NICE appraisal of fludarabine in the first-line treatment for chronic lymphocytic leukaemia; clinical expert report

Introduction

I have asked to represent the British Committee for Standards in Haematology (BCSH) at the NICE appraisal of fludarabine for the first-line treatment of CLL. By way of background, I am a clinical academic with a particular interest in the biology and treatment of CLL. I have a busy clinical practice and run a programme of research into basic and translational aspects of CLL biology. I am a member of the UK CLL Guidelines writing group and play an active role within the National Cancer Research Institute (NCRI) CLL Trials Group. Like most CLL specialists in the UK, I have received payments from Schering in the form of honoraria for advisory board meetings and invited presentations. I have also received funding for research projects that are relevant to Schering products. Nevertheless, the thoughts conveyed are entirely my own, and I have tried to the best of my ability to remain impartial. This document has been written using the template provided in Appendix D. An attempt has been made to cover each of the issues specified in the template document.

What is the place of the technology in current practice?

Chronic lymphocytic leukaemia (CLL) is an important disorder as it is one of the most frequently occurring haematological malignancies in the UK and results in significant morbidity and mortality. CLL usually evolves slowly over a long period of time and is increasingly discovered as an incidental finding due to health screening programmes. Our ability to detect very small CLL clones has also improved with time. The exact point of diagnosis can therefore be very arbitrary and does not necessarily represent a clinical milestone during disease evolution. CLL almost always involves the blood and bone marrow and often the lymph nodes, liver and spleen. One of the most important complications of CLL is immune dysfunction. This can take two forms: immunodeficiency and autoimmunity to red cells and platelets. Autoimmunity can occur spontaneously or can be triggered by therapy. It is standard practice for the treatment of CLL to be deferred until patients experience disease-related symptoms or show clear signs of progression. Most patients required treatment at some stage, and the clinical course thereafter is one of recurrent remissions and relapses. Eventually the disease becomes resistant to therapy, and death usually occurs when the tumour burden exceeds a critical level, or through infection as the result of a failing immune system.

For many years, the alkylating agent chlorambucil has been the mainstay of first-line treatment. However, several recent phase III clinical trials have shown unequivocally and consistently that the purine analogue fludarabine is more effective than chlorambucil, and that combination therapy with fludarabine and the alkylating agent cyclophosphamide (FC) is more effective than fludarabine alone in terms of overall response (OR), complete response/nodular partial response (CR/nPR) and progression-free survival (PFS). The benefit of FC over F or Chl monotherapy is particularly impressive and clinically meaningful. For example, in the UK CLL4 trial, 3-year PFS following FC was 62% compared to 31% with F alone and 23% with Chl alone. FC was more toxic than Chl or F monotherapy in terms of neutropenia, alopecia and gastrointestinal disturbance but was not associated with increased
infections or treatment-related mortality. Autoimmune phenomena were seen more frequently after Chl than F or FC. Quality of life (QoL) correlated with the depth and duration of remissions obtained, and the strong expectation is that longer follow-up will indicate a QoL benefit of FC over F or Chl monotherapy. The benefit of FC over Chl or F extended across all age and prognostic groups, with the possible exception of the small proportion of patients with a 17p (p53) deletion. The latter group of patients are notorious for responding poorly to all types of chemotherapy and are currently eligible for entry into a phase II clinical trial involving alemtuzumab in combination with high-dose methylprednisolone, each of which has established single-agent activity in this setting.

Interestingly, none of the CLL trials showing a PFS advantage of FC over F, or of F over Chl, has shown a beneficial effect on overall survival (OS). However, this is not unexpected in view of the fact that patients failing Chl are usually treated with F or FC as second line therapy, and that these regimens can be highly effective in the second-line setting. In keeping with this idea, data from the CLL4 trial (submitted to ASH 2006) indicate that patients failing Chl (most of whom went on to receive F or FC) did relatively well on second-line treatment in contrast to patients failing FC. Historical data from the MD Anderson Centre in Houston, Texas indicate that survival from the time of first-line treatment is improving in each successive cohort of patients in a way that cannot be explained by patient selection or timing of treatment initiation. This suggests that newer treatments may be having an impact on overall survival but that this is being masked in randomised trials by the ‘crossover effect’ of second-line therapy. The International Workshop in CLL (IWCLL) faced up to these difficulties several years ago, formally concluding that the primary endpoint of phase III clinical trials should be PFS rather than OS, and that routine clinical practice should be informed by trials demonstrating clinically significant improvements in PFS. Accordingly, within the international CLL community, there is universal and unambiguous agreement that FC should be the new standard of care in the first-line treatment of CLL. In keeping with this, major clinical trials of first-line treatment are now using FC as the chemotherapy ‘backbone’. UK guidelines for CLL are currently in the process of being revised, and my personal view is that it would be very strange indeed if FC were not to be recommended as the first-line treatment of choice for the majority of CLL patients who are fit enough to receive this regimen. These guidelines are produced jointly by the UK CLL Forum and the British Committee for Standards in Haematology and are written by a panel of UK CLL experts with patient representation.

In everyday clinical practice, F and particularly FC are being used increasingly in the first-line treatment of CLL based on the PFS advantage demonstrated in phase III clinical trials. However, there is much variation in prescribing patterns across the UK. This is partly due to differences in funding mechanisms, whereby some units have more prescribing freedom than others. In addition, some clinicians are nervous of using F and FC owing to worries about toxicity. Such concerns seem unjustified on the basis of clinical trial data. However, it should be borne in mind that patients entering clinical trials might not be representative of all patients with CLL. Thus, because CLL is common in the elderly, many patients are frail or have significant comorbidity. Such patients are likely to be under-represented in clinical trials as they might fulfil exclusion criteria or be deemed unfit to receive the strongest treatment arm. Thus, although one third of patients in the UK CLL4 trial were over 70 years of
age and suffered no more toxicity than younger patients, these elderly patients are likely to represent the fitter end of the spectrum. For less fit patients for whom the toxicity of FC is a concern, Chl remains a useful and valid treatment option.

From a pharmacological point of view, the main limitation of F is renal impairment, reflecting its predominant route of elimination through the kidney. It is generally recommended that F is contraindicated if the creatinine clearance is less than 30ml/min and should be given at half dose if the creatinine clearance is between 30 and 60ml/min. In addition, at a recent meeting of the data and safety monitoring board for the ongoing REACH trial of FC ± rituximab as second-line therapy for CLL, it was suggested that patients with a creatinine clearance of 60-70 ml/min should receive 75% of the standard dose. Calculating the creatinine clearance is therefore obligatory in all patients receiving fludarabine, either alone or in combination with other drugs, and the dose should be modified accordingly, erring on the side of caution – especially in elderly patients and those with co-morbidity.

One concern about F and FC is the inhibitory effect of these regimens on stem-cell mobilisation, which is usually performed following first- or second-line therapy and which is necessary for subsequent autologous stem-cell transplantation (ASCT). The value of ASCT in CLL has not yet been formally established and is currently under investigation within the MRC CLL5 trial. In fact, stem-cell mobilisation is notoriously difficult in CLL irrespective of what induction chemotherapy has been used. Moreover, the main criterion for entry into the MRC CLL5 trial is achieving a good response to induction chemotherapy. Accordingly, it is currently recommended by the chief investigator of the trial that eligible patients should receive 4 cycles of FC (rather than the usual 6) followed by a break of 4-6 months prior to attempting stem-cell mobilisation. Damage to stem cells probably also underlies the observation that about 5-10% of patients treated with alkylating agents or purine analogues go on to develop therapy-related acute myeloid leukaemia or myelodysplastic syndrome (tAML/MDS). The risk of developing tAML/MDS may be increased when the two classes of drugs are used in combination but hitherto this has not emerged as an important problem in any of the clinical trials of FC. The risk of developing tAML/tMDS needs to be balanced against the effectiveness of FC in controlling CLL and the fact that most patients end up having FC at some stage during the course of their disease, even if they do not receive it as first-line therapy.

Another concern that has been voiced about fludarabine is its notoriety for triggering autoimmune phenomena. However, data from the UK CLL4 trial indicate that the risk of developing auto-immune haemolytic anaemia (AIHA) was actually highest with chlorambucil and lowest with FC. It is good practice to monitor all patients on treatment for therapy-induced AIHA, but patients requiring therapy for their CLL who have a positive Coombs test or, worse still, evidence of active AIHA present a particular problem. Some authorities advocate the avoidance of fludarabine-based regimens in such cases. However, in my opinion giving FC in this situation can be justified provided patients are monitored extremely closely for worsening of their AIHA. Indeed, I have seen examples of AIHA remitting following FC treatment.

F and FC can be given orally or intravenously, and non-randomised data from the UK CLL4 trial indicate that the oral and intravenous routes of administration are probably of comparable efficacy and toxicity when other factors are taken into account. Both
regimens are easy to administer in the out-patient setting and should be easy to deliver within most haematology/oncology units throughout the UK. As with any patient receiving chemotherapy for CLL, patients receiving F or FC should take prophylactic anti-emetics and allopurinol. In addition, PCP prophylaxis with low-dose septrin was recommended as part of the UK CLL4 trial. It was also recommended that, in addition to being thoroughly assessed prior to each cycle of treatment, patients receiving FC should have a blood count performed mid-way between the first and second cycle to detect unexpectedly profound neutropenia. These recommendations have by and large been adopted into routine clinical practice.

The advantages and disadvantages of the technology.

FC is significantly more effective than Chl, the previous gold-standard first-line therapy, only marginally more toxic and just as straightforward to administer if given via the oral route. Patients receiving F or FC should probably receive PCP prophylaxis with septrin and those receiving FC should also have an additional FBC mid-way between cycles 1 and 2. Apart from this, no extra precautions or interventions are required as compared with Chl. In short, there is complete agreement within the international CLL community that, for most patients with CLL requiring first-line therapy, the advantages of FC over Chl or F monotherapy clearly outweigh any disadvantages.

One issue that is sometimes raised is whether it might be better to give Chl first line and reserve FC for second-line therapy in patients who relapse or fail to respond to Chl. This argument is based on the observation that, while most patients who fail Chl respond reasonably well to FC, patients who are resistant to first-line FC are usually resistant to other types of chemotherapy. So if FC is given as first-line therapy, options for second-line therapy are limited. The counter-argument is that all treatments work better first-line than second-line owing to the progressive emergence and selection of drug-resistant CLL clones. Therefore, delaying FC until patients fail Chl is therefore likely to compromise its effectiveness. Put another way, long-term disease control in patients treated with Chl first-line and FC second line is probably very similar to that in patients treated with first-line FC alone. However, the latter approach involves two rather than one course of chemotherapy with all the associated toxicity (including the theoretical increased risk of tAML/MDS), inconvenience, expense and impaired quality of life. Furthermore, non-chemotherapy treatment options such as alemtuzumab are now available for patients who fail F or FC. So on balance, up-front FC is a more attractive and logical approach than first-line Chl followed by second-line FC.

My own personal experience of using first-line FC in everyday clinical practice bears out the clinical trial data, i.e. the regimen appears to be highly effective, is easy to administer (particularly when given via the oral route), and has acceptable toxicity provided due attention is paid to renal function. Occasional patients have experienced unexpectedly profound and prolonged marrow suppression or transient red-cell aplasia but such problems have usually resolved within a few months. My impression is that FC is better tolerated as first-line therapy than as second- or subsequent-line treatment. Nevertheless, clinical acumen still has an important role to play in identifying patients who might experience undue toxicity owing to extreme age, frailty or co-morbidity, and such patients are probably better treated with
chlorambucil or attenuated-dose F or FC. However, most patients requiring first-line treatment for CLL are good candidates for FC and seem to derive considerable benefit from it.

As already mentioned, patients with 17p- CLL respond poorly to all types of chemotherapy and are eligible for entry into a national phase II clinical trial of alemtuzumab in combination with high-dose methylprednisolone. However, there are as yet no data proving that such an approach is superior to chemotherapy. Furthermore, despite the small number of 17p- patients in the UK CLL4 trial, there was nevertheless a suggestion that they fared slightly better with FC than with F or Chl. Taking these considerations together, it does not seem appropriate to single out 17p- CLL as being unsuitable for treatment with FC.

Any additional sources of evidence?

None of the data from the UK CLL4 trial has yet been submitted for publication in peer-reviewed journals. However, a number of oral presentations and posters have been presented at the 2004 and 2005 meetings of the American Society of Haematology (ASH). A further abstract has been submitted to 2006 meeting of ASH. ASH is the main international forum for presenting emerging data from important trials such as this, and all abstracts submitted for presentation undergo a stringent system of peer review. Abstracts from the 2004 and 2005 meetings can be accessed on-line via the ASH website and those relating to the UK CLL4 trial are probably most easily accessed by searching for the name ‘Catovsky’ (Prof Daniel Catovsky being the chief investigator).

Implementation issues

A crucial point to stress is that it would be absurd for NICE to appraise F monotherapy but not FC. Thus, although clinical trials indicate that F is superior to Chl, the real strength of F lies in its ability to act synergistically with alkylating agents, and this is borne out by the marked superiority of FC over both Chl and F monotherapy observed in clinical trials. For NICE not to approve FC in the face of the regimen being the internationally agreed gold standard for the first-line treatment of CLL would represent a major anomaly with credibility implications. On the other hand, if NICE were to approve FC for the first-line treatment of CLL, this would remove the current ‘post-code’ prescribing and allow all patients to benefit from optimal first-line therapy.

Approving FC as first-line treatment for CLL should at the very least be cost neutral and will probably save money as most patients end up receiving FC anyway, and giving the regimen up-front would obviate the need for additional chemotherapy in the form of Chl. No extra education, training or supportive care would be necessary.

Conclusion

Based on available data and international opinion, my strong and clear recommendation is that NICE should approve FC for the first-line treatment of CLL.