1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?

We have conducted a West of Scotland and Lothian audit for all patients treated initially with imatinib 400mg per day from diagnosis. Restricted access to second generation tyrosine kinase inhibitors in the UK could result in suboptimal treatment for almost half of chronic myeloid leukaemia patients: results from a West of Scotland and Lothian population study. Gallipoli P, Shepherd P, Irvine D, Drummond M, Holyoake T. Br J Haematol. 2011 Apr 22. doi: 10.1111/j.1365-2141.2011.08653.x

This audit demonstrates that in the real world approximately 50% of patients who are started on imatinib at diagnosis will remain on imatinib and in good response 5 years later. However 50% of patients will have discontinued imatinib therapy. These patients include a tiny number who proceed to stem cell transplant, some who have intolerance to imatinib (nearly 20%) and switch to one of the second generation agents, either dasatinib or nilotinib, some who fail imatinib and switch to dasatinib or nilotinib and some who are deemed to have a sub-optimal response to imatinib and are switched to dasatinib or nilotinib. The study included 122 patients diagnosed between 2002 and 2010. 44 patients of 122 stopped imatinib because of intolerance or failed response of whom 39 went onto second generation drugs dasatinib or nilotinib. For these 39 patients the median time on imatinib was 13.2 months but 19.2 months on second generation strongly suggesting the second generation drugs were both tolerated and effective. Indeed 25 of 39 patients were deemed to have had a satisfactory response, 10 were intolerant and 4 failed to respond. The EFS on second generation drugs was 58% which was better than for imatinib first line at 53%. Both the intolerant to imatinib and the failed imatinib groups did equally well on
second generation drugs going against the idea of reviewing intolerance separately to resistance. In other words 60% of patients who do not do well with imatinib will be rescued by dasatinib or nilotinib.

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations?

My take on this is that both nilotinib and dasatinib are exceptionally good drugs when used for those who fail imatinib either for INTOLERANCE or for RESISTANCE. In the worst case scenario (hypothetical) if a patient became imatinib resistant and imatinib was discontinued the person might die the following day, whilst in the very best case scenario they would go on to dasatinib or nilotinib and live a normal life (eg more than 10 years). If in this setting the drug price is too high then the threshold for QALY set at £30,000 is likely to be bridged simply because dying immediately is cheaper than living on drug for 10 years. In reality if we stop imatinib in these cases they will not die the following day but their life expectancy would be limited to months/few years as they are already a high risk group as they are imatinib resistant and given palliative therapy with hydroxyurea they would all enter blast crisis and die with a median somewhere around 24 months. If these same patients were given dasatinib or nilotinib we know from the audit above, performed in Scotland on real Scottish CML patients, that their EFS would be 57.9% at 3 years and overall survival 91% (only 4 deaths 2 of which were CML unrelated causes, 1 post-transplant and 1 from CML).

These drugs cannot be any better from a response point of view therefore the only way to reduce the QALY threshold is to cut the cost of the drugs.

3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound?

The recommendations are completely out of line with our clinical experience of using these drugs. These drugs work in 60% of patients who become resistant to imatinib. These drugs are very well tolerated and given on an out patient basis. Only today I have been in a clinic full of patients on second generation TKI dasatinib and nilotinib who would have died from disease progression had they not been given these drugs. The doctors all know that this is FACT. The decision by NICE is only made on the basis of cost – this being the case the only way out of this situation is to try to force the drug companies to lower their price.

4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland?

What happens in Scotland currently is that every patient diagnosed with CML is commenced on imatinib 400mg or entered into SPIRIT 2 trial which offers a 50:50 randomisation between dasatinib and imatinib. The patients are monitored every 3 months. We apply the ELN recommendations (JCO 2009, Baccarani M et al, ). If the patients fail imatinib they either go onto dasatinib or nilotinib (95%) or are considered for a stem cell transplant (no one recently in Glasgow). Similarly if patients show a suboptimal response according to ELN they go onto dasatinib or nilotinib. Similarly if intolerant they switch to one of these agents. In a tiny number of patients we find they develop
haematological toxicity with all 3 available TKI and if not fit for stem cell transplant (the vast majority) we use hydroxycarbamide. NO patient is on interferon for treatment of CML in WOSCC.

5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be.

Absolutely. If we cannot give the 50% of patients who become intolerant or resistant to imatinib either nilotinib or dasatinib then we would use stem cell transplant with mortality of 10-40% depending on age and with +++ long term complications (only applicable in a small minority of cases <15%) or hydroxycarbamide a palliative agent thus condemning these patients to disease related death within a short time window when we know there are good drugs out there for these patients. I hope that by applying for each case individually we would still be able to prescribe nilotinib or dasatinib for all those cases who develop imatinib resistance as there is really no other choice that makes any sense.

6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.

I would hope our extensive experience with these drugs in Scotland and our careful audit and analysis of outcome would be taken into account. I have led these studies from the beginning (PI Scotland for all imatinib, nilotinib and dasatinib trials to date) with huge input from Dr Mark Drummond. It has been our privilege to be able to secure amazingly good drugs for patients with CML all over the country – Arran, the Borders, Fife, Wick etc (even one case by sleeper from Kent and another from London). Please ensure we can continue to serve our patients as we have been doing until now.

7. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment

Simply please do everything you can to reverse this decision.
1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?

I would suggest reading the following article:

**Restricted access to second generation tyrosine kinase inhibitors in the UK could result in suboptimal treatment for almost half of chronic myeloid leukaemia patients: results from a West of Scotland and Lothian population study.** Gallipoli P, Shepherd P, Irvine D, Drummond M, Holyoake T. Br J Haematol. 2011 Apr 22. doi: 10.1111/j.1365-2141.2011.08653.x

As with the use of all TKIs since they became available in 2002 we have audited their use extensively in Scotland. This clearly illustrates that we would be doing almost 50% of our CML population a disservice by removing their availability. These patients MAY have recourse to transplant (approximately a 30% mortality rate depending on source data used and pt factors) a procedure which costs £70,000 with approx £2,400 ongoing monthly cost thereafter (which includes a £21,000 per readmission sum). In the NICE economic model this probably looks fairly attractive; killing patients with the treatment certainly does reduce ongoing drug costs.

How out of step this decision is can be easily gleaned from the literature on the subject (see ELN Guideleines, JCO 2009 Baccarini et al). This is a Europe-wide consensus guideline produced with UK representation. Our audit results show that 60% of patients who go onto these drugs achieve an excellent response. Without them this group would now comprise patients on high dose imatinib (600-800mg daily, expensive, toxic & less effective than nil or das, dead as a result of
transplant, some cured and well as a result of transplant with a significant cohort alive but with serious transplant induced co-morbidities including downstream secondary cancers, heart disease etc, patients on palliation with hydroxycarbamide, a useless- but cheap-treatment but keeps white cell count down, and perhaps a few individuals on interferon. The latter remains expensive (approx £1000 per month) and produces acceptable responses in only 10-20%, with considerable toxicity. In short treatment would return to a hodge-podge of unsatisfactory treatments from the useless to reasonably effective (HD IM) to the downright lethal.

2 Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations?

Any drug that prevents death, but demands ongoing administration, is going to be unattractive to our current economic modelling systems. It is my understanding that the economic model used by NICE (& produced by PENTAG) was hugely flawed, specifically with regard to the comparator drugs in which Hydroxy carbamide (which costs pennies) featured highly. This comparator is laughably inappropriate, as all doctors asked to comment on the model (including myself) pointed out. The correct comparator should have been high dose imatinib. This is even more expensive (approx £40,000 pa) and significantly more toxic than either dasatinib or nilotinib.

I appreciate that cost-modelling does not take into account the ‘social’ costs of therapy however I would appeal to the SMC / QIS to give some thought to this: CML patients may now have a near normal life expectancy thanks to these drugs. This is entirely down to scientific and pharmaceutical advances and is a triumph of modern medicine. Furthermore, these patients also function normally and importantly RETURN TO WORK. If we didn’t have 2nd line TKIs many patients would be held on imatinib either at standard or high dose; this would still cost a significant amount (in the case of high dose IM considerably more than das or nil). Uncomfortable imatinib side effects would have to be tolerated (after all the alternative is not there) and QoL would suffer. Many patients would stop functioning and many would stop work. I cannot think of a single working patient in our large CML practice (60-80 patients) who has stopped work for disease or treatment related reasons.

2. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound?

No. For all the reasons above.

4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland?
I refer you to the comment of Professor Holyoake provided under this section, with whom I share a large WoS CML practice:

“What happens in Scotland currently is that every patient diagnosed with CML is commenced on imatinib 400mg or entered into SPIRIT 2 trial which offers a 50:50 randomisation between dasatinib and imatinib. The patients are monitored every 3 months. We apply the ELN recommendations (JCO 2009, Baccarani M et al. ). If the patients fail imatinib they either go onto dasatinib or nilotinib (95%) or are considered for a stem cell transplant (no one recently in Glasgow). Similarly if patients show a suboptimal response according to ELN they go onto dasatinib or nilotinib. Similarly if intolerant they switch to one of these agents. In a tiny number of patients we find they develop haematological toxicity with all 3 available TKI and if not fit for stem cell transplant (the vast majority) we use hydroxycarbamide. NO patient is on interferon for treatment of CML in WOSCC”.

5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be.

Yes. We would do more transplants, have more transplant related deaths and have more patients remaining on imatinib (including high dose) with chronic toxicity. We would use interferon in some circumstances (again at considerable expense & toxicity) in the knowledge it would only benefit a minority (10-20% at most). For those denied 2nd Gen TKIs a proportion would still get them; we would make a good case on a non-formulary / exceptionality basis. Please note; while I am no health economist I rather suspect that by the time you add all these cases up (HD IM, Transplant, 2GTKIs granted on a NF application) and factor in the chronically ill who are unable to work we are not going to be saving very much money after 'unapproving' these drugs.

6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.

We have a strong CML background in this country with a Scotland-wide network of interested expert clinicians and a nationwide Treatment Guideline in preparation. This will incorporate the role of nilotinib as first line therapy if approved (see below). These drugs are used within tight local guidelines and are audited regularly (as we have demonstrated). The same cannot be said for England outwith the larger interested centres.

A final and important comment is with regards the availability of Nilotinib as a first line treatment. I understand that this is currently going through the SMC and will involve a price reduction to that of Imatinib when used first line. The implications of this for the use of the second line agents are two-fold:

1. Less patients will fail first line therapy. Nilotinib is more effective than imatinib. My estimates from the literature are that 10-20% of patients will require a 2nd line agent with nil as compared to 30-40% in our IM audit / literature. Furthermore, for patients intolerant of nilotinib, imatinib will be used (cost neutral) as a second line therapy (a major
shift in Scottish practice). Therefore we are looking at only 10% or so of patients escalating to dasatinib, a marked reduction from before. I would therefore expect the treatment of CML to become gradually more cost effective with less use of these agents in the second line.

2. Nilotinib cost reduction. This is available for patients treated with nilotinib as first line. This immediately produces a grey ‘first line area’. What if a patient is rapidly intolerant of imatinib, say within days or even 4-6 weeks, who has not yet achieved a remission (and this does happen)? I would still consider use of nilotinib here as ‘first-line’ as far as long-term disease control is concerned. Thus a proportion of what we would have considered 2nd line (and paid for accordingly) might, quite legitimately, be accepted for first line discounted therapy. I should point out that I have discussed this issue with Novartis (in my view the fairest and most ethical company involved in treating blood cancers) and they agree that the line is a blurred in this regard but that they would honour the agreement (indeed they do not ask for evidence re line of therapy).

These two important issues need to be taken into account when making the decision on 2G TKIs in a Scottish context.

7. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment

I would reiterate Professor Holyoake’s plea to reverse this NICE MTA. As I have illustrated above it is based on a flawed economic model with unrealistic cost comparators. First line Nilotinib will alter the picture in the coming years. If these drugs are refused we can safely predict that many patients will die unnecessarily from inappropriate and ineffective treatments in the years to come. I think it would be a grave error to align ourselves with this decision while the rest of Europe looks on in disbelief.

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