Clinical Expert Submission Template

Thank you for agreeing to give us a personal statement on your 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. Your statement can be as brief as you like, but we suggest a maximum of 8 pages.

If there are special reasons for exceeding this 8-page limit please attach an Executive Summary to your statement.

What is the place of the technology in current practice?

How the condition is currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in 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?

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?

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)?

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?

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.

Fludarabine has been licensed for the initial treatment of advanced CLL or after first line treatment in patients with sufficient bone marrow reserves.


There is clear evidence that there is no benefit in treating CLL at diagnosis unless or until one of the following occurs: there is progressive marrow failure with the development of worsening of anaemia or thrombocytopenia; there is massive (>10 cm) lymphadenopathy or massive (>6 cm below the costal margin) splenomegaly; there are serious systemic symptoms such as >10% weight loss I 6 months, a fever >38°C for two weeks unrelated to infection, night sweats sufficient to cause a change in nightclothes, or extreme fatigue sufficient to prevent a patient going to work; the lymphocyte count doubles in <6 months; or there are autoimmune cytopenias unresponsive to management with corticosteroids. Note lymphadenopathy and splenomegaly must be assessed clinically, not by imaging techniques.

For patients who do need treatment the outcome depends far more on the nature of the disease than on the treatment used. The major determining factor on overall survival is the whether or not the variable region genes of the immunoglobulin molecule have undergone somatic mutation. Those with mutated genes survive much longer than those with unmutated genes. Other prognostic factors, such as the expression of CD38 and ZAP-70, and the detection of chromosomal deletions at 11q and 17p also play a major part in prognosis.

So far no study has shown an improvement in overall survival with any treatment, over and above that achievable by using chlorambucil as first line treatment. Chlorambucil has been available since the 1950s and is much cheaper than any other available drug.
Nevertheless, very few countries in the world use chlorambucil as first line treatment. Its use as the first line treatment for CLL is confined to countries where cost is the major determinant of choice of treatment.


The recently completed LRF CLL4 trial (unpublished but presented at the NCRI Haematologica Oncology Study Group Annual Review 2006, 22nd May), which used a higher dose of chlorambucil than previous trials, did not find either a higher response rate or longer remissions in those treated with fludarabine compared with those treated with chlorambucil. Overall survival was 61% at 5 years with chlorambucil compared with 54% with fludarabine. This difference is not statistically significant. The use of a higher dose of chlorambucil may be relevant following the trial from Croatia which compared a more intensive chlorambucil regimen with conventional doses of chlorambucil, and found a higher response rate and longer survival for the more intense arm (Jaksoc B, Brugiatelli M. Nouv Rev Fr Hematol 1988; 30:437-42.) This study was criticised for not using the NCI criteria for remission.

Outside the UK these comparisons receive little interest. Hardly anybody uses either chlorambucil or fludarabine as a single agent to treat CLL any more.

The combination of fludarabine plus cyclophosphamide was introduced by the MD Anderson Cancer Center in Houston several years ago after a phase II study showed higher response rates and longer remissions than had been achieved with fludarabine alone (O’Brien et al J Clin Oncol 2001; 19:1414-20.) Houston doesn’t do Phase III studies, and immediately embarked on a new Phase II study of fludarabine, cyclophosphamide and rituximab, about which more later.

Meanwhile the fludarabine plus cyclophosphamide (FC) combination has been evaluated in two Phase III studies. In the German study, which was confined to patients younger than 66 years, the FC combination gave a significantly higher response rate and complete response rate than fludarabine alone. Progression free survival was twice as long in the FC arm but overall survival was not significantly different. (Eichhorst et al. Blood 2006; 107:885-91).

In the British LRF CLL4 trial (unreported), which had no age cut off, FC gave a significantly higher response rate and complete response rate than either fludarabine or chlorambucil. There was also a longer progression free survival, but no difference in overall survival.

The addition of Rituximab to FC (FCR) was initiated by the Houston group and in 2005 they published the results of two very large phase II studies in respectively untreated and previously treated patients. In the up-front study the overall response rate was 95% with a complete response rate of 70%. These responses are much higher than have been seen with any other regimen. (Keating et al J Clin Oncol 2005; 23:4079-88). In the second-line study the overall response rate was 73% and the complete response rate was 25%; again very good response rates for this group of patients. (Wierda et al J Clin Oncol 2005; 23:4009-12).

Sometimes improvements in outcome are so great that physicians are satisfied with the results of phase II trials and want to introduce the new technology immediately without waiting for the results of phase II trials and cost-benefit analyses. Something like this has happened in the USA with FCR, and many other countries have followed suit. However, Phase III trials of FCR against FC have been initiated.
There is a first line study in Germany that has fully recruited, but because both arms give such good results as a first-line treatment, not enough 'events' have accrued to assess the outcome.

There is also a second-line study being performed throughout Europe, which is still recruiting and due its first interim analysis at the end of this year.

There are reasons to await the results of these trials before pronouncing on FCR.

1] Fair or not, Houston has a reputation of entering patients into phase II trials at an earlier stage of the disease than other centres. Only 33% of the patients entered into the first line FCR trial were stage C.
2] Historical controls are notoriously unreliable. In this disease successive MRC trials have shown successive improvements in survival in patients treated with the same chlorambucil arm.
3] The use of surrogate end-points such as response rate or progression-free survival may be misleading in chronic haematological malignancies, as has been shown in the recent thalidomide/double autograft trial in myeloma from the US. (Barlogie et al N Engl J Med 2005; 354:1021-30).

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, if already available, compares with current alternatives used in the UK. Is the technology 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 use?

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.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology in clinical practice reflects that observed under clinical trial conditions. 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?

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?

In the UK, though not in America or Germany, fludarabine is available orally. This is undoubtedly of great benefit to the NHS. There are studies suggesting that similar blood levels are obtained by the oral formulation. The LRF CLL4 study (unpublished) allowed oral fludarabine for the second two thirds of the trial. Results in these patients were worse than in the first third of the trial, but similar decline in effectiveness was seen in the chlorambucil arm. This can only be accounted for by a change in the nature of patients entering the trial when patients did not to have intravenous chemotherapy – either frailer patients were entered or less experienced centres participated. Even oral fludarabine need careful attention to renal function and observation of the nadir of the white count as well as some form of antibacterial prophylaxis.

All forms of chemotherapy produced some degree of bone marrow suppression and fludarabine is no exception, but it is not particularly toxic in this regard. However in the CLL4 trial it was significantly more likely to produce neutropenia and necessitate hospitalisation for infection than chlorambucil (around twice as likely). More important is its effect on T cells. Mean CD4+ T-cell levels after six courses of fludarabine are at AIDS levels and persist at this sort of level for more than two years. Consequently prophylaxis against Pneumocystis carinii and herpes viruses is recommended.

There are other side effects and complications of note.
Appendix D

1] Autoimmune complications. Autoimmune haemolytic anaemia occurs in 15-20% of patients with CLL and it is often triggered by treatment. Previous studies have suggested that this is commoner with fludarabine than with chlorambucil. In LRF4 (which uses a higher dose of chlorambucil than some other studies, the incidence of haemolytic anaemia is not significantly different between the two arms, though there is some evidence that those occurring after fludarabine are more severe. Autoimmune thrombocytopenia can also be triggered, but it is much rarer.

2] Richter’s transformation. Historically, the transformation of CLL into a high grade lymphoma occurred in 2-3% of cases. Since the introduction of fludarabine, this seems to occur more frequently - up to 12% in one study (Thornton et al. Leuk Res 2005; 19:389-95). It is thought to be a consequence of the T-cell depletion as many of the lymphomas are EBV related.

3] Second malignancies. It has long been thought that skin cancers and other second malignancies are commoner in patients with CLL. It has proved difficult to prove this, but anecdotally there seem to be a greater number in patients treated with fludarabine.

4] Myelodysplastic syndrome. There have been a number of recent reports noting an association of fludarabine treatment in CLL and the later development of myelodysplastic syndrome and in some cases acute myeloid leukaemia. (Milligan et al Brit J Haem 2006; 133:173-5; Bowcock et al. Brit J Haematol 2006; 134:242-3.)

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.

As I see it there is little evidence that fludarabine alone offers any benefits over chlorambucil as first line treatment for CLL. However, the combination of fludarabine plus cyclophosphamide produces a higher response rate and longer remissions. Overall survival is no better, because patients relapsing after chlorambucil may easily be salvaged with FC.

I very strongly suspect that adding rituximab to FC will produce better results, but any effect on overall survival must await the completion of prospective trials.

Using any fludarabine combination as first line treatment is much more expensive than using chlorambucil, but if patients will eventually come to such combinations second line then there will be no cost advantages to delaying the use of them.

Quality of life studies are being completed for CLL4. We know that the only major factor determining a better quality of life is being in remission. Therefore it can be anticipated that regimes that keep patients in remission for longer will show better quality of life.

It may well be that an argument could be advanced for FC being the standard treatment for CLL. However, it is certainly my experience that some patients continue to be responsive to chlorambucil after relapse and live for close to normal life-spans with no recourse to fludarabine with its attendant side effects. Such patients usually have mutated IgVH genes. Trials have shown that the mutational status of IgVH genes are more important survival determinants than the type of treatment used, so it might well be argued that there should be stratification of CLL for the most appropriate treatment.

The forthcoming CLL6 trial seeks to stratify patients in this way.

Although prognostic markers have been performed in the most recent clinical trials so that they have been evaluated prospectively, they are not available for most NHS patients, even
though they cost far less than a single round of fludarabine. I believe that NICE should recommend that these prognostic tests should be available for all NHS patients with CLL.

**Implementation issues**

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 NHS is required by the Department of Health and 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 Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.