interventions considered were imatinib at doses of 600 and 800 mg/day, sunitinib, or BSC only. Outcomes considered included overall response, overall survival (OS), disease-free survival, progression-free survival (PFS), time to treatment failure, health-related quality of life (HRQoL) and adverse effects.

The titles and abstracts of all identified reports were screened and full-text reports of potentially relevant studies assessed. Data were extracted from included studies, including details of study design, participants, interventions, comparators and outcomes. These studies were quality assessed using a checklist developed for non-randomised studies and case series, adapted from several sources, including the Centre for Reviews and Dissemination's guidance for those carrying out or commissioning reviews, Verhagen *et al.*, Downs and Black, and the Generic

Appraisal Tool for Epidemiology (GATE) (Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, *et al.* The Delphi List: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;51:1235–41; Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care intervention. *J Epidemiol Community Health* 1998;52:377–84). The Cochrane Collaboration's risk of bias tool was also used to evaluate the quality of sequence generation and allocation concealment of RCTs. Data analysis was confined to a comparison of data extracted from published Kaplan–Meier curves, and a narrative synthesis of results was presented.

For the review of economic evaluations, electronic searches were undertaken to identify cost or cost-effectiveness analyses relevant to the study question. Selection of relevant papers used similar methods to the review of clinical effectiveness. For included studies, data were extracted and critically appraised according to the guidelines produced by the Centre of Reviews and Dissemination for the critical appraisal of economic evaluations, and guidelines relevant to modelling studies. A Markov model was developed to compare the cost-effectiveness of seven clinically plausible alternative care pathways. The data used to populate the model were derived from the review of clinical effectiveness as well as the review of economic studies. Within the model people were assumed to move to the next therapy specified for a care pathway unless they had responded to treatment. All pathways ended with BSC, which patients would enter if they had exhausted all other treatments in a pathway. Both deterministic and probabilistic sensitivity analyses were conducted. The latter was restricted to considering distributions for the probability of death and non-response to focus attention on uncertainty in these data.

Results

Clinical effectiveness

Five studies (containing 669 patients in relevant treatment arms) met the inclusion criteria, with four ($n=318$) reporting outcomes for patients who received escalated doses of imatinib and one ($n=351$) reporting outcomes for patients who received sunitinib. No studies meeting our inclusion criteria were identified for BSC. The included studies were essentially observational in nature and subject to the biases associated with such data, consisting mostly of reporting of subgroups of patients who had been enrolled in RCTs that were not designed to assess the effects of dose escalation on patients with advanced and/or metastatic GIST whose disease had progressed on the 400 mg/day dose. Therefore, the selection of patients was neither randomised nor consecutive.

At an escalated dose of 600 mg/day, between 26% and 42% of patients showed either a partial response (PR) or stable disease (SD). Median time to progression was 1.7 months (range 0.7–24.9 months). No data on other outcomes were available.

At an escalated dose of 800 mg/day between 29% and 33% of patients showed either a PR or SD. The median OS was 19 months [95% confidence interval (CI) 13 to 23 months]. PFS ranged from 81 days to 5 months (95% CI 2 to 10 months). The median duration of response was 153 days (range 37–574 days). Treatment progression led to 88% discontinuations but between 16% and 31% of patients required a dose reduction, and 23% required a dose delay. There was a statistically significant increase in the severity of fatigue ($p < 0.001$) and anaemia ($p = 0.015$) following dose escalation.

For sunitinib, median OS was 90 weeks (95% CI 73 to 106 weeks). No data were available for other outcomes.

Insufficient data were available on the subgroup population of interest with *KIT* mutations, and these were not considered in the economic analysis.

Cost-effectiveness

Although seven economic studies were identified, only one full-text study and one abstract, comparing imatinib at an escalated dose, sunitinib and BSC, were identified. Neither was based on a UK context. The definition of BSC was not consistent across the studies, and the pattern of resources (including drugs for treatment) and measures of effectiveness also varied.

For economic evaluation, a Markov model was developed to compare the alternative treatment strategies for people with *KIT* (CD117)-positive unresectable and/or metastatic GISTs, whose disease has progressed on treatment with imatinib at a dose of 400 mg/day.

The assumed pathway of the model

The model was based on seven clinically plausible care pathways. The states considered in the model were those thought to reflect care pathways for people with GIST. Patients entering the pathways were those who failed on imatinib 400 mg/day. The alternative treatments considered were imatinib 600 mg/day, imatinib 800 mg/day, sunitinib (within its licensed dose regimen), and BSC. The patient pathways considered in the model were:

- start with imatinib 600 mg then imatinib 800 mg if the patient fails on 600 mg, *or*
- start with imatinib 600 mg then imatinib 800 mg if the patient fails on 600 mg, and then sunitinib if the patient progresses or fails on 800 mg, *or*
- start with imatinib 600 mg then move to treatment with sunitinib if the patient fails to respond to 600 mg.

Within the model, Path-1, BSC (which was assumed to include continuing medication to prevent tumour flare), was the least costly and least effective pathway. It would be the care pathway most likely to be cost-effective when the cost per quality-adjusted life-year (QALY) threshold was less than £25,000. Path-4, imatinib at 600 mg/day, was most likely to be cost-effective at a threshold of between £25,000 and £45,000. Imatinib at 600 mg/day followed by further escalation followed by sunitinib was most likely to be cost-effective at a threshold >£45,000.

Sensitivity analysis

The results did not greatly alter under the majority of the sensitivity analyses conducted. However, all of the economic data were based upon point estimates for mortality and response rates that were, in turn, based upon sparse and potentially biased data.

It was also not possible, owing to lack of data, to make alternative assumptions about probabilities of death and response change over time, or reductions in utility associated with adverse effects of treatment. Further assumptions that were required to be made in the model were that patients who move on to BSC would remain on treatment with imatinib at 400 mg/day to prevent tumour flare (but that this would have no impact on effectiveness).

Discussion

Relatively few relevant data were identified for this review and what data were available are essentially observational and non-comparative. Such data are potentially biased, with both the magnitude and direction of the bias being uncertain. Therefore, all results should be interpreted with caution.

Approximately one-third of unresectable and/or metastatic patients with GIST who receive dose-escalated imatinib show either response or SD, which can be maintained over several months. However, few data were available for imatinib at 600 mg/day and median OS for imatinib at 800 mg/day and sunitinib was < 24 months. Few data were available on adverse events but up to one-third of patients may need a dose reduction or a dose delay. Patients may see a significant worsening of anaemia and/or fatigue upon dose escalation.

The results of the economic model showed that pathways involving dose escalation would be cost-effective should the cost per QALY threshold be \geq £30,000. Treatment with sunitinib after progressing on imatinib at 400 mg/day was not likely to be cost-effective. However, this result was based on limited non-comparative data for this treatment and is probably unreliable.

There are a number of remaining uncertainties, including:

- The results are suggestive of a benefit from dose escalation but the non-randomised, non-comparative data available for review are potentially biased. This limits the usefulness of both the review of effectiveness and the economic model.
- There was a lack of evidence on quality-of-life (QoL) outcomes, which would have informed the economic model, and would also be of importance to patients.
- There was little evidence on response and survival on escalated doses of imatinib, specifically for those with different mutations in the *KIT* gene.
- There is uncertainty surrounding the effects of dose modifications and potential differential effects of sunitinib for both the population being given this drug because of intolerance to imatinib and those receiving sunitinib after failure on imatinib.
- There is also uncertainty surrounding the nature and severity of adverse events and their impact on quality and quantity of life and costs.

Conclusions

Implications for service provision

There was very limited evidence available from very few studies on the effects of escalated doses of imatinib or treatment with sunitinib for the target population. The evidence that was available was essentially observational in nature and subject to the biases associated with such data, consisting mostly of reporting of subgroups of patients in RCTs that were not designed to assess the effects of dose escalation.

The limited evidence base suggests that around one-third of patients with unresectable and/or metastatic GIST who have failed on a dose of 400 mg/day may show response or SD with escalated doses of imatinib, and those who do respond may have a reasonable chance of maintaining this response over a longer period of time than would otherwise have been the case.

For all patients receiving either dose-escalated imatinib, or sunitinib, median OS, where reported, was < 2 years.

The results of the economic model are surrounded by a considerable degree of uncertainty due to the limited nature of the available evidence base, and the direction and magnitude of biases in the results is unclear, so these results need to be interpreted with caution. They indicate that should society's threshold for willingness to pay be less than £25,000 per QALY a pathway of BSC only has the highest probability of being cost-effective. Between a threshold of £25,000 and £45,000 provision of an escalated dose of imatinib would be most likely to be cost-effective. Above a

threshold of £45,000 a pathway of escalated doses of imatinib followed by sunitinib, if necessary, would be most likely to be cost-effective.

In terms of policy-making, the degree of uncertainty itself, in the authors' opinion, clearly illustrates that at present there is insufficient available evidence to show that dose escalation of imatinib upon progression at the 400 mg/day dose (for patients with unresectable and/or metastatic GISTs) would be a cost-effective strategy for the NHS.

Recommendations for research

Suggested priorities for further research are made:

- Ideally, an RCT involving patients who progress on 400 mg/day imatinib in which patients are randomised to pathways describing alternative combinations of dose escalation with imatinib and the use of sunitinib should be performed. Such a study may be difficult to organise as neither patients nor practitioners may be in equipoise. Therefore, alternative quasi-experimental or observational designs should be considered but with sufficient focus on understanding and controlling for selection biases.
- The pathways most likely to be cost-effective at thresholds society might be willing to pay and hence, potentially, the most useful to assess in any further primary study are dose escalation with imatinib and dose escalation with imatinib followed by sunitinib if necessary. A trial should include an economic evaluation and measurement of health-state utilities and have sufficiently long enough follow-up to capture all outcomes of interest.
- Where possible further studies should also report outcomes for subgroups of patients with specific *KIT* mutations.
- In any prospective comparative study a wider perspective on the consideration of costs might also be informative (e.g. costs that fall on Personal Social Services, which would be relevant for NICE to consider, and costs for patients and their families, which goes beyond NICE's reference case).

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