NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA29; Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia

This guidance was issued in September 2001.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

"Clinical & cost effectiveness of fludarabine for lymphocytic leukaemia and rituximab for chronic lymphocytic lymphoma"

3. Current guidance

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:

1.1.1 cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)

1.1.2 cyclophosphamide, doxorubicin and prednisolone (CAP) or

1.1.3 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.

4. Rationale [1]

No new evidence has been identified that would impact on the current recommendations in technology appraisal guidance 29. It is therefore appropriate for the guidance to be to be transferred to the 'static guidance list'.

5. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January, 2004

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

6. Summary of evidence and implications for review

At the time of technology appraisal 29, fludarabine was licensed for 'patients with B-cell chronic lymphocytic leukaemia 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' (licence received in 1994). Since then, the marketing authorisation has changed to:

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

- First line treatment with Fludara oral 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.'

Although the current licensed indication for second-line treatment is broader than the original one considered by the Committee, the recommendations in technology appraisal 29 remain within the marketing authorisation of fludarabine. Guidance on the first-line indication was issued in February 2007 (Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia; NICE technology appraisal guidance 119).

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. In NICE technology appraisal guidance 119, the Committee did not make recommendations with respect to fludarabine plus cyclophosphamide combination therapy for this reason. Because this also applies to the licence for fludarabine as a second-line treatment, this review does not consider evidence relating to fludarabine combination therapy for the second-line treatment of chronic lymphocytic leukaemia.

In technology appraisal 29, the Committee considered that the appropriate comparators for second-line fludarabine were cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP); cyclophosphamide, doxorubicin and prednisolone (CAP); and cyclophosphamide, vincristine and prednisolone (CVP). This review did not identify any new or ongoing clinical trials comparing fludarabine monotherapy with any of these comparators in the second-line setting.

The Committee recommended further research to directly assess the impact of fludarabine on quality of life, and to determine with greater certainty whether oral fludarabine is as clinically effective as intravenous fludarabine. This review did not identify any new studies for fludarabine monotherapy that would address either of these recommendations.

In 2001, the cost of a 6-cycle course of fludarabine (either as an intravenous infusion or orally) was £3900. In 2013, it was £2419. Because the Committee considered that fludarabine was cost effective at the original cost of £3900, the reduced cost would not affect the recommendations in technology appraisal 29.

Overall, this review did not identify new evidence that warrants the review of technology appraisal 29. The evidence base for fludarabine appears mature, and clinical experience with fludarabine has likely developed given that fludarabine was licensed for chronic lymphocytic leukaemia many years ago. The marketing authorisation of fludarabine has changed after technology appraisal guidance 29 was published, but this does not affect the recommendations in that appraisal. Likewise, the reduced cost of fludarabine would not change the Committee's conclusion about the cost effectiveness of fludarabine for the second-line treatment of chronic lymphocytic leukaemia. In view of the above information, a review of technology appraisal 29 is not needed.

7. Implementation

A submission from Implementation is included in Appendix 3.

8. Equality issues

No equality issues were raised in the original guidance.

GE paper sign off: Helen Knight, Associate Director 10/09/13

Contributors to this paper:

Information Specialist:	Daniel Tuvey
Technical Lead:	Ahmed Elsada
Implementation Analyst:	Rebecca Braithwaite
Project Manager:	Andrew Kenyon

Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	YES

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Cancer service guidance, CSGHO Improving outcomes in haemato-oncology cancer Issued: October 2003

Technology appraisals TA119 Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia Issued: February 2007.Reviewed May 2010 - guidance transferred to the static list.

Technology appraisals TA174 Rituximab for first line treatment of chronic lymphocytic leukaemia Issued: July 2009. Reviewed: October 2012 - deferred until publication of clinical trial MO20927

Technology appraisals TA193 Rituximab for the treatment of relapsed chronic lymphocytic leukaemia Issued: July 2010 Reviewed: October 2012 - deferred until publication of clinical trial MO20927

Technology appraisals TA202 Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab Issued: October 2010. Review date: September 2013

Technology appraisals TA216 Bendamustine for the treatment of chronic lymphocytic leukaemia Issued: February 2011. Review date: December 2013

Referred - Quality Standard

Haematological cancers

Details of changes to the indications of the technology

Indication considered in original appraisal	Current indication (for this appraisal)
Fludara is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (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. (SmPC, 2000)	Treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves. First line treatment with Fludara oral 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.(SmPC, 2013)

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Rituximab (MabThera) subcutaneous formulation	For all current licensed oncology indications in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
Obinutuzumab	For first line chronic lymphocytic leukaemia in combination with chlorambucil
Ofatumumab	For the maintenance treatment of relapsed chronic lymphocytic leukaemia following response to induction therapy
Ofatumumab in combination with chlorambucil	For the first line treatment of chronic lymphocytic leukaemia
Ponatinib	For philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia resistant or intolerant to prior tyrosine kinase inhibitor therapy
Idelalisib in combination with rituximab	For previously treated and recurrent chronic lymphocytic leukaemia patients
Ibrutinib	For relapsed or refractory chronic lymphocytic leukaemia (CLL)
Lenalidomide (Revlimid)	For chronic lymphocytic leukaemia
Ofatumumab (Arzerra)	For relapsed chronic lymphocytic leukaemia

Appendix 3 – Implementation submission

Review of NICE technology appraisal guidance No. 29 Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia

Contents

Please contact Rebecca Braithwaite regarding any queries
rebecca.braithwaite@nice.org.uk

1. Routine healthcare activity data

1.1. Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost (NIC) and volume of Fludarabine prescribed and dispensed in hospitals between July 2000 and December 2012 in England.

Figure 1 Cost and volume of Fludarabine prescribed and dispensed in hospitals in England.

2. Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

2.1 Richards M (2004) "Variations in usage of cancer drugs approved by NICE: Report of the Review undertaken by the National Cancer Director." Department of Health: London.

This review conducted by the National Cancer Director in 2004 reported that (i) overall usage of cancer drugs had generally increased following a positive NICE appraisal, (ii) there was considerable variation in usage among cancer networks that could not be accounted for by differences in case-mix alone. A further review was conducted in 2005 and published in September 2006 showing significant reductions in the levels of variation across cancer networks.

2.2 Richard M (2006) Usage of cancer drugs approved by NICE: Report of Review undertaken by the National Cancer Director London: Department of Health

The 2006 report shows: (i) a continued increase in uptake of cancer drugs following a positive NICE appraisal, (ii) a reduction in the variation in usage of all 15 NICE-approved drugs since a 2003 analysis. Variations in usage between cancer networks were wider for some NICE-approved drugs than others. The X-fold variation in usage for Fludarabine (Fludara) over the first half of 2005 was 2.2, a reduction in variation of 30% since the second half of 2003.

2.3 Richards, M (2010) Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

3. Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing specific to add.

Appendix A: Healthcare activity data definition

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: 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.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.