

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA 119 fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia

This guidance was issued in February 2007 with a review date of October 2009.

Recommendation

- That the guidance should be transferred to the static guidance list. That we consult on the proposal.

Consideration of options for recommendation:

Options	Comment
A review of the guidance should be planned into the appraisal work programme.	It is proposed that this appraisal should be added to the static list, as the newly identified evidence is not likely to change the current guidance.
The decision to review the guidance should be deferred.	It is proposed this appraisal should be added to the static list.
A review of the guidance should be combined with a review of a related technology and conducted at the scheduled time for the review of the related technology.	No update to the guidance is needed as the new evidence does not confer any material benefit in favour of fludarabine as a mono-therapy.
A review of the guidance should be combined with a new appraisal that has recently been referred to the Institute.	No update to the guidance is needed as the new evidence does not confer any material benefit in favour of fludarabine as a mono-therapy.
A review of the guidance should be incorporated into an on-going clinical guideline.	No update to the guidance is needed as the new evidence does not confer any material benefit in favour of fludarabine as a mono-therapy.
A review of the guidance should be updated into an on-going clinical guideline.	No update to the guidance is needed as the new evidence does not confer any material benefit in favour of fludarabine as a mono-therapy.
A review of the guidance should be transferred to the 'static guidance list'.	The newly identified evidence is not likely to change the current guidance and therefore the guidance should be transferred to the 'static list'.

Original remit(s)

To assess the clinical and cost effectiveness of fludarabine for B-cell chronic lymphocytic leukaemia relative to current standard treatments in the NHS.

Current guidance

This technology appraisal considers the clinical and cost effectiveness of fludarabine monotherapy only. No recommendations have been made with respect to fludarabine plus cyclophosphamide combination therapy because the current marketing authorisation does not specifically provide a recommendation that fludarabine should be used concurrently with other drugs for the treatment of chronic lymphocytic leukaemia.

Clarification was sought with the MHRA on the issue of the inclusion of the combination of fludarabine and cyclophosphamide in the marketing authorisation of fludarabine. In all correspondence received from the MHRA, including that shared with NICE by Schering Health Care Limited, it has been made clear that 'the MHRA does not consider that the current marketing authorisations for oral and intravenous (i/v) Fludara (PL/0053/0239 and /0290) specifically provide a recommendation that fludarabine should be used concurrently with other drugs for the treatment of chronic lymphocytic leukaemia'.

The MHRA has further clarified that, in general, it would expect a manufacturer or sponsor to request a variation in the marketing authorisation when: 1. The summary of product characteristics (SPC) in general, and specifically the 'therapeutic indications' section, does not contain references to the combination therapy and the company wishes to promote the use of combination therapy, and 2. The use of the combination has implications for the dosage specifications in the 'posology and method of administration' section of the SPC.

In the case of fludarabine, the SPCs do not contain references to the combination therapy. With reference to the second point, the dosage of fludarabine (i/v 25 mg/m² for 3 days and oral 24 mg/m² for 5 days) in the evidence base for the combination therapy that was submitted by the manufacturer (the CLL4 trial) is different from the fludarabine dosage specified in its SPCs (i/v 25 mg/m² for 5 days and oral 40 mg/m² for 5 days).

1.1 Fludarabine monotherapy, within its licensed indication, is not recommended for the first-line treatment of chronic lymphocytic leukaemia.

Relevant Institute work

Published/completed

CSGHO Improving outcomes in haemato-oncology cancer. October 2003. Expected review date: TBC.

TA 174 Rituximab for first line treatment of chronic lymphocytic leukaemia. July 2009. Expected review date: TBC.

In progress

Technology Appraisal (STA) - Rituximab for the treatment of relapsed chronic lymphocytic leukaemia. Expected publication date: April 2010.

In topic selection



Safety information

None

Details of new indications

There are no new indications for fludarabine.

Details of new products

None

On-going trials

None

New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline(R) In-Process and Embase. References from 2007 onwards were reviewed.

Implementation

A submission from Implementation is attached at the end of this paper.

Equality and diversity issues

None

Appraisals comment and summary

Fludarabine is not recommended for use. All three of the trails in progress do not provide evidence for a material effect in favour of fludarabine as a mono-therapy. Since, its licence indications remain the same, in terms of it being administered as a mono-therapy, there is no need for an update of the guidance.

In the 'Fludarabine (F) Versus Fludarabine Plus Cyclophosphamide (FC) in First Line Therapy of Younger Patients (Up to 65 Years) With Advanced Chronic Lymphocytic Leukemia (CLL)' clinical trial, the FC combination chemotherapy resulted in significantly higher complete remission rate and overall response rate compared with F (p-value <

0.001). FC treatment also resulted in longer median progression-free survival (p-value = 0.001) and longer treatment-free survival (p-value < 0.001)¹.

In the Fludarabine With or Without Cyclophosphamide in Treating Patients With Chronic Lymphocytic Leukemia clinical trial, treatment with FC was associated with a significantly higher complete response (p-value < 0.001) and a higher overall response rate (p-value = 0.013) than treatment with F. Progression-free survival was also superior in patients treated with FC than those treated with F (p-value < 0.001)².

In the published abstract of the 'Fludarabine Versus Chlorambucil in First Line Therapy of Elderly Patients (More Than 65 Years) With Advanced Chronic Lymphocytic Leukemia' clinical trial, the F arm showed a significantly higher complete remission rate (p-value = 0.008) and overall response rate (p-value <0.001). However, there was no significant difference in progression-free survival (p-value = 0.72). In addition, overall survival curves showed no significant difference too (p-value = 0.21)³

GE paper sign off:

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¹ Eichhorst B.F., et al. (2006). Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Bloo*, 107;885-891

² Flinn, I.W., (2007). Phase III Trial of Fludarabine Plus Cyclophosphamide Compared With Fludarabine for Patients with Previously Untreated Chronic Lymphocytic Leukemia: US Intergroup Trial E2997. *Journal of Clinical Oncology*, 25;7

³ Eichhorst B.F., et al. (2007). No significant Clinical Benefit of First Line Therapy with Fludarabine (F) in Comparison to Chlorambucil (Clb) IN Elderly Patients (pts) with Advanced Chronic Lymphocytic Leukemia (CLL): Results of a Phase III Study of the German CLL Study Group (GCLLSG). *Blood (ASH Annual Meeting Abstracts)*; 110: Abstract 629

IMPLEMENTATION DIRECTORATE

Guidance Executive Review

Technology appraisal 119: Fludarabine monotherapy for the first line treatment of chronic lymphocytic leukaemia.

1. National Hospital Prescribing Data

Data showing trends in prescribing costs are presented below. Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance. Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Figure 1. The overall usage of Fludarabine (oral, intravenous & unidentified)

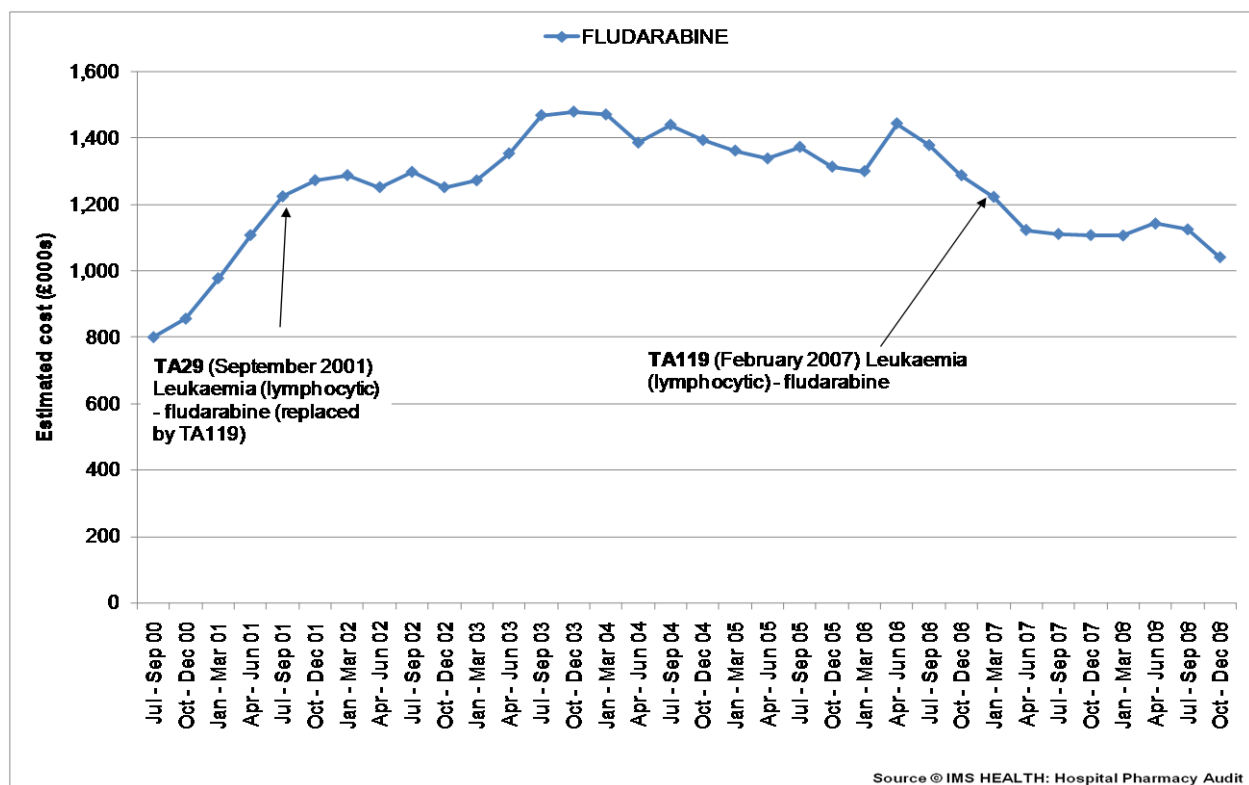
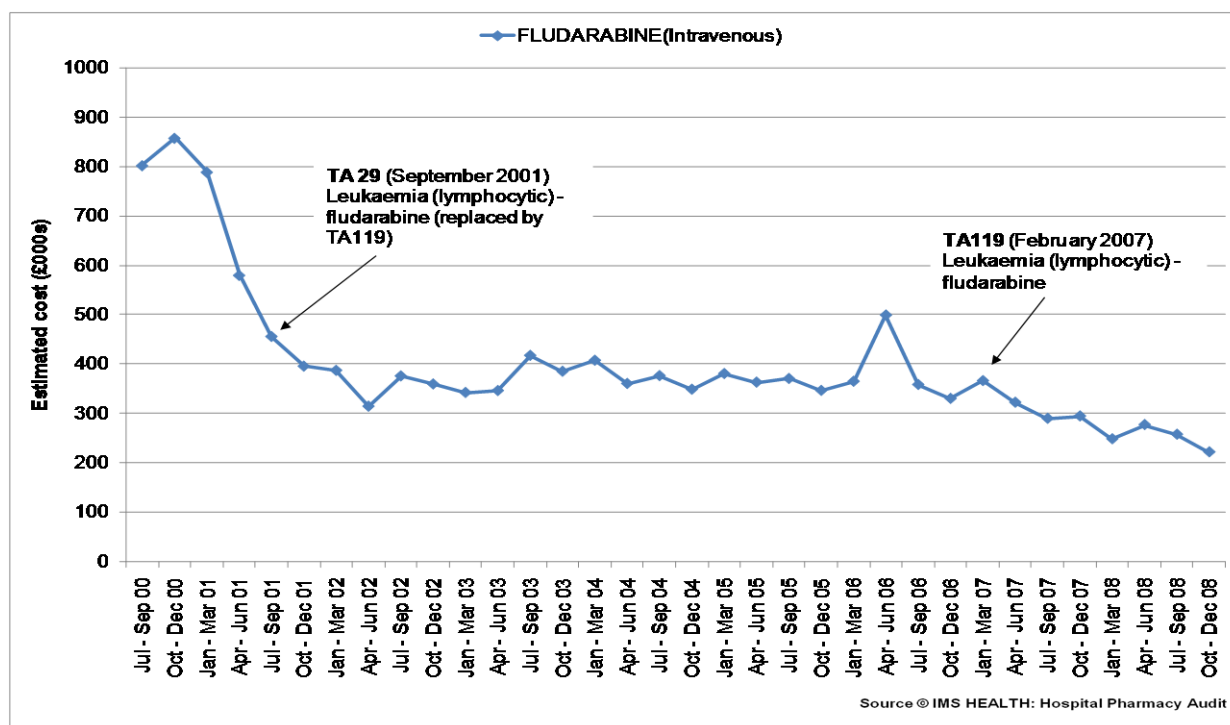


Figure 2. The usage of fludarabine (intravenous)



2. External literature

2.1 The Information Centre for Health and Social Care (2008) Hospital Prescribing, 2007: England

<http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/hospital-prescribing-2007:-england>

Data showing the use of Fludarabine in primary care, in hospitals and those prescribed in hospitals, but dispensed in the community.

Cost (£000s)	Primary care	% growth primary	FP10HP*	% growth	Hospital	% growth hospital	Total	% growth total
Fludarabine	4.7	79.7	9.1	-49.6	4563.3	-15.7	4577.1	-15.8

*FP10HP = prescriptions written in hospitals but dispensed in the community

Overall the data shows that the majority of prescribing for fludarabine is carried out in a hospital setting.

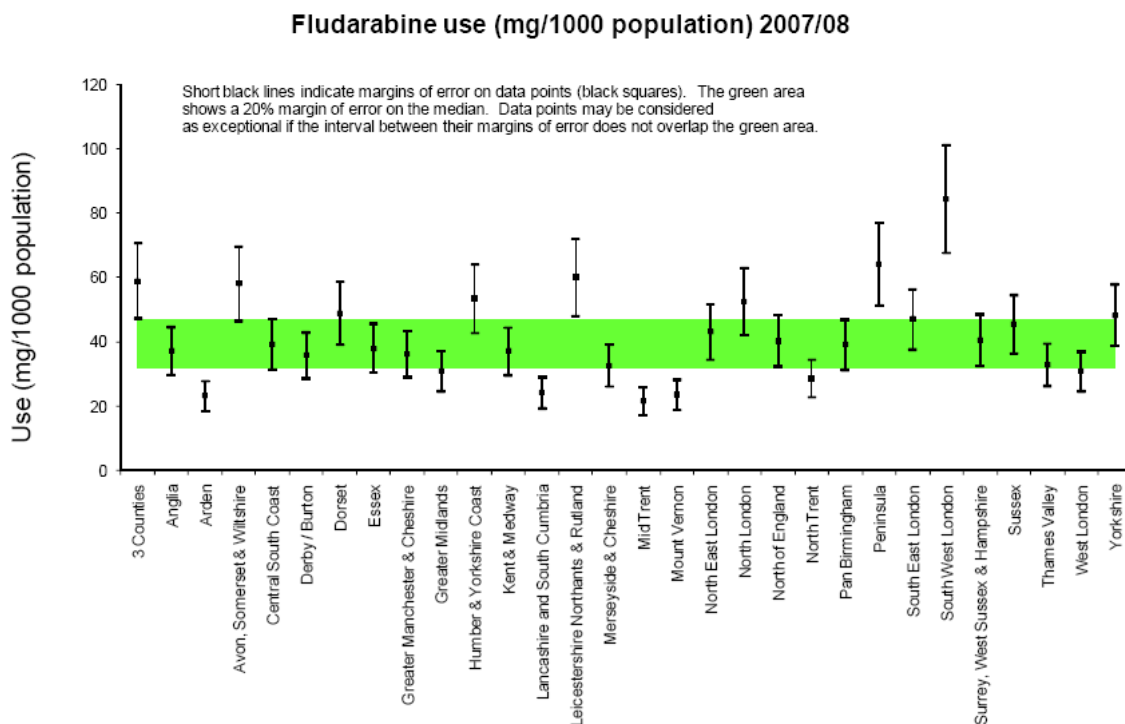
2.2 Richard M (2009) ["Uptake of NICE approved cancer drugs: Report of Review"](#)

[undertaken by the National Cancer Director](#)" Department of Health: London.

The 2009 report shows: (i) Overall usage of 13 of the 14 NICE drugs have increased (median 73%, range 4% to 291%) (ii) Usage has decreased for only one NICE drug - fludarabine (-18%). This is likely to be due to other drugs being used in preference, for example rituximab.

Variations in usage between cancer networks were wider for some NICE approved drugs than others. There was a small increase in the variation of usage of Fludarabine (2.2 to 2.4), an increase in variation of 10% since 2005.

The following chart shows regional variation in prescribing of Fludarabine:



A literature search was carried out using the following databases:

- Cinahl (EBSCO Host)
- Embase (Ovid)
- HMIC (Search 2)
- Medline (Ovid)
- Medline in Process (Ovid)

The search found no results that linked directly to the uptake of this piece of guidance.