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 [redacted]

Name of your organisation

Royal College of Pathologists and BSH

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- 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.)? **Yes**
- other? (please specify) [redacted]

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?

CLL is the commonest leukaemia in adults in the UK with an annual incidence of about 3-5 per 100,000 per year and typically presenting in the 7th decade. The disease runs a chronic relapsing course and usually requires multiple treatment episodes. Treatment is indicated for symptoms or clear-cut disease progression. This strategy is based on the fact that pre-emptive treatment with chlorambucil is of no benefit in patients with asymptomatic early-stage disease.

Combination therapy with rituximab, fludarabine and cyclophosphamide (R-FC) has recently emerged as the internationally accepted first-line treatment of choice for fit patients. This consensus is based on the clear superiority demonstrated in several large phase III clinical trials of FC over either fludarabine monotherapy or chlorambucil, and more recently the clear superiority of R-FC over FC demonstrated in the German CLL8 trial. Somewhere in the order of 50% of CLL patients in the UK are currently likely to be candidates for R-FC as their initial therapy. For less fit patients chlorambucil remains the standard of care, although this is almost certain to change when results are available from the Roche MO20927single arm phase II trial of chlorambucil in combination with rituximab and/or GSK 110911 (COMPLEMENT-1) phase III trial of chlorambucil ± ofatumumab.

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 one CLL subgroup that stands out above all others by virtue of poor response and short PFS/OS following first-line chemotherapy or immunochemotherapy is deletion of TP53 at 17p13 (17p-). However such patients are relatively uncommon (<10%) in the frontline setting.

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)?

Secondary care haematology services should be capable of safely administering bendamustine in this clinical setting. There may be manpower and staffing implications relating to the preparation and administration of the drug on haematology day-units.

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?

The technology was recently available as part of a compassionate use programme but this has been discontinued.

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.

UK guidelines for CLL are currently under revision. International guidelines were produced in 2008 but these pre-date the publication of the pivotal bendamustine study and are largely concerned with the conduct of clinical trials.

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?

Since bendamustine is given intravenously over 2 consecutive days, it will require additional pharmacy input and day unit capacity relative to chlorambucil which is given by mouth. Since bendamustine appears to be more myelosuppressive than chlorambucil, it is possible that it will also require more supportive care in the form of blood transfusion, growth factor support, antibiotics and hospital admissions. However, these additional supportive care requirements are likely to be minimal given the magnitude of the additional toxicity.

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.

Patients with CLL who are considered possible candidates for bendamustine should be tested for TP53 defects. The latter are strongly predictive of resistance to a range of chemotherapeutic agents including bendamustine. Patients with TP53 defects should be offered alternative therapy that is more likely to be effective.

With regard to assessing response, there is nothing different about bendamustine compared to other types of chemotherapy. Treatment would be continued to the end of the planned 6 cycles unless there were indications of disease progression.

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?

Concerns have been raised concerning the chlorambucil arm of the Knaupf et al study which produced a median PFS of only 8.3 months compared with 20 months in the chlorambucil arm of the UK CLL4 trial – strikingly similar to the results obtained in the bendamustine arm of the Knaupf et al study (median PFS 21.6 months). Importantly, the chlorambucil regimen employed in the Knaupf et al trial involved administering a dose of 0.8mg/kg on day 1 and 15 of each cycle rather than the standard UK regimen (10mg/m^2 over 7 consecutive days) that was used in the CLL4 trial. Based on these considerations, it has been suggested that the apparent superiority of bendamustine over chlorambucil in the Knaupf et al trial might actually reflect the inadequacy of a sub-optimal chlorambucil regimen rather than the true superiority of bendamustine. Alternatively, it is possible that patients recruited into the Knaupf et al trial had a worse risk profile than those recruited into the CLL4 trial.

The trial endpoints are appropriate.

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?

Grade 3+ infection is the most important toxicity in CLL trials. The rate of grade 3+ infection in the bendamustine arm of the Knaupf et al trial was acceptable (8%) and comparable to that in the chlorambucil arm (3%). There was more marrow toxicity with bendamustine but this was manageable. Discussions with colleagues who have used bendamustine in CLL suggest that the toxicity profile presented in the Knaupf et al study is reflected in everyday clinical practice and of acceptable magnitude in less fit patients.

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.

A phase II study of bendamustine in combination with rituximab in 81 patients with relapsed CLL was presented at the 2008 meeting of the American Society of Hematology.[1] The CR and OR rates were 14% and 77% respectively and the rate of grade 3+ infection was 5%.

A phase II study of bendamustine in combination with rituximab in 117 patients with untreated CLL was presented at the 2009 meeting of the American Society of Hematology.[2] The CR and OR rates were 91 and 33% respectively. Grade 3+ infection occurred in 6% of treatment cycles.

These studies are encouraging and indicate that bendamustine is safe and effective when used in chemo-immunotherapy combinations in CLL.

References

1. Fischer K, Stilgenbauer S, Schweighofer CD, et al. Bendamustine in combination with rituximab (BR) for patients with relapsed chronic lymphocytic leukemia (CLL): a multicentre phase II trial of the German CLL Study Group (GCLLSG). Blood 2008;112.330a
2. Fischer K, Cramer P, Stilgenbauer S. Bendamustine Combined with Rituximab (BR) in First-Line Therapy of Advanced CLL: A Multicenter Phase II Trial of the German CLL Study Group (GCLLSG). Blood 2009;114:205a

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)?

The replacement of oral chlorambucil with intravenous bendamustine in the frontline treatment of CLL would result in more work for pharmacists and nurses and would require more day unit capacity. Training requirements should not be significant as both pharmacists and nurses will already be familiar with the administration of other types of chemotherapy, and bendamustine has no particular difficulties with regard to preparation or administration.