Scottish Medicines Consortium

fludarabine, 10mg tablet and 50mg for injection or infusion (Fludara®) (No. 176/05)

Schering Health Care Ltd

6 October 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Fludarabine phosphate (Fludara®) is accepted for restricted use within NHS Scotland for the treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves. First line treatment should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease related symptoms or evidence of progressive disease.

Fludarabine phosphate has been associated with higher response rates than chlorambucil in clinical trials. No overall survival advantage over other therapies has been demonstrated.

Fludarabine is restricted to use by specialists in haemato-oncology.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves.

First line treatment should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease related symptoms or evidence of progressive disease.

Dosing information

By the oral route, the recommended dose is 40 mg fludarabine phosphate/m^2 body surface area given daily for 5 consecutive days every 28 days.

By the intravenous route the recommended dose is 25 mg/m^2 body surface area given daily for 5 consecutive days every 28 days.

The optimal duration of treatment has not been clearly established. The duration of treatment depends on the success of treatment and the tolerability of the drug. It should be administered until best response is achieved (complete or partial remission, usually 6 cycles), and then discontinued.

There are no licensed dose recommendations for fludarabine as part of combination therapy. In clinical trials, when it has been combined with other cytotoxic agents, the dose and/or frequency of fludarabine administration have been modified.

UK launch date

January 2005

Comparator medications

Chlorambucil monotherapy is the principal comparator for first-line use in B-cell CLL but combinations of various cytotoxic agents, mainly alkylator therapy, are also used.

Cost of relevant comparators

The duration of treatment for CLL varies according to response and/or tolerability in individual patients. The numbers of courses for regimens in the table below are taken from summaries of product characteristics (SPCs) and trials described in this document. The lower range corresponds to the recommended maximum number of courses, and the upper range corresponds to permitted extensions, some of which are not precisely specified in the relevant protocol or SPC.

Product	Regimen	Number of courses	Cost (£)
Fludarabine 50mg injection	25mg/m^2 for 5 days each 28 days	6-8	4680-6240
Fludarabine tablets 10mg	40mg/m^2 for 5 days each 28 days	6-8	3906-5208
Fludarabine 50mg injection and cyclophosphamide 500mg for injection	Fludarabine 25mg/m^2 and cyclophosphamide 250mg/m^2 for 3 days each 28 days	6-8	2860-3813
Fludarabine tabs 10mg and cyclophosphamide 50mg tabs	Fludarabine 24mg/m^2 and cyclophosphamide 150mg/m^2 for 5 days each 28 days	6-8	2248-2997
Chlorambucil tablets 2mg	10mg/m^2 for 7 days each 28 days	13-15	274-316

Assumptions
Doses based on body surface area (BSA) are for BSA=1.8m^2
Doses based on body weight are for range 60-80kg

Regimens are taken from an ongoing clinical trial and may not correspond to licensed doses.

Doses are shown for general comparison and do <u>not</u> imply therapeutic equivalence.

Summary of evidence on comparative efficacy

Chronic lymphocytic leukaemia is the most common adult haematological malignancy and incidence increases with age. Fludarabine, a nucleoside analogue, is an anti-metabolite that is a potent inhibitor of DNA synthesis and reduces synthesis of RNA and proteins.

One published study compared the licensed 5-day regimen of intravenous (IV) fludarabine with a regimen of chlorambucil 40mg/m^2 on day 1 of up to twelve 28-day cycles (n=179 and n=193 respectively). The primary endpoint following protocol modification was progression-free survival, and fludarabine was associated with a significantly longer median time to progression of the disease (20 months) than chlorambucil (14 months) ($p<0.001$). At a median follow-up of 62 months there was no significant difference in the median overall survival (66 months fludarabine versus 56 months with chlorambucil, $p=0.10$).

The overall response rate (complete or partial remission) was significantly higher for fludarabine than chlorambucil: 63% versus 37% respectively ($p<0.001$), and complete remission (CR) rates also significantly favoured fludarabine: 20% versus 4% ($p<0.001$). The difference for partial remission (PR) was not significant (43% versus 33%).

Median duration of response was significantly longer in 107 patients who had a complete or partial remission with fludarabine than in 67 responders to chlorambucil (25 versus 14 months, $p<0.001$). Patients in the fludarabine or chlorambucil group who did not have a partial remission or who had evidence of disease progression could cross over onto the other drug, as could patients who relapsed within six months of stopping therapy. Of 79 patients who crossed over from chlorambucil to fludarabine, 46% had complete or partial remission. For crossover from fludarabine to chlorambucil the equivalent proportion was 7% of 29 patients.

Another published study had a similar design to the above but compared the licensed 5-day IV regimen of fludarabine with a combination of IV fludarabine 30 mg/m^2 and cyclophosphamide 250 mg/m^2 on days 1-3 of up to six 28-day cycles (n=182 and n=180). At a median follow-up of 22 months, median overall survival had not been reached in either group, and there was no significant difference between the combination and fludarabine alone for 3-year survival rates (80% and 81% respectively). Median progression-free survival was significantly longer for the combination arm (48 months versus 20 months for fludarabine alone, $p=0.001$). The overall response rates (CR + PR) for fludarabine monotherapy and the combination regimen were 83% and 94% respectively ($p=0.001$); the CR rate was 6.7% versus 24% ($p<0.001$) and the PR rate was 78% in both treatment arms ($p>0.99$).

An ongoing open-label randomised controlled trial was designed primarily to ascertain whether fludarabine at the licensed oral or intravenous dose prolongs survival of previously untreated patients with CLL compared with chlorambucil, and whether fludarabine in combination with cyclophosphamide (FC) had any additional survival benefit. Follow-up is continuing, but after 21 months the medians for overall survival, duration of response and time to progression had not been reached. At the time of analysis there was no significant difference between the groups for overall survival, and 3-year progression-free survival was 23% for chlorambucil, 31% for fludarabine and 62% for FC. The combination of fludarabine and cyclophosphamide was numerically superior to chlorambucil for overall response (90% and 69% respectively) and for complete response (38% versus 8%). Overall and complete response rates for fludarabine monotherapy were 77% and 15% respectively. The manufacturer presented a more recent analysis based on individual patient data from this trial and this continued to show fludarabine monotherapy as intermediate between chlorambucil and fludarabine/cyclophosphamide in terms of response rates.

A meta-analysis compared fludarabine with various alkylator-based regimens: chlorambucil monotherapy; chlorambucil plus prednisone and a regimen incorporating cyclophosphamide, vincristine, doxorubicin and prednisone (ChOP). This showed significant superiority of fludarabine over comparators for complete response but no significant advantage in overall response or survival.

Summary of evidence on comparative safety

Fludarabine has been associated with myelosuppression and auto-immune haemolytic anaemia; however it is not clear whether these occur more frequently than with other therapies with which it has been compared. Fludarabine, alone and in combination with cyclophosphamide, has been associated with a higher incidence of infection than chlorambucil in one trial and there was a significantly higher incidence for fludarabine in a sub-set of the meta-analysis described above where the comparators were chlorambucil and ChOP. However, this finding is not consistent (e.g. fludarabine and high-dose chlorambucil were associated with similar rates of infection in one study).

Summary of clinical effectiveness issues

The ongoing trial comparing chlorambucil, fludarabine alone and fludarabine in combination with cyclophosphamide is likely to become the pivotal trial for this indication. However, at present there are only preliminary results from this trial and no statistical analysis has been presented. Clinical experts inform us that this product will be used as combination therapy; though it will also be used as monotherapy for some patients.

One published trial indicates significant superiority of fludarabine over chlorambucil in inducing and maintaining response, while a second demonstrates significantly better response rates with a combination of fludarabine and cyclophosphamide than fludarabine alone. The latter trial recruited relatively younger patients (aged 18-65).

Progression-free survival was significantly longer with fludarabine than chlorambucil in one published trial, but there was no significant difference between treatments for overall survival, and this is the only study in which median survival has been reached. This may have been influenced by the crossover arrangements for patients with a lack of response, evidence of disease progression or relapse.

There was no significant difference in overall survival between fludarabine and alkylator-based comparator regimens in a meta-analysis of three trials, though the authors comment that this analysis may be inconclusive because of heterogeneity.

Summary of comparative health economic evidence

The manufacturer provided a cost utility analysis making three treatment comparisons; fludarabine and cyclophosphamide (FC) treatment versus chlorambucil, fludarabine monotherapy versus chlorambucil and FC versus fludarabine monotherapy. The analysis was structured using a lifetime Markov model containing four key states and allowing for three lines of active treatment which seemed appropriate. The model used patient-level data from the key clinical trial to estimate survival and duration of response data. The model did not assume that there was a survival advantage associated with fludarabine treatment but duration of response was assumed to differ between treatments, as was the relative percentage of patients showing a response. A comprehensive costing was carried out using a sub-sample of patients from the key clinical trial. Utility values were taken from published literature sources.

The results of the analysis indicated an incremental cost per QALY of FC compared to chlorambucil of either £2600 or £3200 depending on the assumptions made in the calculations of life years. FC treatment dominated fludarabine monotherapy and the ICER of fludarabine monotherapy versus chlorambucil was £19600 or £26100 depending on the method used to calculate life years.

The comparators used in the analysis were appropriate and broadly reflective of current practice.

The model structure was acceptable and the provision of sensitivity analysis on the impact of changes to survival and duration of benefit data was useful given the uncertainty associated with these figures.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer estimated that if 10% of patients who would have received chlorambucil were switched to fludarabine monotherapy then the additional budget impact would be £100k per year over the next five years. The manufacturer also estimated the net budget impact of moving from the current treatment pattern to a treatment pattern that would see 80% of eligible patients treated with FC off-label. This was estimated as £279k, £205k, £135k, £83k and £60k in years 2007 to 2011 respectively. These figures include a range of costs, not just drug costs. The manufacturer indicated that drug costs were generally around 70% of the estimated additional budget impacts presented.

Guidelines and protocols

The following guidelines pre-date licensing of fludarabine for first-line use.

Guidelines compiled by the Guidelines Working group of the UK CLL Forum on behalf of the British Committee for Standards in Haematology (BCSH) were published in 2004 and considered evidence up to 2003. For initial treatment they recommend that the majority of patients who are ineligible for a transplant procedure and in whom there is no contra-indication to fludarabine (severe renal impairment or an auto-immune cytopenia) should be offered entry to study MRC CLL4. Both fludarabine and chlorambucil are treatment options for people who do not wish to enter the study. Patients in whom fludarabine is contra-indicated and for whom a palliative approach has been adopted should be treated with chlorambucil. There is no survival advantage for including an anthracycline with chlorambucil.

In 2001 the National Institute for Clinical Excellence (NICE) recommended oral fludarabine as second-line therapy for B-cell CLL for patients who have either failed, or are intolerant of first-line chemotherapy and for who would otherwise have received combination chemotherapy of either; cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP); cyclophosphamide, doxorubicin and prednisolone (CAP) or cyclophosphamide, vincristine and prednisolone (CVP). Oral therapy was favoured over intravenous administration on the grounds of cost effectiveness and iv fludarabine should only be used when oral fludarabine is contra-indicated. NICE is conducting a single-technology appraisal of fludarabine in CLL at the time of preparation of this document.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 18 October 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The under noted references were supplied with the submission.

Rai KR, Peterson BL, Appelbaum FR et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med 2000; 343(24):1750-1757.

Eichhorst BF, Busch R, Hopfinger G et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood 2006; 107(3):885-891.

Zhu Q, Tan DCL, Samuel M, Chan ESY, Linn YC. Fludarabine in comparison to alkylator-based regimen as induction therapy for chronic lymphocytic leukemia: a systematic review and meta-analysis. Leukaemia Lymphoma 2004; 45(11):2239-2245.