

Response to Appraisal Consultation Document of the STA of fludarabine for the treatment of lymphocytic leukaemia

1. The STA has reviewed all the relevant trial information on the use of fludarabine alone and in combination for the first line treatment of B-CLL though it has excluded useful data from its conclusions on debatable grounds (e.g. the studies reported by Johnson and Leporrier on the grounds that CHOP or CAP are not routinely used in CLL patients in the UK). It is not clear how the application of such selection criteria affect the validity of the data derived from those patients treated with fludarabine; these studies emphasise the long duration of fludarabine use in clinical practice and contribute useful data on response rates at the time of re-treatment. Eighty five per cent of patients previously responsive to fludarabine respond to re-treatment with the same agent but the response rate falls to 12% in patients who are refractory to previous fludarabine therapy. A Cochrane review of single-agent purine analogues has been published since the completion of the ERG's report (Steurer et al *Cancer Treat Rev* 2006; 32:377-89) which concluded that 'there was a trend for improved overall survival for patients receiving purine analogues as initial therapy but statistical significance was just not reached (HR 0.89[95% CI 0.78-1.01]'. This is an encouraging finding in the context of the efficacy of purine analogue salvage therapy in patients receiving alkylator based treatment initially and its effect on improving the survival results of this group. The report also noted that 'the RR for achieving an overall (RR 1.22[95% CI 1.13-1.31]) and complete response (RR 1.94 [95% CI 1.65-2.28]) was significantly improved resulting in a longer progression free survival (HR 0.70 [95% CI 0.61-0.82])'.
2. The summaries of clinical and cost effectiveness are reasonable interpretations of the evidence but should explicitly acknowledge the high likelihood of fludarabine use at re-treatment in the total cost of treating a patient (i.e. chlorambucil may be cheap and moderately effective first line therapy but you are still likely to need fludarabine based treatment later).
3. The provisional recommendations of the Appraisal Committee are clinically inappropriate and will be detrimental to patients because of the arbitrary decision not to consider the use of fludarabine plus cyclophosphamide (FC). The BCSH guidelines for the management of CLL are currently under revision and the authors' analysis of the new trial data available since the last version concludes that
'current strategies for the management of CLL, particularly in those patients with good performance status, mirror those in other haematological malignancies and seek to achieve Minimal Residual Disease (MRD) negative responses. An important consideration on beginning treatment in CLL is whether to adopt a palliative approach and treat symptomatic disease with regimens causing minimal treatment-related toxicity, or to aim for prolonged disease-free survival in the hope that this will translate into superior overall survival. Two recent studies have shown that patients who achieve MRD negativity have a survival advantage and this should therefore be the therapeutic aim in all patients fit enough to receive chemotherapy regimens capable of achieving MRD negativity (Bosch 2003, Moreton 2005)'. MRD negativity can only be realistically obtained by the use of fludarabine combination therapy such as FC so the guidelines propose that
'for the majority of patients who are ineligible for a transplant procedure and in whom there is no contraindication to fludarabine e.g. renal failure, the first line treatment should be combination chemotherapy with fludarabine and

cyclophosphamide (grade A recommendation, level 1b evidence). Both fludarabine and chlorambucil are options for patients who are deemed unfit for combination FC therapy (grade A recommendation, level 1a evidence)'.

By fixing the review date of this STA at 2009, NIHC will effectively deny patients with CLL access to effective and cost-effective treatment as most Clinical Haematology Departments in the UK will be refused funding for FC by their PCTs for treatment that has not been endorsed.

In this context the ACD's call for further research is unhelpful and inappropriate since it appears to be simply a tactic for avoiding the task of addressing the clinically appropriate question of whether fludarabine plus cyclophosphamide is an effective and cost-effective treatment of CLL. Indeed the data in the STA clearly shows this to be the case on the evidence currently available.

Research into prognostic markers as a means of selecting treatment for patients with CLL is well advanced and is incorporated into the planning of the next generation of trials within the UK. Unfortunately the next principal initial therapy study (CLL6 comparing FC plus Mitoxantrone with FCM plus Rituximab) has not received funding support from the MRC so the research questions will remain unanswered in the UK and British patients will have no opportunity to enter a trial with the chance of achieving MRD negativity. It will present haematologists with an interesting problem in obtaining consent from patients with CLL who require therapy when they are obliged to explain that the only funded choice of treatment available to them is chlorambucil while recent trials data and the national guidelines suggests that they would be most effectively treated with fludarabine plus cyclophosphamide

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On behalf of the British Committee for Standards in Haematology.

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