NHS England

NHS England Response to NICE ACD – Leukaemia (chronic lymphocytic) - obinutuzumab (with chlorambucil, 1st line)

Please find NHS England's response to the ACD as requested.

Has all of the relevant evidence been taken into account?
Yes
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes NHS England believes this is a robust review of the clinical and cost effectiveness data.
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
Yes – NHS England supports the recommendations within the draft guidance.
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
None have been identified
Any other comments
The National CDF panel have also considered obinutuzumab – please see the summary of the panels considerations below: The application was for the use of obinutuzumab as part of 1st line chemotherapy with chlorambucil for patients with chronic lymphocytic leukaemia with significant comorbidities contraindicating full dose fludarabine-based combination therapy. A trial has been published in the New England Journal of Medicine (NEJM) in 2014 which was in two parts. The first phase compared the 3 options of chlorambucil (Cb) plus obinutuzumab vs Cb plus rituximab vs Cb alone. The second part just randomised patients to obinutuzumab plus Cb vs rituximab plus Cb. All patients had a clinically meaningful burden of comorbidities: either a score of >6 on the Cumulative

Illness Rating Scale (CIRS, range of potential scores 0-56) or an estimated creatinine clearance of 30-69 mls/min. Cross over was allowed for the Cb patients if they progressed whilst on Cb or within 6 mo of completing Cb. Chlorambucil was taken on 2 days of a 28 day cycle. A maximum of 6 cycles of treatment was given. The median durations of follow-up were not stated in the publication.

In terms of the the comparison between obinutuzumab plus Cb vs Cb alone, the response rate was significantly superior (77 vs 31%). Median progression free survival (PFS) was significantly superior with obinutuzumab plus Cb arm (26.7 vs 11.1 months). Overall survival was significantly superior in the obinutuzumab plus Cb arm but the median survivals were not reached. Quality of life using the EORTC QLQ C30 tool was assessed and did not deteriorate but there are no details or statistics in the appendix to the NEJM paper. Toxicity was increased with obinutuzumab plus Cb with any WHO grade ≥3 toxicity being 70 vs 50% and grade ≥3 neutropenia being 33 vs 16% but there was no difference in infections.

The panel noted that the schedule of administration of Cb in the trial was not one that is standard in the UK. The current British Committee for Standards in Haematology (BCSH) guideline in CLL states that the highest response rate and longest PFS have been reported in the UK Leukaemia Research Fund CLL4 trial in which chlorambucil was administered at a dose of 10 mg/m² for 7 days every 4 weeks initially for 6 months but extending to 12 months in those patients still responding after 6 months of treatment. This schedule of Cb is the only one specifically mentioned in the guideline. The CDF panel heard from experts that this BCSH documented dose and schedule is by far the most commonly used way of administering Cb in England.

The CDF panel noted that the publication did not state the median duration of follow-up. The panel also observed that in the OS analysis there were relatively few patients at risk after 27 mo. In a disease such as CLL where there are likely to be a number of treatment options and in which the median survival is measured in years, the survival difference is of great interest but needs further follow-up.

The CDF panel scored the application as follows: 9 for PFS (using the revised CDF scoring system for PFS differences beyond 12 mo), 0 for OS (this recognised the significant difference in OS in the comparison between obinutuzumab plus Cb vs Cb alone but also that the median duration of follow-up was not stated and there were relatively few patients at risk beyond 27 mo), 0 for QOL (no details or statistics), -1 for toxicity and 0 for unmet need. The overall score was 8 B.

The CDF panel was mainly concerned about 2 aspects of the design of the trial, both impinging on the control arm of Cb in this study. The trial employed a schedule of Cb which is not one that is recommended as standard by the BCSH and hence one that is not in general use in England. The CDF panel noted that in the appendix of the obinutuzumab NEJM publication, the dose of Cb per cycle for a patient of 70 kg and 170 cm body height in the obinutuzumab trial was calculated to be 70 mg as opposed to 129 mg in the CLL4 study (an 84% increase in Cb dose). In addition, the maximum duration of treatment with Cb in the obinutuzumab trial was 6 mo, in contrast to a potential treatment duration of up to 12 mo as stated in the BCSH guideline.

The CDF panel recognised the clear superiority of obinutuzumab plus Cb over a schedule of Cb alone. It considered that this twice monthly schedule may be inferior to the standard schedule of administration of Cb used in England which delivers a much higher dose in a very different way but is one that is recommended by the BCSH. A similar issue was also considered to apply to the shorter duration of Cb treatment employed in the trial vs standard practice as indicated in the BCSH guideline. The

CDF panel therefore declined to approve the inclusion of obinutuzumab in combination with Cb in the 1st line treatment of CLL as it could not separate the positive contribution of obinutuzumab from the potential effect of the reduced dose intensity of Cb.

The manufacturer also submitted an application for obinutuzumab plus Cb to be the preferred option to the combination of rituximab and Cb. In this part of the randomisation in the above clinical trial, the response rate was significantly superior with obinutuzumab plus Cb (78 vs 65%), as was PFS (26.7 mo vs 15.2months). There was no significant difference in overall survival. Quality of life as measured by the EORTC QLQ C30 instrument was stated to not deteriorate with obinutuzumab plus Cb but the only details were in the appendix of the NEJM publication and no statistics were given. WHO grade ≥3 toxicity was greater in the obinutuzumab plus Cb arm (70 vs 55%). The manufacturer proposed the option of obinutuzumab plus Cb for those patients with CLL who could not tolerate full dose fludarabine-based therapy.

The CDF panel noted these results and again had the same concern about the scheduling of chlorambucil in this trial being one that was not standard in England and potentially inferior to the one recommended by the BCSH in its 2012 guideline. In addition, the panel heard from experts at the CDF meeting that there was a group of patients who, whilst not being fit enough to tolerate full dose fludarabine-based therapy, were nevertheless able to cope with more robust treatment than Cb alone: these patients received the combination of bendamustine and rituximab and not the combination of Cb plus rituximab nor single agent Cb. The CDF panel was also aware that the combination of Cb plus rituximab is not routinely commissioned in England (whereas bendamustine plus rituximab is). The CDF panel therefore did not regard the comparison of Cb plus obinutuzumab with Cb plus rituximab as being a relevant decision problem to England. The CDF panel thus declined to approve the inclusion of obinutuzumab as part of 1st line chemotherapy in the treatment of CLL.

The panel observed that there was now an evidence base for the comparison of Cb plus rituximab vs Cb alone from this trial which demonstrated the superiority of Cb plus rituximab. However, this conclusion also suffered the same criticism as regards the dose and scheduling of Cb employed in this trial.