Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Bortezomib for previously untreated mantle cell lymphoma [ID724]

Thank you for agreeing to make a submission 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 submission, 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: RCPath
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)? **No**

- 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?

The approach to therapy of Mantle Cell Lymphoma (MCL) is relatively uniform across the UK. For younger patients this involves an intensive course of chemotherapy (cytarabine based) followed by an autologous transplant and for older patients combination chemotherapy together with rituximab followed by rituximab maintenance. For frail and elderly patients there is no standard of care. It is for the older fitter patients that this technology applies. Generally the chemotherapy of choice would be CHOP, but Bendamustine and to a lesser extent FC (fludarabine and cyclophosphamide) are the regimens of choice.

This technology incorporates Bortezomib into the CHOP regimen (VR CAP) as part of front line therapy for MCL. CHOP has been slightly modified in this trial by the removal of the vincristine (the 'O') as this can cause peripheral neuropathy which is a common toxicity associated with Bortezomib.
In the randomised trial the addition of the Bortezomib into R-CHOP significantly improves the PFS over standard R-CHOP regimen when applied as first line therapy. There was a 59% increase in PFS observed in this trial and whilst there was no survival benefit it is a relatively immature trial with respect to follow up. MCL is an incurable condition that has one of the worst outcomes of the lymphoma sub-types so any advance in therapy is to be welcomed.

There was more toxicity associated with the Bortezomib combination, especially haematological with thrombocytopenia being the major problem. There was not a major difference in other toxicities particularly neurotoxicity. One of the disadvantages of the trial as designed was the lack of rituximab maintenance following the chemotherapy phase. This has now become standard of care and the outcomes of patients treated with R-CHOP followed by R maintenance are better than those seen in this study but there is no reason to suspect that this benefit would not be seen if applied following VR CAP as well. The other issue is that the Bortezomib is given intra-venously and twice a week for 2 weeks in the VR CAP arm. This would now be given sub-cut and weekly as we know more about the PK of the drug and this form of delivery significantly reduces toxicity. Both of these design issues were unfortunate as the evidence did not exist at the time this study was designed and run.

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?

No

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 therapy that is only delivered through secondary care by clinicians expert in the management of haematological malignancies.

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?

It is available in the context of the treatment of multiple myeloma and used widely. It has been used through the CDF for mantle cell lymphoma in the context of relapsed disease where the drug has a license. It is no longer available through this route.

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.

BCSH guidelines which you have seen. Other guidelines (European and American) include R-CHOP with maintenance as an option for front line therapy for elderly patients not fit for an autologous transplant. There is very little clinical trial data in this disease as it is rare and very little randomised data.

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?

This therapy, if adopted, would be used in place of R-CHOP chemotherapy. The only modification to standard of care would be the delivery of the Bortezomib. This is IV as stated in the paper but I suspect many people would use it sub cut. Delivering this is easy from a nursing perspective but there is an inconvenience for the patient as there are an additional 3 visits for therapy per treatment course.

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.

Not over and above standard of care and normal clinical practice.

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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?

The only criticism of this trial is that there were younger patients treated within the study than would be the case in the UK. This reflects where the trial was performed and the lack of access to stem cell transplantation. To be fair to the company this was recognised early on in the study and younger patients were then excluded from entering.
Broadly these results do translate to UK practise. PFS is an appropriate end point to use. In MCL the first remission is generally the best and one may well expect significant differences in PFS to be reflected in survival differences as outcomes with treatment at relapse are generally poor in this disease.

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?

The meaningful difference seen was in haematological toxicity and this did translate into more infections being seen. Neurotoxicity can be a major issue for patients especially with respect to quality of life with Bortezomib. By not including the vincristine this appeared to prevent significant problems. We now know that giving this drug sub cut significantly reduces neurotoxicity and I suspect there would be widespread adoption of that mode of delivery if we were to be able to give this treatment.

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.

No other data that I am aware of although there is a very good registry covering Yorkshire which has very good real world data on outcomes and treatments for haematological malignancies. This gives a very sobering view of how well we really do rather than how well clinical trials tell us we do.

Implementation issues

The NHS is required by the Department of Health 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 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)?

Would not be a problem to deliver in this time scale. It is a commonly given drug.

Equality

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.

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No implications from an equality perspective.