HEALTH TECHNOLOGY APPRAISAL: NICE Health Technology Appraisal - Imatinib for unresectable and/or metastatic gastrointestinal stromal tumours

Assessment Report

TO: NICE	FROM: NHS Quality Improvement Scotland 12 May 2010

This report was produced by Health Services Research Unit and the Health Services Economics Research Unit in the Institute of Appliance Sciences, University of Aberdeen. The aim was to assess the effectiveness and cost-effectiveness of imatinib at escalated doses of 600 mg and 800 mg per day following progression of disease at a dose of 400 mg per day, with sunitinib, or the provision of best supportive care only for patients with unresectable and/or metastatic GIST's.

The authors identified published and ongoing randomised clinical trials, comparative studies and case series. Outcomes considered included overall response, overall survival, disease-free survival, progression-free survival, time to treatment failure, health related quality of life and adverse effects.

For the review of the economic evaluation a Markov model was developed to compare the cost-effectiveness of seven clinically plausible alternative care pathways.

At an escalated dose of 600 mg of imatinib per day between 26% and 42% of patients showed either a partial response or stable disease. At an escalated dose of 800 mg per day between 29% and 33% of patients showed a partial response or stable disease. The median overall survival was 19 months, (95% CI 13 to 23 months). For Sunitinib, the median overall survival was 90 weeks (95% CI 73 to 106 weeks).

Within the economic model best supportive care, (which was assumed to include continuing medication to prevent tumour flare) was the least costly and least effective. It would be the care pathway most likely to be cost-effective when the cost per QALY threshold was less than £25,000. Imatinib at 600 mg per day was most likely to be cost-effective at a threshold between £25,000 and £45,000. Imatinib at 600 mg per day followed by further escalation, followed by sunitinib was most likely to be cost-effective at a threshold over £45,000.

The authors concluded that there was limited evidence available on the effects of escalated doses of Imatinib 600mg per day and 800mg per day or treatment with Sunitinib for people with unresectable or metastatic GIST that had progressed on 400mg per day. They recommend an RCT involving patients who progress on 400mg per day to randomisation to dose escalation with Imatinib and dose escalation with Imatinib followed by Sunitinib. Such studies should include an economic evaluation and measurement of health state utilities.

Comments

The assessment is detailed obtaining all published and some unpublished information on patient outcome with progressive GIST's on a dose of 400mg per day of Imatinib. The methods used to assess outcome are appropriate and the alternative care pathways seem reasonable. The authors do not however take into account the role of surgery in these patients. Progression can often be unifocal and in those there is some evidence that resection of that focus of tumour may be associated with prolonged survival. DeMatteo and colleagues (1) operated on 40 patients with metastatic GIST's treated with Tyrosine Kinase Inhibitors. In 13 with focal resistance (1 area of tumour increasing in size) the median time

to progression after resection was 12 months with a two year survival of 36%. The median time to progression after resection for patients with multifocal resistance was three months.

This is similar to our experience between 10/02 and 8/09. We have performed 10 operations on 9 patients with progression of GIST's on Imatinib (Table 1). The median survival for the group is 15 months with 3 surviving two years or longer. 3 patients were commenced on Sunitinib for progression after operation while 4 have died of their disease.

These findings obviously add to the complexity of assessing outcome in patients with metastatic GIST resistant to Imatinib. The authors of the assessment need to take this into account as it will impact on both cost and outcome in the care pathways. Our local policy has been to assess patients with progression on 400mg per day of Imatinib for operation. For those with one (9 events) or two foci (1 event) of progression we will resect those areas of GIST only. It is likely that a similar policy has been in effect in other centres (1,2,3) and without individual patient data from the trials reference in the assessment it is difficult to separate the effect of resectional surgery from escalated Imatinib or Sunitinib. In this regard it would be important for the authors to determine the frequency and outcome of patients with focal and multifocal resistance to Imatinib for metastatic or unresectable GIST.

References

(1) DeMatteo R P, Maki R G, Singer S, Gonen M, Brennan M, Antonescu C
Results of Tyrosine Kinase Inhibitor Therapy Followed by Surgical Resection for Metastatic Gastrointestinal Stromal Tumor. Annals of Surgery 2007, 245: 347-352

(2) Gronchi A, Fiore M, Miselli F, Largonigro M S, Coco P, Messina A, Pilotti S, Casali P G
Surgery of Residual Disease Following Molecular-targeted Therapy With Imatinib Mesylate in Advanced/Metastatic GIST. Annals of Surgery 2007, 245: 341-352

(3) Al-Batran S E, Hartmann J T, Heidel F, Stoehlmacher J, Wardelmann E, Dechow C, Dux M, Izbicki J R, Kraus T, Fischer T, Jager E
Focal progression in patients with gastrointestinal stromal tumors after initial response to Imatinib Mesylate: a three-centre-based study of 38 patients. Gastric Cancer (2007) 10: 145-152

Table (1)

Outcome of patients undergoing operation for Imatinib resistant GIST.

Case	Date of Operation	Time to Progression/Death (months)
*1	10/2002	70
2	11/2002	1
3	8/2007	33
4	10/2007	31
5	4/2008	5
6	6/2008	5
7	7/2008	20
*8	8/2008	19
9	8/2008	11
10	8/2009	5

* Patient operated on twice for progression at 1 and then 2 sites. Imatinib before 2nd operation escalated to 800mg per day.

Yours sincerely

[redacted]