

Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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1 Recommendations

- 1.1 Oral fludarabine is recommended as second line therapy for B-cell chronic lymphocytic leukaemia (CLL) for patients who have either failed, or are intolerant of, first line chemotherapy, and who would otherwise have received combination chemotherapy of either:
- cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
 - cyclophosphamide, doxorubicin and prednisolone (CAP) or
 - cyclophosphamide, vincristine and prednisolone (CVP)
- 1.2 The oral formulation of fludarabine is preferred to the intravenous formulation on the basis of more favourable cost effectiveness. Intravenous fludarabine should only be used when oral fludarabine is contra-indicated.

2 Clinical need and practice

- 2.1 Chronic lymphocytic leukaemia (CLL) is a malignant disorder of the white blood cells (lymphocytes). CLL causes abnormal lymphocytes to proliferate, thus impairing the production and function of red blood cells, platelets and normal lymphocytes. This in turn causes anaemia, failure of the blood to clot and increased susceptibility to infection.
- 2.2 There are two main types of lymphocytes called B-cells and T-cells. B-cell CLL comprises about 95% of all CLL.
- 2.3 Often, the disease goes undiagnosed either until it is well advanced, or until a chance test shows abnormally high levels of lymphocytes in the blood.
- 2.4 CLL is a chronic, life-threatening and incurable disease. It is the most common form of leukaemia in the Western world, affecting about 2.7 people in every 100,000. Predominantly, it is a disease of older people, with 75% of those diagnosed being over the age of 60 years, although 6% are below the age of 50 years. Twice as many men as women are affected.
- 2.5 Life expectancy depends on the stage at which the disease is diagnosed (see the [appendix for definition of stages](#)). For those in the early stages of the disease, median life expectancy is over 10 years, while for patients with advanced disease it is only 6 to 9 months. Other adverse prognostic factors include early age of onset.
- 2.6 Despite the apparently better prognosis in early disease, there is no evidence that early treatment is beneficial, and it may indeed be harmful. Since many patients have limited disease, they do not require anything more than general observation, referred to as 'watchful waiting'.
- 2.7 When the disease progresses, a hierarchy of treatments is used. There is a trade-off between the likelihood of halting or reversing progression of the disease and the side-effects of drug treatment.
- 2.8 Response rates to chemotherapy of about 70% are seen in intermediate-stage

disease, dropping to about 30% in later stages. In patients at intermediate or advanced stages of their disease an alkylating agent such as chlorambucil (with or without corticosteroids), cyclophosphamide or fludarabine (currently unlicensed in this indication) has been used as a first-line treatment.

- 2.9 When patients relapse or fail to respond to one of the first-line treatments (usually chlorambucil or, occasionally, cyclophosphamide), either combination treatment (such as CHOP, CAP or CVP) or fludarabine monotherapy is employed. A single cycle of combination therapy usually consists of drugs given by both the intravenous route (day 1) and orally (for a further 4 days). Cycles are repeated monthly for up to six months. Fludarabine is sometimes used as third-line treatment after combination therapy has failed.

3 The Technology

- 3.1 Fludarabine is a cytotoxic agent of the antimetabolite class. It is currently licensed for patients with B-cell CLL with sufficient bone marrow reserve and who have not responded to, or whose disease has progressed during or after, treatment with at least one standard alkylating-agent containing regimen.
- 3.2 It is administered either as an intravenous infusion (over 30 minutes) or orally. This is repeated each day for 5 days, and this cycle is then repeated every 28 days for up to 6 cycles. The drug acquisition cost (for either intravenous or oral formulation) of a course of 6 cycles is about £3,900. Each intravenous infusion requires a day-case admission to hospital, while the oral preparation usually needs only a small number of hospital visits.
- 3.3 Although the immediate side effects of fludarabine (nausea, vomiting, alopecia) are less troublesome than those of CHOP, there are frequent haematological adverse events (granulocytopenia, anaemia and thrombocytopenia), as well as other important long-term effects. Of these, the principal effect is T-cell immunosuppression, leading to a recommendation for prophylactic antibiotic treatment against *Pneumocystis carinii* pneumonia, and irradiation of all blood products given to the patient to prevent transfusion-related graft-versus-host disease. Concurrent corticosteroids increase this risk due to the additive lymphocytic activity and should therefore be avoided unless otherwise indicated. Additionally, autoimmune haemolytic anaemia is relatively common in patients with CLL. It occurs in about 1% to 5% of patients receiving fludarabine as a second line treatment. The haemolysis is often severe, may be difficult to treat, and is potentially fatal.
- 3.4 Nevertheless, on a day-to-day basis, fludarabine is generally tolerated better than conventional second line chemotherapy regimens, particularly in patients currently considered too frail to withstand combination therapies.

4 Evidence

4.1 Clinical effectiveness

- 4.1.1 There are two randomised controlled trials (RCT) evaluating intravenous fludarabine as a second line agent in CLL. In one of these, comparing fludarabine with cladribine, an unknown number of patients had B-cell CLL. It is not possible therefore to derive from this study, results relevant to the indication under consideration.
- 4.1.2 The second RCT compared fludarabine with CAP. Only 96 of 196 patients studied had been previously treated with a first line agent. Response rates (RR) for these previously treated patients were 48% with fludarabine versus 27% with CAP (95% confidence interval on the difference of 21 percentage points was 2 to 40 percentage points). The fludarabine response rate was much higher than that seen in the case series (see below). Mostly, the responses were partial, with just 13% complete responses for fludarabine versus 6% for CAP (the difference is not statistically significant). Time to progression for previously treated patients (responders only) had a median of 324 days for fludarabine versus 179 days for CAP (the difference is not statistically significant). In addition there were 9 deaths in 48 patients with fludarabine compared with 3 out of 48 in the control arm (the difference is not statistically significant). No data on quality of life were collected as part of the trial. Adverse events, mostly haematological, were common in both arms of the trial.
- 4.1.3 For intravenous fludarabine, six case series with an aggregate population size of almost 1000 were found. Response rates averaged 32%. The response rate appears to decline in patients who have been treated more heavily prior to treatment with fludarabine, and is generally lowest for patients for whom fludarabine is the treatment of last resort. Where reported, mild or moderate side effects were common although 72% of patients experienced severe haematological adverse events (based on laboratory results). The degree and length of response in these studies is greater than those of comparable studies for combination therapy, although it is not known whether there is an impact on length of survival. The quality of all such studies is lower than that of randomised

controlled trials, due to the possibility of unrepresentative or biased patient selection, heterogeneity between studies, and placebo effects of unknown size.

- 4.1.4 Quality of life data have not been formally collected as part of these studies. Some evidence, however, is available from the Lymphoma Association, whose survey showed that 74% of patients consider that they are in as good or better health during fludarabine treatment as they would have been with other chemotherapy.
- 4.1.5 Recent data from the MRC-sponsored CLL3 study show that, for patients who failed to respond to first-line treatment with chlorambucil or chlorambucil plus epirubicin at 6 months, 80% responded to fludarabine (17% complete, 63% partial). This evidence is in general supportive of the use of fludarabine second line. It is, however, subject to the biases of being an uncontrolled case series, the difficulty in defining non-responders and the variation in times to recruitment into the study following 'failure' of first line treatment.
- 4.1.6 Other evidence in the form of four randomised controlled trials for fludarabine alone against other chemotherapeutic agents for first line treatment (for which fludarabine is not currently licensed) shows that fludarabine gives higher rates of remission and longer remission than CAP, CHOP, or chlorambucil plus prednisolone, but no demonstrated survival advantage. For fludarabine against chlorambucil, one study favours fludarabine as above, but the other finds no difference between the two drugs. Assuming that a high positive correlation exists between the relative performance of fludarabine against its comparators in first and second line therapies, this evidence supports the case for the use of fludarabine in second-line therapy.
- 4.1.7 For oral fludarabine, an open study of 78 previously treated patients with CLL showed that 46% of patients responded (20% complete and 26% partial remission). Evidence on the bioavailability of the oral formulation and equivalence of blood levels of oral fludarabine with those of the intravenous preparation indicates that orally administered fludarabine is likely to have similar clinical efficacy to the intravenously administered preparation.

4.2 Cost effectiveness

- 4.2.1 No single piece of evidence is strong enough to establish whether fludarabine is a clinically effective agent for second line treatment of CLL. When the evidence is taken in aggregate, however, it is supportive of fludarabine as a clinically effective drug for this indication. The assessment of cost effectiveness, however, is also subject to considerable uncertainty, because reliable figures for the costs of dealing with adverse side effects are not available.
- 4.2.2 Three sources have been used to examine the costs of overcoming adverse events in using fludarabine and CHOP. The first (described as the low estimate), submitted by the manufacturer, is based on very small numbers of patients, and is therefore subject to large sampling error. The second (described as the high estimate) was submitted by a different manufacturer for the treatment of a different type of lymphoma, and was also based on a small sample. This source yielded cost estimates over six times as high as the first source, much of which appears to be attributable to the disease having advanced much further, on average, in patients from the second source. The third was from the MRC trial CLL3, which may have included costs associated with the disease per se, as well as of side effects of fludarabine, yielded costs comparable with those of the high estimate.
- 4.2.3 The cost effectiveness estimates have been examined separately for oral and intravenous fludarabine, and for both of these against the comparators of CHOP and of no treatment, for both high and low estimates of the cost of side effects.
- 4.2.4 Oral fludarabine is less costly to administer than intravenous fludarabine. The estimated combined cost of acquisition and administration, based on an average of 4.1 cycles administered, is £3,000 for oral fludarabine (comprising £2,700 for acquisition and £300 for administration) against £5,300 for intravenous fludarabine (£2,700 acquisition, £2,600 administration).
- 4.2.5 The mean cost per year of remission from CLL of oral fludarabine against no treatment is estimated to be £9,000 (low cost of treating side effects) or £21,000 (high cost of treating side effects); for intravenous fludarabine, the corresponding estimates are £14,000 and £28,000; and for CHOP are £22,000 and £67,000.

- 4.2.6 The mean incremental cost-effectiveness ratio for oral fludarabine against CHOP is estimated to be £2,700 per year of remission (low cost of treating side-effects) and £200 per year of remission (high cost of treating side-effects) (the latter figure is smaller than the former because the cost of treating side-effects for CHOP is also much higher in the high-cost scenario). The corresponding estimates for intravenous fludarabine against CHOP are £10,600 and £10,500. Even if there is no increase in overall survival using fludarabine compared with that of CHOP, it is probable that oral fludarabine is cost effective against CHOP.
- 4.2.7 In clinical practice it is likely that if fludarabine were not given, then patients who would otherwise have been prescribed it would be prescribed CHOP or an equivalent combination. In this situation oral fludarabine is both a more clinically effective and a more cost effective drug than its alternatives, as well as being more likely to be acceptable to patients.

5 Implications for the NHS

- 5.1 This guidance is not expected to result in a net increase in NHS expenditure in England and Wales, because fludarabine is already in common use. Increases in drug acquisition costs are likely to be offset by the transfer to the oral formulation, and because the switch from combination therapies to fludarabine should reduce the costs of treating adverse side effects.
- 5.2 (a) For each patient already being treated with fludarabine, it can be expected that cost savings in drug administration in switching from intravenous to oral fludarabine will be about £2,300 per course of an average 4 cycles (there was an average of 4 cycles of oral fludarabine given in one of the key trials).
- (b) For each patient new to fludarabine therapy who would otherwise have been prescribed combination chemotherapy (CHOP, CAP or CVP), the increased drug acquisition cost of fludarabine should be partially or fully offset by cost savings from avoiding the necessity of treating the side effects of combination drug therapy. For this group of patients, the net cost effect, on average, is likely to have a range of zero to £2,000, although this does not include the further costs of those who might subsequently also be treated with combination chemotherapy.
- (c) For each patient new to fludarabine therapy who would not have been able to tolerate combination chemotherapy, the additional costs are likely to be of the order of £6,000 to £9,000 per patient.

6 Implementation

- 6.1 Section 7 of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 6.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 6.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has B-cell chronic lymphocytic leukaemia and the doctor responsible for their care thinks that fludarabine is the right treatment, it should be available for use, in line with NICE's recommendations.

7 Further Research

- 7.1 Further appropriately constructed clinical trials should assess impact on quality of life directly.
- 7.2 Further research into fludarabine as a first line therapy, either singly or in combination with current first line drugs, would be of value. Recruitment of patients to the current CLL4 trial is recommended.
- 7.3 More comprehensive research, in the form of an adequately powered randomised controlled trial, to determine with greater certainty whether oral fludarabine is as clinically effective as intravenous fludarabine, is required.

8 Appraisal committee members

The appraisal committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The committee are supplemented by technology specific experts.

Professor R. L. Akehurst

Dean, School of Health Related Research Sheffield University

Professor David Barnett (Chairman)

Professor of Clinical Pharmacology University of Leicester

Professor Sir Colin Berry

Professor of Morbid Anatomy St Bartholomew's and Royal London School of Medicine

Dr Sheila Bird

MRC Biostatistics Unit, Cambridge

Professor Martin Buxton

Director of Health Economics Research Group Brunel University

Dr Karl Claxton

Lecturer in Economics University of York

Professor Duncan Colin-Jones

Professor of Gastroenterology University of Southampton

Professor Sarah Cowley

Professor of Community Practice Development Kings College, London

Dr Nicky Cullum

Reader in Health Studies University of York

Mr Chris Evennett

Chief Executive Mid-Hampshire Primary Care Group

Professor Terry Feest

Clinical Director and Consultant Nephrologist Richard Bright Renal Unit and Chairman of the UK Renal Registry

Ms Jean Gaffin

Formerly Executive Director National Council for Hospice and Specialist Palliative Care Service

Mrs Sue Gallagher

Chief Executive Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs

International Medical Operations Director GlaxoWellcome R&D Ltd

Mr John Goulston

Director of Finance The Royal Free Hampstead NHS Trust

Professor Philip Home

Professor of Diabetes Medicine University of Newcastle

Dr Terry John

General Practitioner The Firs, London

Dr Diane Ketley

Research into Practice Programme Leader NHS Modernisation Agency

Dr Mayur Lakhani

General Practitioner, Highgate Surgery, Leicester and Lecturer, University of Leicester

Mr M Mughal

Consultant Surgeon Chorley and South Ribble NHS Trust

Mr James Partridge

Chief Executive Changing Faces

Professor Philip Routledge

Professor of Clinical Pharmacology University of Wales

Professor Andrew Stevens (Vice-Chairman)

Professor of Public Health University of Birmingham

9 Sources of Evidence

The following documentation and opinion was made available to the committee:

a. Assessment Report prepared by the Department of Public Health and Epidemiology, University of Birmingham (Fludarabine as second line therapy for B-Cell chronic lymphocytic leukaemia, January 2001)

Assessment Report Annexe prepared by the Department of Public Health and Epidemiology, University of Birmingham (Fludarabine as second line therapy for B-Cell chronic lymphocytic leukaemia: Effectiveness Annexe, May 2001)

Assessment Report Cost- Effectiveness Annexe prepared by Dr A J Fischer, NICE Appraisals Team, May 2001

b. Manufacturer/Sponsor submissions:

- Schering Health Care Ltd

c. Professional/Specialist Group, Patient/Carer Group and Trade Association submissions:

- British National Lymphoma Investigation and UK CCCR
- British Committee for Standards in Haematology (BCSH)
- CancerBACUP
- Lymphoma Association
- Macmillan Cancer Relief
- Royal College of Pathologists

d. External expert and patient advocate submissions:

- Dr Andrew MacMillan, Oncologist, Mount Vernon Hospital
- Dr Peter Hoskin, Consultant Clinical Oncologist, Mount Vernon Hospital
- Dr Tracey Murray, Lecturer/Practitioner, St George's Healthcare NHS Trust

- Catriona Moore, Policy Officer, CancerBACUP
- Judith Brodie, Head of Cancer Support Services, CancerBACUP
- Catriona Gilmour Hamilton, Assistant Head of Information Services, The Lymphoma Association

Appendix on staging systems

Rai	Characteristics	Median Survival
Stage 0	Lymphocytosis in blood and bone marrow only	12 years
Stage I	Lymphocytosis plus lymphadenopathy	7 years
Stage II	Lymphocytosis plus splenomegaly or hepatomegaly	7 years
Stage III	Lymphocytosis plus anaemia (Hb < 110 g/L)	< 1 year
Stage IV	Lymphocytosis plus thrombocytopenia (platelets < 100 x 10 ⁹ /L)	< 1 year
Binet*	Characteristics	Median Survival
Stage A	< 3 sites involved, Hb > 100 g/L, platelets > 100 x 10 ⁹ /L	9 years
Stage B	> 3 sites involved, Hb > 100 g/L, platelets > 100 x 10 ⁹ /L	5 years
Stage C	Hb < 100 g/L, platelets > 100 x 10 ⁹ /L	2 years

* Involved sites are liver, spleen and lymph nodes in inguinal, axillary and cervical regions.

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