Professional organisation statement template

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: Dr Rodney Burnham, RCP Registrar

Name of your organisation NCRI/RCP/RCR/ACP/JCCO

Comments coordinated by Dr Christopher Fegan – clinical expert nominee of the above organisations

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) Dr Fegan sits on the Clinical Trials Committee of the UK CLL Forum who run the NCRN trials in CLL in the UK. Also on the Clinical Guidelines Committee of the UK CLL Forum who are presently updating its treatment guidelines (last published 2004) for the UK.

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?

The present recommendations by the BSH/UK CLL Forum is that patients who are fit enough should receive fludarabine/cyclophosphamide (FC) combination therapy. Those who are unsuitable for FC will almost certainly be receiving chlorambucil monotherapy. There is virtually universal acceptance within the UK of this guideline.

The very soon to be published NICE appraisal is probably going to allow the use of fludarabine/cyclopohsphamide/rituximab (FCR) for first line therapy for CLL patients deemed fit enough for such intensive treatment. Patients who are deemed not suitable for FCR therapy will almost certainly still be treated with chlorambucil – probably monotherapy.

Thus the new technology is for relapsed/refractory patients to receive rituximab in addition to the chemotherapy they would almost certainly have received anyway.

As of present those patients who have received prior FC therapy are, depending on the duration of response and cytogenetic results going to be offered repeat FC therapy or possibly CHOP (Cyclophoshamide, adriamycin, vincristine, prednisolone) or if fit enough an allogeneic stem cell transplant following re-induction therapy. Thus we would anticipate that rituximab will simply be added to the FC or CHOP therapy. We are very well experienced with the R CHOP regimen with high grade NHL so if this technology is approved then RCHOP would replace CHOP alone. Obviously FCR would replace FC if approval for this technology is granted.
Those not suitable for more intensive therapy will again probably receive a chlorambucil but if this technology is approved will include rituximab.

If at relapse there is a p53 deletion or if the patient is deemed refractory to fludarabine an alemtuzumab or steroid based regimen is commonly used. However there is evidence from the Wierda et all 2005 J Clin Oncol 2005 23;4070-4078 that fludarabine refractory patients can still respond to FCR therapy – overall response 58% with a complete response of 6% which compares with 33% OR with only 2% complete responses in fludarabine failure patients with alemtuzumab– Keating et al Blood 2002 99: 3554-3561.

At this present time we also have bendamustine being used in the UK free of charge on a named patient basis. The license for Bendamustine we understand is imminent but its role in CLL has yet to be resolved. I suspect it will be used for those patients deemed not fit enough for repeat FC (=/- rituximab) but with a reasonable performance status. However if this technology is approved it is likely that rituximab will be given with bendamustine therapy – there is already an ongoing randomised study comparing bendamustine with and without rituximab. The advantage of FCR or similar regimens over alemtuzumab based therapy is that it is less immunosuppressive, better against bulky disease and doctors/nurses.pharmacists are very familiar with giving rituximab based regimens whereas many clinicians are not so comfortable with alemtuzumab therapy due to the infective problems –

infective prophylaxis/monitoring is a major limitation of alemtuzumab therapy. It may also be more effective in the fludarabine failure subgroup as alemtuzumab led to a 33% overall response rate but with only 2% complete responses – Keating et al Blood 2002 99: 3554-3561, compared to the overall response rate of 73% with a complete response rate of 25% seen with FCR therapy Wierda et al 2005 J Clin Oncol 2005 23;4070-4078. Indeed in the subgroup analysis patients who had received prior FC there was a 74% overall response rate with 24% complete responders. This subgroup analysis is more akin to practice in the UK.

Also this technology may be cheaper than alemtuzumab and if not yet will probably become so over the next 2-3 years when the patent for rituximab expires and the generic companies make their products available. There are also infective problems with steroid usage and the duration of response to steroids is typically short ~8-12 months.

Thus the new technology will be used for those patients who have probably failed upfront FC or chlorambucil. Of course should this technology be approved we will very soon – within 12-24 months have patients relapsing following upfront FCR therapy (assuming NICE do approve this). What the role of this technology will be therefore in patients who have relapsed following upfront FCR is yet to be resolved. Probably an anthracycline based regimen such as FCR plus mitixantrone or RCHOP.

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?

The addition or rituximab to presently used regimens – FC, CHOP or chlorambucil does not appear to significantly alter their effectiveness when it comes to patients with p53 deletions and as there are more effective and established therapies really couldn't be recommended for p53 deleted patients.

As outlined above it also would not seem appropriate to give this technology to a patient who had received upfront FCR if they had relapsed within 12 months – although some clinicians might disagree about the duration quoted.

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)?

This is a secondary care technology only due to the infusional problems which can occur with rituximab infusion. Also the monitoring of side effects and the effectiveness of the therapy is really only possible within the secondary care sector.

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?

We understand the license for this technology is expected in September 2009. Already within the private sector this technology is being used all the time. Within the NHS Dr Fegan has personally sort and received funding off license for this technology – We know many of my colleagues who have likewise sort and received

funding approval to use this technology in the NHS – as stands availability is therefore variable dependent on the location.

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.

The UK CLL Forum/BSH updated guidelines for the management of CLL are well advanced. Dr Fegan is a member of the guidelines committee and it is going to be recommended that some (the subgroups have yet to be finalised) of the FC relapses/refractory patients should be offered this technology (subject to Licensing approval). The guidelines are expected to be published by the end of this year and indeed have been held back to include the NICE appraisal for upfront FCR therapy. The original guidelines published back in 2004 were extremely well received not only in the UK but around the world and we have no doubt the updated guidelines are equally as comprehensive and hence will be very well received. The guidelines specify the level of evidence for each recommendation and grade the recommendation. This new technology (or at least the addition of rituximab to FC) is supported by a single randomised trial and its inclusion in the present draft of the updated guidelines is based on it being regarded as Level Ib evidence.

As of present there is no published randomised study showing the addition of rituximab to chlorambucil in the relapsed/refractory setting is superior to re-treatment with chlorambucil monotherapy. Likewise the effectiveness of bendamustine with rituximab has also yet to be fully established.

Of course the Guideline Committee primarily considers efficacy of the various treatment options as there is no published data for cost effectiveness to be taken into consideration.

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?

As this technology is identical (at least with regards to the addition of rituximab to FC) to that we expect to be recommended very shortly for the upfront treatment of CLL there really are no issues about departments competencies in being able to deliver this technology. There will be issues around capacity of Day Units around the UK as at present patients receiving chlorambucil, FC or alemtuzumab (assuming it is given subcutaneously) do not impact on Day Units. Obviously those patients presently receiving CHOP do use Day Unit resources but there probably won't be any saving because if for example a patient fails this technology then they will probably be offered an anthracycline based regimen such as CHOP, or FCM (RCHOP or FCMR if this technology is approved) before being allowed to succumb.

Rituximab will need to be given on a Day Unit with space and resource implications – staffing, pharmacy time etc. There will probably be a small impact in terms of in-

patient bed usage as FCR is slightly more toxic than FC therapy and RCHOP is slightly more toxic than CHOP chemotherapy although in REACH if we recall correctly the neutropenic sepsis rate was not significantly different.

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.

The technology if approved as Rituximab plus chemotherapy effectively means that rituximab can/should/will be given in addition to whatever salvage therapy one was planning- chlorambucil, CHOP, Bendamustine, FC. The rules for starting and stopping of therapy that apply therefore will be the same as presently used for the non-rituximab based regimens.
Although there have been studies using FCR therapy within the UK these have been in limited number centres. The UK is about to embark on two new studies for frontline therapy in which FCR will be compared with FC plus reduced dose rituximab or mitoxantrone will be added to FCR. Thus those centres not particularly experienced in giving FCR therapy will rapidly become so.

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?

We believe that the REACH study is very comparable with UK practice in terms of the types of patients entered into the study – age, previous therapies etc and we therefore see no reason certainly in the setting of previous FC therapy why the results achieved in clinical practice should not be too dissimilar to those seen in the REACH study. There is a wealth of phase II data showing that adding rituximab to other therapies eg chlorambucil appears to be beneficial and hence approval of this technology has the potential to enhance outcomes in the UK population.

To a patient the two most important outcomes are response rates as these directly impact on the quality and duration of life. The overall and complete response rates were 70% v 58% and 13.8% v 9.1% in favour of the FCR arm compared to FC. This translates into a significantly superior progression free survival – 30.6 months v 20.6 months. Although the overall survival is not superior in the FCR treated arm in reality there is yet to be a randomised CLL study showing a superior OS with any particular type of chemotherapy due to comfounding factors such as cross over of therapies- i.e the FC failure being given FCR, co morbidities, need for long follow up etc. Thus with further follow up this may indeed become the first study showing a significantly improved OS.

We cannot recall seeing any Quality of Life data from the REACH study. However we know from the published UK CLL 4 study that QOL is directly related to the response rate so it would be surprising if FCR did not lead to a superior QOL given the significant difference in OR and PFS.

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 is a small difference in adverse events from the REACH study when Rituximab was added to FC therapy. However we think this marginal increase risk is offset by the bigger benefits accrued by giving rituximab.

We don't anticipate that time will reveal new unforeseen AE's given the extensive use over two decades of fludarabine and > 12 years of rituximab.

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.

Sorry – no.

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 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)?

My only concern is the physical space and staff resources available within Day Units/Pharmacies that will be required to deliver this technology.