The clinical effectiveness and cost-effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia: an evidence review of the submission from Roche

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia (CLL) based upon a review of the manufacturer’s submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The manufacturer’s searches for clinical effectiveness and cost-effectiveness data were appropriate and included all relevant studies. The submission’s evidence came from a single, unpublished, well-conducted randomised controlled trial (RCT) comparing rituximab in combination with fludarabine and cyclophosphamide (R-FC) with fludarabine and cyclophosphamide (FC) alone for the first-line treatment of CLL. There was a statistically significant increase in progression-free survival (PFS) with R-FC compared with FC alone {median 39.8 months vs 32.2 months; hazard ratio [HR] 0.56 [95% confidence interval (CI) 0.43 to 0.72]}. However, the initial significant treatment benefit for R-FC compared with FC for overall survival was not maintained at a slightly longer follow-up time [median 25.4 months; adjusted HR 0.72 (95% CI 0.48 to 1.09)]. Response rates, numbers of patients with event-free survival and duration of response all favoured treatment with R-FC. Additional evidence from a mixed-treatment comparison model indicated R-FC to be significantly superior to chlorambucil alone for both PFS and overall survival.

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).
and complete response rates. The incidence of grade 3 or 4 adverse events was higher in the R-FC arm (77%) than in the FC arm (62%). Dose modifications were also more frequent in this arm, but this did not lead to differences in treatment discontinuation. Roche used a three-state Markov model (PFS, progressed and death) to model the cost-effectiveness of R-FC compared with FC and chlorambucil alone. The model used a cycle length of 1 month and a lifetime time horizon. The approach taken to modelling was reasonable and the sources and justification of estimates were generally sound. The base-case analysis produced an incremental cost-effectiveness ratio (ICER) of £13,189 per quality-adjusted life-year (QALY) for R-FC versus FC, and £6422 per QALY for the comparison of R-FC versus chlorambucil, suggesting that R-FC is cost-effective at normal willingness-to-pay thresholds. One-way sensitivity analyses produced a range of ICERs from £10,249 to £22,661 per QALY for R-FC versus FC, and £5612 and £6921 per QALY for R-FC versus chlorambucil. Probabilistic sensitivity analysis results matched the deterministic results very closely. However, the sensitivity analysis did not fully investigate the uncertainty associated with differential values across arms or with the structural assumptions of the model, and utility values were not drawn from an empirical study. The NICE guidance issued as a result of the STA states that: Rituximab in combination with fludarabine and cyclophosphamide (R-FC) is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia in people for whom fludarabine in combination with cyclophosphamide (FC) is considered appropriate. Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of chronic lymphocytic leukaemia.

Description of the underlying health problem

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia, comprising approximately 30% of all adult leukemias. The incidence is about 3 per 100,000, but this varies with age and sex. The median age of diagnosis is between 65 and 70 years, and men are twice as likely to be affected as women. Incidence increases significantly with age, with a rate of almost 50 per 100,000 in patients over 70 years.

The exact causes of CLL remain unknown; however, a combination of genetic and environmental factors is thought to be involved. The presentation of patients with CLL to health-care providers is typically heterogeneous, with about 70–80% of patients diagnosed as an incidental finding following a full blood count test for some other reason. A definitive diagnosis of CLL has a characteristic lymphocyte morphology on blood film, with a specific immunophenotype (as shown by flow cytometry), and requires an absolute B-cell lymphocytosis of at least 5×10^9/l.

Two methods have been devised to stage CLL: the Binet and Rai systems. The Binet system is more commonly used in Europe and comprises three stages: stage A, less than three lymphoid areas involved; stage B, more than three lymphoid areas involved; and stage C, haemoglobin < 10 g/dl or platelets 100×10^9/l. The course of CLL is heterogeneous and it is generally anticipated that approximately one-third of patients (usually with Binet stage A disease) will never need any form of treatment and will die with, rather than of, their disease. For the remaining majority of patients (usually with Binet stage B or C disease) CLL is incurable and has a median life expectancy...
of between 5 and 10 years. Standard criteria from the International Workshop on Chronic Lymphocytic Leukaemia are used to guide whether patients should start treatment with a first-line chemotherapeutic regimen.4

As CLL is characterised by periods of active disease, during which patients are symptomatic, separated by chemotherapy-induced remissions, once patients have started treatment the main aim of therapy is to induce durable remissions during which patients are free of disease symptoms, the psychological burden of active life-threatening illness and the toxicity of chemotherapy.

Scope of the ERG report

Research question

What is the clinical effectiveness and cost-effectiveness of rituximab in combination with fludarabine therapies versus fludarabine therapies alone or chlorambucil for the first-line treatment of CLL?

Intervention

- Brand name: MabThera®.
- Approved name: rituximab.
- Therapeutic class: antineoplastic agents.
- Product licence holder: Roche Products.

Outcomes

Clinical effectiveness outcomes were progression-free survival (PFS), overall survival (OS), event-free survival, disease-free survival, response rates, duration of response, time to new CLL treatment, health-related quality of life and adverse effects of treatment. Cost-effectiveness outcomes were incremental cost per quality-adjusted life-year (QALY), resource utilisation and the cost of treating adverse events (blood transfusions and bone marrow transplants).

Type of clinical effectiveness/cost-effectiveness data used

For clinical effectiveness, ‘time to event’ data were used, reported as median time in either days or months with the point estimates expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). For cost-effectiveness, Roche built a three-state Markov model. For the comparison of rituximab (R) in combination with fludarabine and cyclophosphamide (R-FC) versus fludarabine and cyclophosphamide (FC) alone the model was parameterised by effectiveness data from the German Chronic Lymphocytic Leukaemia trial (CLL-8).5 For the comparison of R-FC versus chlorambucil monotherapy, HRs for PFS were derived using a mixed-treatment comparison (MTC) model. Health-state utility values were taken from a report by Hancock and colleagues6 on the use of fludarabine as first-line treatment for CLL; these values were estimated by the report authors. Costs were based on an NHS and Personal Social Services perspective.

Stated potential health effects

Rituximab is a chimeric murine/human monoclonal antibody that binds selectively to the CD20 cell antigen expressed on the surface of mature B lymphocytes and any tumour cell that expresses CD20, including B-cell CLL. It causes depletion of normal and malignant B cells. Although its mechanism of action is not precisely defined, antibody-directed cytotoxicity, complement-dependent cytotoxicity, induction of apoptosis and sensitisation of cells to conventional cytotoxic drugs are all likely to be important.7–9

Stated costs

Rituximab is available in two vials sizes: 10-ml vial (minus VAT) = £174.63; 50-ml vial (minus VAT) = £873.15.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer’s/sponsor’s submission to NICE as part of the STA process.

The manufacturer’s search strategy was reviewed by an information scientist and the searches were rerun with text words and a full clinical trials filter to see if any relevant trials had been omitted. The methods used by the manufacturer to report clinical effectiveness were critiqued using the principles advocated in the Centre for Reviews and Dissemination’s (CRD) guidance for undertaking reviews in health care.10 Roche’s economic evaluation was assessed against the following study quality checklists: NICE reference case,11 Drummond and colleagues12 and Philips and
Rituximab for chronic lymphocytic leukaemia

Results

Summary of submitted clinical evidence

The evidence for the submission was based on one phase III randomised controlled trial (RCT) comparing R-FC with FC for the first-line treatment of people with CLL (the CLL-8 trial;\textsuperscript{5} \(n = 810\)). Additional evidence was provided in the form of an MTC model based on PFS hazards from five trials allowing for an indirect comparison of R-FC with chlorambucil monotherapy.\textsuperscript{5,14–17}

Chlorambucil had been included as a comparator in two of the five trials.\textsuperscript{13,16}

The CLL-8 trial was a randomised, parallel-group, multicentre trial; however, blinding of both patients and outcome assessors to treatment allocation was not attained, which may have introduced bias into the results. The trial was stopped early (median follow-up 20.7 months) at the time of the planned interim analysis because of significant differences in PFS between treatment arms. Data from four different sets of analyses of the trial are presented: (1) interim analysis (median follow-up 20.7 months); (2) snapshot analysis 1 (median follow-up 25.4 months); (3) snapshot analysis 2 (median follow-up 25.5 months); and (4) economic analyses snapshot (median follow-up 26.4 months).

At 20.7 months follow-up there was a statistically significant increase in PFS with R-FC compared with FC alone [median 39.8 months vs 32.2 months; HR 0.56 (95% CI 0.43 to 0.72)]. However, for OS, the initial treatment benefit for the R-FC regimen noted at the time of the interim analysis was no longer maintained at slightly longer follow-up (snapshot analysis 1) [HR 0.72 (95% CI 0.48 to 1.09)]. Patients in the R-FC arm remained event free (disease progression, relapse, death or start of new CLL treatment) significantly longer than those in the FC-arm [39.8 months vs 31.1 months; HR 0.55 (95% CI 0.43 to 0.70)]. Response rates also significantly favoured treatment with R-FC, with 36.0% of patients in this arm achieving complete response compared with 17.2% in the FC arm. Partial response rates were not significantly different between trial arms at 50.1% for R-FC and 55.5% for FC respectively.

The incidence of grade 3 or 4 adverse events was higher in the R-FC arm (77%) than in the FC arm (62%), mostly because of a higher incidence of blood and lymphatic system disorders (57% versus 41%). Dose modifications were also more frequent in this arm. However, this did not lead to differences in treatment discontinuation. There were also no difference between arms in the rate of deaths considered related to therapy (2%).

Mixed-treatment comparison model

Based on results of the five trials included in the MTC\textsuperscript{5,14–17} (with chlorambucil used as the reference treatment), R-FC significantly increased PFS compared with chlorambucil alone [mean HR 0.24 (lower bound 0.17, upper bound 0.34)].

Summary of submitted cost-effectiveness evidence

Roche used a Markov model with a three-state structure (PFS, progressed and death) to model the cost-effectiveness of R-FC compared with FC and chlorambucil alone. The model used a cycle length of 1 month and a lifetime time horizon (equating to 15 years).

Roche’s base-case analysis produced an incremental cost-effectiveness ratio (ICER) of £13,189 per QALY for R-FC versus FC, and an ICER of £6422 per QALY for the comparison of R-FC versus chlorambucil. One-way sensitivity analyses produced a range of ICERs from £10,249 per QALY to £22,661 per QALY for the comparison of R-FC versus FC, and £5612 per QALY and £6921 per QALY for R-FC versus chlorambucil. Results from further probabilistic sensitivity analysis matched the deterministic results very closely.

Commentary on the robustness of submitted evidence

Strengths

The searches for clinical effectiveness and cost-effectiveness data were appropriate and included all relevant studies. The identified RCT was well conducted and the findings were likely to be reasonably robust.

The approach taken to modelling was reasonable and the sources and justification of estimates were generally sound.
Weaknesses

The evidence was based on only one completed and unpublished RCT.

The sensitivity analysis was limited and did not fully investigate the uncertainty associated with differential values across arms or with the structural assumptions of the model. Utility values were not drawn from an empirical study.

Conclusions

There was a statistically significant increase in PFS with R-FC compared with FC alone [median 39.8 months vs 32.2 months; HR 0.56 (95% CI 0.43 to 0.72)]. However, the initial significant treatment benefit for R-FC compared with FC for OS was not maintained at a slightly longer follow-up time [median 25.4 months; adjusted HR 0.72 (95% CI 0.48 to 1.09)]. Response rates, numbers of patients with event-free survival and duration of response all favoured treatment with R-FC.

The MTC model indicated R-FC to be significantly superior to chlorambucil alone for both PFS and overall and complete response rates.

With an ICER of £13,189 per QALY for R-FC versus FC, and £6422 for R-FC versus chlorambucil alone, there is a strong probability that R-FC is cost-effective at normal willingness-to-pay thresholds.

Areas of uncertainty

It was unclear whether the observed treatment benefit for use of rituximab combination therapy for PFS was associated with longer-term gains in OS and how plausible it was to extrapolate any PFS benefits in the longer term.

Key issues

Almost all data parameters for effectiveness were drawn from the CLL-8 trial. Although this trial was of reasonable quality, there are inherent limitations in an analysis that relies on data from a single clinical trial.

The issue of structural uncertainty in the model relating to the treatment of OS rates between the trial arms was not adequately explored in sensitivity analyses. This relates specifically to the assumption of aggregation in the post-relapse state. The ERG felt that this was likely to be clinically unrealistic as patients will receive further treatment at progression that may then result in further periods of PFS. The relapsing nature of CLL means that subsequent periods of progression are less likely to respond to further treatment, implying that later periods of progression in the course of disease are likely to be associated with higher disease-related mortality. This casts doubts over the simplifying assumption of a constant hazard of death after progression as modelled by Roche.

Additionally, it should be noted that once any assumed benefit for OS is removed, model outputs become highly sensitive to the utility parameters assumed for the PFS and progressed states, and these values are not currently available from an appropriate source.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the Appraisal Consultation Document issued by NICE on 26 March 2009 states that:

Rituximab in combination with fludarabine and cyclophosphamide (R-FC) is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia in people for whom fludarabine in combination with cyclophosphamide (FC) is considered appropriate. Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of chronic lymphocytic leukaemia.

References


