NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (review of TA196)

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Prof Ian Judson

Name of your organisation Royal Marsden Hospital

Are you (tick all that apply):

√ a specialist in the treatment of people with the condition for which NICE is considering this technology?

√ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Imatinib is routinely used as the first treatment for patients with advanced gastrointestinal stromal tumour (GIST), worldwide. The use of adjuvant treatment for patients at high risk of recurrence has become standard practice following the publication of the Scandinavian Sarcoma Group SSGXVIII study (1)). This trial, which compared 12 months adjuvant imatinib with 36 months in patients at very high risk of recurrence not only demonstrated a progression-free survival benefit, as had the original Z9001 study from the ACOSOG group (2), which compared 12 months adjuvant imatinib with placebo, but also showed a survival advantage for 36 months of treatment. Adjuvant imatinib has been made available to physicians treating GIST via the Cancer Drugs Fund and following the results of the SSGXVIII study it has become routine to give 3 years of treatment.

As yet no benefit has been demonstrated in patients at low risk of relapse and this remains a treatment that should only be administered in specialist units by physicians trained in the administration of imatinib. The determination of risk is not trivial and although this is usually determined using the scheme proposed by (3) there is also a need to know the mutational status of the *KIT* and *PDGFRA* genes. Most GISTs are driven by a mutation in *KIT,* sometimes *PDGFRA*, but about 10% of patients, especially young women with the disease, have no mutation in either gene, so-called wild-type (WT) disease. Although imatinib is of uncertain benefit against advanced cases of WT GIST it remains unclear what role imatinib plays against micro-metastatic WT disease, presumed to be present in many patients with high risk resected GIST. A percentage of patients with *KIT* mutations, probably approaching

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10% of primary cases (4) have a mutation in exon 9, which confers relative resistance to imatinib, though higher doses are effective (5). Although there are no data to suggest that higher doses of imatinib should be given in the adjuvant setting for such tumours, this is to be permitted in certain trials currently being proposed. The *KIT* exon 9 mutation is associated with poorer prognosis and aggressive disease, and is usually found in small bowel or rectal GIST, rather than gastric tumours, which may explain in part the worse outlook for GIST arising at these other sites. In contrast, the commonest *PDGFRA* mutation is in exon 18, termed D842V for the amino acid substitution it produces, and is usually found in gastric GIST. This mutation is resistant both to imatinib and sunitinib and adjuvant imatinib is not recommended for patients with this genetic variant (6). However, it is usually a more indolent disease, with a lower rate of relapse than *KIT* exon 11.

Current clinical guidelines that address the issue of adjuvant imatinib include those produced by the European Society of Medical Oncology (2012), the British Sarcoma Group and the National Cancer Coordinating Network (NCCN). The ESMO guidelines (2012) contain a good discussion of risk assessment, emphasise the need for mutational analysis, address the uncertainties concerning WT GIST and the appropriate adjuvant dose for *KIT* exon 9 but basically recommend as standard therapy 3 years of adjuvant imatinib 400 mg daily for patients at high risk of relapse. It is also pointed out that patients with tumour rupture, either occurring prior to resection of the primary, or at the time of surgery, should essentially be regarded as having metastatic disease, since the risk of relapse is almost 100%.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

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What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

There are no alternatives to adjuvant imatinib. The use of imatinib is straightforward to experienced clinicians and the side effect profile is very manageable, with no apparent long term adverse effects. Quality of life appears good in everyday clinical practice. Although in all adjuvant studies reported to date a small percentage of patients have stopped treatment because of side effects (including patients on placebo in Z9001), very few patients appropriately managed with dose adjustments and attendance to the amelioration of side effects such as diarrhoea, are unable to continue treatment.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

There are no obvious issues to consider, in that there are no patient groups who would be unable to receive this therapy.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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In addition to the published trials, a large study (62024) has been conducted by the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group. This study compared two years of adjuvant imatinib with observation alone in patients with intermediate and high risk disease. One concern in conducting the study was that patients treated with imatinib in the adjuvant setting who subsequently relapsed off treatment might experience a shorter duration of disease control owing to the induction of secondary resistance. The primary endpoint of the study was altered from survival to imatinib failure-free survival in order to be able to detect such a phenomenon, should it occur. One of the important findings of this study has been that exposure to imatinib in the adjuvant setting has had no adverse impact on the duration of disease control of patients who have subsequently relapsed. This indicates that the lead time of disease control in the adjuvant setting should result in a total increase in survival, given that once resistance to imatinib in the advanced setting does occur survival is then limited.

The total number of participants IN STUDY 62024 was 908 and an interim analysis of the study findings was presented at the American Society of Clinical Oncology meeting in 2013 by Prof Casali – a summary of which is below:

"This planned interim analysis was conducted after the occurrence of 115 events according to the Imatinib failure-free survival primary end-point with a significance level of 1.5%. At a median follow-up of 4.7 years, the 5-year Imatinib failure-free survival was 87% in the Imatinib arm and 84% in the observational arm (HR=0.80, 98.5% CI [0.51; 1.26], p=0.23). At three years, relapse-free survival was 84% in the Imatinib arm and 66% in the observational arm, while at five years relapse-free survival was 69% in the Imatinib arm and 63% in the observational arm (p<0.001). The 5-year overall survival was 100% versus 99%. There were 528 patients with high-risk GIST as determined by local pathology, and for these patients the 5-year Imatinib failure-free survival was 79% (Imatinib arm) versus 73% (Observational arm) (p=0.11). Among 682 patients with centrally reviewed pathology, there were 336 patients with high-risk GIST, and the 5-year Imatinib failure-free survival in these patients was 77% (Imatinib arm) versus 73% (Observational arm) (p=0.44). In the Imatinib arm, 17% of the patients stopped early due to toxicity or refusal."

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within

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3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Although GIST is the commonest sarcoma to affect the gastrointestinal tract it remains an uncommon disease and there are no implementation or training issues for adjuvant imatinib.

Bibliography

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2. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;373(9669):1097-104. Epub 2009/03/24.
3. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Seminars in diagnostic pathology. 2006;23(2):70-83.
4. Cassier PA, Ducimetiere F, Lurkin A, Ranchere-Vince D, Scoazec JY, Bringuier PP, et al. A prospective epidemiological study of new incident GISTs during two consecutive years in Rhone Alpes region: incidence and molecular distribution of GIST in a European region. British journal of cancer. 2010;103(2):165-70. Epub 2010/07/01.
5. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol. 2010;28(7):1247-53. Epub 2010/02/04.
6. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23 Suppl 7:vii49-55. Epub 2012/11/20.