

Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment

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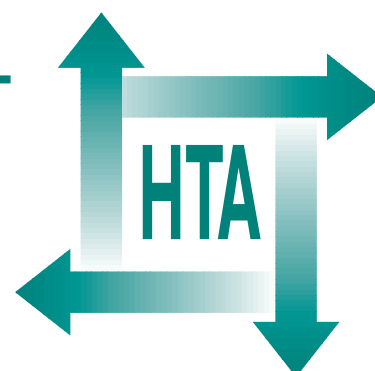
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Executive summary

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Executive summary

Background

Launched in 1994, intravenous fludarabine is a relatively new chemotherapeutic agent. It is currently licenced for use in 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 (i.e. as a second-line treatment).

CLL is a cancer of the lymphocytes, which is slowly progressive with gradual accumulation of malignant cells in blood, bone marrow and lymph nodes. This gives rise to anaemia, thrombocytopenia and immunosuppression among other effects. The disease is widely acknowledged to be incurable, although median overall survival is 10 years. An average health authority of 500,000 may have approximately 16 new patients presenting each year, most of whom will be aged > 60 years and asymptomatic. Only about 50% will require treatment at some stage during the course of their disease.

Specific anti-cancer treatment does not commence until the disease becomes symptomatic. The main aim of treatment is to maximise quality of life (QoL) by inducing remission and abolishing symptoms associated with relapse with minimal side-effects. First-line therapy is usually oral chlorambucil (or an equivalent alkylating agent). Second-line treatment is usually an anthracycline-containing chemotherapy regimen, such as cyclophosphamide plus doxorubicin plus vincristine plus prednisolone (CHOP) or fludarabine.

Objective

Although the use of intravenous fludarabine is already well established in its current licensed indication, this review considers whether this should be supported and further encouraged.

Methods

A systematic review of effectiveness was undertaken using a predefined protocol. Databases, including

MEDLINE, EMBASE and the Cochrane Library, were searched until September 2000. Ascertainment of relevant literature was augmented by citation checking of the studies and reviews obtained and the reference list of the single industry submission, contact with experts in the field and Internet searches. Randomised controlled trials (RCTs) and case-series with ≥ 50 patients assessing any effects of fludarabine as a second-line treatment were focused on. Inclusion decisions, quality assessment and data abstraction were performed independently by two reviewers. Synthesis was qualitative and meta-analysis was not employed. The economic analysis comprised in the main a systematic review of past economic evaluations.

Results

Number and quality of studies, and direction of evidence

The systematic review of effectiveness identified two RCTs, but only one of these contributed data to the analysis. Although well conducted, this RCT was small comparing disease progression, survival and adverse events in 48 previously treated patients given fludarabine with 48 given cyclophosphamide plus doxorubicin plus prednisolone (CAP). Overall response rates (RRs) were 48% with fludarabine versus 27% with CAP – a difference of 21% (95% confidence interval, 2 to 40). Improvements in RR were seen for both complete and partial response. The time to progression in responders was increased from a median of 179 days (CAP) to 324 days (fludarabine) but this was not statistically significant ($p = 0.22$). No difference was seen in overall survival. In the entire trial, which included a further 100 previously untreated patients (total $n = 196$ – 100 given fludarabine and 96 given CAP), adverse events were common in both arms, but nausea and vomiting, and alopecia and hair loss were markedly less with fludarabine. Deaths during treatment were greater with fludarabine than with CAP (nine versus three), but this difference was not statistically significant.

Seven case-series were also considered. The variability of the results for RRs and times to

progression suggested that a cautious interpretation of the results of the evidence on effectiveness provided by the single small RCT identified was appropriate.

Summary of benefits

On the evidence provided by the single small trial, qualitatively, it appears reasonably clear that the balance between beneficial effects and adverse events favoured fludarabine over CAP. However, the degree to which beneficial effects outweighed adverse events was difficult to quantify, particularly in the absence of any direct measures of the impact of fludarabine on QoL.

Costs

The drug cost of a recommended course of intravenous fludarabine is £3900. The wider cost of administration is estimated to be £6000, but this could be subject to variation depending on the true incidence, severity and costs of treating adverse events. The total annual budget impact is highly uncertain – we derived an approximate upper estimate of £5.5 million per annum for the NHS in England and Wales, which equates to a cost of £50,000 per annum for an average health authority of 500,000 persons.

Cost-effectiveness and cost-utility

Apparently favourable estimates of the incremental cost-effectiveness of fludarabine relative to CHOP were identified. However, they need to be interpreted very cautiously. The cost-utility of fludarabine cannot be accurately calculated and thus cannot assist a judgement on whether, for a given investment of resources, encouraging the

use of fludarabine is likely to achieve more net benefit than investing in other areas of healthcare.

Conclusions

Implications for healthcare

Based on the limited evidence available, intravenous fludarabine seems to be an effective second-line treatment for CLL. Whether fludarabine used in this way is an efficient use of healthcare resources is uncertain. The recent licensing of an oral preparation of fludarabine has implications for cost and patient acceptability. Its effectiveness, cost and cost-effectiveness will need to be assessed, as this could not be covered in this report.

Need for further research

Ideally, there should be further RCTs on second-line therapy with fludarabine in relapsed/refractory CLL. Realistically, attention has now focused on the effectiveness of fludarabine as a first-line therapy in CLL. Arguably, the priority should be to support and amplify ongoing RCTs to ensure an adequate evidence base for future decisions on the use of fludarabine. Future RCTs should assess impact on QoL directly.

Publication

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