Patient Group Submission to NICE about the re-appraisal of imatinib for metastatic or unresectable GIST

20th November 2009

Background

Imatinib is a very effective drug with relatively few side effects in most patients, which are usually easy to deal with. In some, it provides stable disease for many years. For others, it is effective for shorter periods. We know that some patients tolerate imatinib much better than others, and that some patients have to reduce the dose to have a tolerable quality of life, but still often have stable disease for years. We know from the results of clinical trials that patients with exon 9 mutations respond better to 800mg/d than 400mg/d. We also know that many patients who develop resistance to imatinib, and whose tumours start to re-grow on 400mgs, re-gain stability if that dose is increased to 800mgs. We also know of patients going from 400mgs to 800mgs on developing resistance, then to sunitinib and experimental treatments, before returning to 400mgs of imatinib in a palliative/end-of-life setting, with renewed periods of stability with each change.

The understanding of the mechanisms of imatinib activity and the mutations causing GIST is increasing rapidly. It is quite apparent that gaining and retaining a response to imatinib is the core strategy for treating GIST. Other treatments in second and subsequent lines are purely palliative. It calls for a managed approach through the course of imatinib treatment to try to prevent resistance and relapse, not an event-focused approach, changing treatment subsequent to resistance.

However, there are still many unanswered questions and many questions for which the answers are beginning to appear. The recent (early November) CTOS conference produced many papers on the topic of managing GIST. The guesswork as to why different patients respond in so many different ways is being replaced by some certainties.

Current Position

The current NICE guidelines only allow for the use of 400mgs/day for GIST patients with CD117 +ve GIST. Doses up to 800mg/day were licensed by the EU in 2005, over four years ago, but were not approved by NICE in TA86 published in 2004.

We know that most clinicians with expertise in treating GIST patients do not follow NICE guidelines, since they do not represent good clinical

practice, and these clinicians want the best for their patients. We also now have more accurate diagnostic tools than CD117, so the limitation of imatinib treatment to CD117+ve GISTs makes no sense. We also have so much more knowledge from peer-reviewed research about the mutations causing GIST, the ways in which these different mutations affect the treatment needs of the patient, and the ways that patients respond differentially to treatment, that we need a more flexible approach.

The Managed Pathway

The paramount importance of retaining a response to imatinib is well demonstrated. Why should some patients first treated in 2000 still be responding to 400mg/d, others still responding to 600 or 800mg/d (having been randomised to that treatment in early trials), while others who started treatment more recently have relapsed and died despite many lines of therapy following imatinib? If this disease had a single manifestation then such differences would not be so dramatic.

Research already reported, and confirmed by new studies at CTOS in November 2009 with papers due for publication in the coming months, tells us that:

- neo-adjuvant use of imatinib, permitted through TA86, is an important option for patients initially regarded as unresectable
- imatinib clearance from the body increases over time. Ironically this is probably caused by increased liver function due to the beneficial response of liver metastases to the treatment
- response to imatinib can be monitored through blood plasma level testing with dose adjustments targeted at retaining a response by maintaining a level of 1000ng/ml of imatinib in blood
- mutation analysis is a reliable prognostic tool - patients with an exon 9 mutation can attain progression free survival intervals on 800mg/d similar to that attained by exon11 patients on 400mg/d

We also believe that:

- surgery can play an important role in managing the delay of resistance through resection of tumours at the time of optimal response to imatinib
- imatinib at 400mg/d to provide symptomatic relief in end-of-life care is an important contribution to patient benefit
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Our Recommendations

We would therefore like to suggest that:

1. All GISTs are diagnosed by the best means available, not restricted to one test.

2. All GIST should be analysed for mutations and the information considered as prognostic, helping determine the treatment approach

3. All GISTs which are unresectable or metastatic should be treated with imatinib, at whichever dose provides the best tumour stability and QoL for the patient, allowing dose reduction or escalation as appropriate, depending on the stage in the pathway of disease that patient has reached

4. Data should be recorded centrally so that the UK can advance its understanding of the most efficient ways of managing the treatment of GIST patients.

5. The resection of tumours which have been reduced in size by imatinib, should be part of the whole treatment pathway, and that imatinib should be available after such surgery.

We believe that this approach will leave future treatment options open as research develops. We recognise that there will be cost issues to address but we would remind the Appraisal that history tells us that, left untreated, patients with metastatic GIST have a median survival of 9 months. With imatinib and subsequent treatments that becomes 5 years. We believe that with a managed treatment pathway focused on retaining a response to imatinib that will extend much further.

We also recognise that clinical trials that are either on-going or planned for the future will enable us to compare:

- 800mgs of imatinib with sunitinib, on progression on 400mgs imatinib
- 400mgs imatinib with sunitinib as first line treatment,
- imatinib with nilotinib as first line treatment

However, none of this will address the current core issue which we identify as increasing the length of the time of response to imatinib and, where it is feasible, avoiding the development of resistance to it.

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