Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia

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:

Name of your organisation: Royal College of Pathologists
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)?
- other? (please specify)

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia

What is the expected place of the technology in current practice?

This STA - Obinutuzumab with chlorambucil for previously untreated chronic lymphocytic leukaemia (CLL) - addresses the management of CLL in "older" patients, in whom coexisting comorbidities are common. As the median age of patients with CLL is 72 years, this STA concerns the majority of patients with CLL, who ultimately require treatment. CLL may follow an indolent course, during which time no therapy is required.

Current NHS management

In the population relevant to this STA, until very recently, the most widespread treatment in the NHS was single agent chlorambucil, usually administered as per the UK MRC study dosing of 10mg/m^2 for 7 days every 28 days. In patients who responded well, ie, with disease control for a prolonged period of time, then this treatment was often repeated. However, current management options in the NHS are more complex. With NICE approval for the original anti-CD20 monoclonal antibody (MAb), Rituximab, for use in CLL with chemotherapy, many patients now receive Rituximab+chlorambucil as first line treatment, who would previously have received singe agent chlorambucil. The other option in this patient population is single agent bendamustine. Like chlorambucil, it has become widespread to use bendamustine in combination with Rituximab in the first line setting for patients who would have previously received single agent bendamustine.

Chlorambucil+Rituximab – this is, in fact, one arm of the randomised controlled trial (RCT) which supports this STA review and the advantages/disadvantages will be addressed below.

Bendamustine+Rituximab – bendamustine has a higher response rate than chlorambucil when both are used as single agents. The combination with Rituximab achieves a 90% overall response (OR) rate in previously untreated CLL, with a 23% complete remission (CR) rate, although only one quarter of patients over in this phase II study were over the age of 70 years (Fischer et al J Clin Oncol; **30**: 3209; 2012). This regimen is entirely intravenous. Bendamustine is administered as a short infusion on days 1 and 2 every 28 days. This may be considered as either an advantage or a disadvantage, as compared to the standard 7 days of oral administration of chlorambucil. From my personal experience, patients (who are in the target population for this STA) are increasingly opting for completing their treatment in 2 days every cycle, even though it means two trips to the Day Unit, rather than a longer period of oral therapy.

The technology under consideration

Obinutuzumab+chlorambucil has been studied in a single, large RCT in a three-way randomisation between chlorambucil alone, Obinutuzumab+chlorambucil or Rituximab+chlorambucil (Goede et al. N Engl J Med; **370**:1101; 2014). This study focussed specifically on older patients, with a median age of 73 years, and only recruited patients with comorbidities (CIRS score >6) and/or an estimated creatinine clearance of 30 – 69 ml/minute. Both combination therapies were superior to chlorambucil alone in terms of OR and CR rates, as well as progression-free survival (PFS; 26.7 vs 16.3 vs 11.1 months), but only Obinutuzumab+chlorambucil showed an overall survival (OS) benefit compared to chlorambucil alone (hazard ratio for

death 0.41, p = 0.002). The median OS was not reached in any arm. Obinutuzumab+chlorambucil or Rituximab+chlorambucil were both associated with more adverse events than chlorambucil alone.

Special risk groups:
Regardless of age or comorbidities, one cytogenetic subgroup of patients with CLL have a particularly poor outlook, namely, those with deletion of the short arm of chromosome 17 (17p deletion). The same poor outlook is associated with mutation of the *TP53* tumour suppressor gene, which is located on 17p. None of the therapies being discussed in this STA show significant efficacy in this poor risk group.

Clinical setting
All the therapies considered above are administered in the hospital – secondary or tertiary – setting. Other than chlorambucil alone, all the chemotherapy+MAb combinations require Day Unit facilities, equipped to deal with anaphylaxis, a rare but known complication of MAbs. Infusional reactions during the first MAb dose are common and mean close monitoring is required and patients are usually in the Day Unit for most of the day. These treatments are only given by units experienced in administration of MAbs, with written protocols and trained nursing staff.

Obinutuzumab+chlorambucil is not currently available in the NHS as Obinutuzumab is not yet licensed in Europe. This regimen has only been used for CLL in the context of the RCT cited above. Obinutuzumab+chlorambucil has recently been approved by the U.S. Food and Drug Administration for use in previously untreated CLL. There are, as yet, no clinical guidelines including this regimen, or Rituximab+chlorambucil, as routine because the data are so new. Indeed, the British Committee for Standards in Haematology guidelines for CLL (Oscier et al, Brit J Haematol; **159**: 541, 2012) recommended either chlorambucil or bendamustine for the patient population relevant to this STA. Combining either agent with an anti-CD20 MAb was recommended in the context of clinical trials. However, as mentioned above, NICE approval means that Rituximab + either chlorambucil or bendamustine are available and widely used in the NHS.

The advantages and disadvantages of the technology

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia

The licensing of Obinutuzumab in Europe will mean the combination of Obinutuzumab+chlorambucil will be an option in the NHS. As discussed above, anti-CD20 MAb therapy with Rituximab combined with either chlorambucil or bendamustine are routine and NICE approved in the NHS. Therefore, from the perspective of practical implementation, Obinutuzumab+chlorambucil does not raise any technical issues as all units are already familiar with MAb administration and the RCT has not highlighted any need for increased resource in terms of concomitant treatments, patient acceptability/ease of use or the need for additional tests.

As with the other current options, Obinutuzumab+chlorambucil would be used for 6-cycles of treatment.

The RCT providing the evidence base for the use of Obinutuzumab+chlorambucil was unique in its design, as it carefully focussed on the majority of patients with CLL, ie, older patients with significant comorbidities. This is in marked contrast to almost all other studies where elderly patients and those with significant comorbidities are frequently excluded. Therefore, the trial population is a good reflection of the real world. However, this raises the question of whether the data can be extrapolated to medically fitter and younger patients - should such patients be treated with alternative regimens that are known to be at least as effective as Obinutuzumab+chlorambucil, but potentially have more side-effects?

The side-effect profile of Obinutuzumab+chlorambucil was notable for the higher rate of infusional reactions that Rituximab+chlorambucil and a higher rate of neutropenia. However, significant infusional reactions were not seen after the first cycle and in all three arms, despite the greater neutropenia with Obinutuzumab+chlorambucil, there was no differences in grade 3-5 infections. The trial report suggests the quality of life data was the same in all three arms of the study.

The data for Obinutuzumab+chlorambucil indicates superiority over chlorambucil alone, which is clinically relevant. The differences with Rituximab+chlorambucil are smaller and the clinical relevance is harder to be certain about at this point in time. It should be considered that study design led to significantly more Obinutuzumab being administered per patient than Rituximab – it is known that there is a dose-response effect with Rituximab in CLL. The relevance of this is that with Rituximab coming off patent and the availability of biosimilar anti-CD20 MAbs, it will be important to know if Obinutuzumab is inherently a better drug in combination with chemotherapy or is it a question of dosing? The cost implication of biosimilar anti-CD20 MAbs may be significant if they are as effective as Obinutuzumb (not to mention Rituximab) at equivalent dosing.

Another caveat with the Obinutuzumab+chlorambucil data is that in the UK a higher dose of chlorambucil is used. There is evidence of a dose-response effect with chlorambucil as a single agent, although the trial report tries to suggest otherwise.

Any additional sources of evidence

Nil

Implementation issues

There are no implementation issues with Obinutuzumab+chlorambucil in terms of the facilities, training or staffing required. The cost-effectiveness of Obinutuzumab+chlorambucil is clearly an important issue. With biosimilar anti-CD20 MAbs potentially becoming available, it is likely they will be licensed as biosimilar drugs to Rituximab and, presumably, be priced competitively. Where the answer will lie is impossible to say, as the information is lacking on the cost of Obinutuzumab and the efficacy and cost of biosimilar anti-CD MAbs.

As the data for Obinutuzumab+chlorambucil was obtained in a highly selected population of patients with CLL, it may be appropriate to use the same criteria for selecting patients suitable for this regimen. For patients who are medically fitter and/or younger than the study population, Rituximab+bendamustine could be recommended.

Equality

There are no issues of equality or variable access to care regarding Obinutuzumab+chlorambucil.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia