Scottish Medicines Consortium

rituximab, 100mg and 500mg concentrate for solution for infusion (MabThera®) No. (591/09)
Roche

04 December 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

rituximab (MabThera®) is accepted for restricted use within NHS Scotland.

Licensed indication under review: for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Rituximab in combination with fludarabine and cyclophosphamide resulted in significantly longer progression-free survival than fludarabine and cyclophosphamide alone. The patient population in the pivotal clinical study had an Eastern Cooperative Oncology Group Performance Status of 0 or 1 and was a younger population than that generally seen in clinical practice. Evidence in patients over 70 years of age is limited.

Restriction: Rituximab is restricted to use by specialists in haematology and haemato-oncology.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

The treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia, in combination with chemotherapy.

Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy.

Dosing information

375mg/m^2 body surface area administered on day 0 of the first treatment cycle followed by 500mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total.

The chemotherapy should be given after the rituximab infusion.

Product availability date

21 August 2009

Summary of evidence on comparative efficacy

Chronic lymphocytic leukaemia (CLL) is a chronic incurable disease and the most common form of leukaemia in the UK. It is characterised by a progressive accumulation of monoclonal B lymphocytes, expressing CD5 and CD23 molecules. Rituximab is a chimeric monoclonal antibody that binds specifically to the trans-membrane antigen, CD20, located on mature B lymphocytes.

Rituximab was initially licensed for the first-line treatment of CLL, in combination with cyclophosphamide and fludarabine; the licence has now been extended to include relapsed and/or refractory disease. The evidence to support the extended marketing authorisation for rituximab is from one unpublished phase lll, open-label, randomised study comparing rituximab in combination with fludarabine and cyclophosphamide with fludarabine and cyclophosphamide alone in 552 adult patients with previously treated CD-20 positive relapsed CLL (according to National Cancer Institute [NCI] criteria). Many phase ll studies were also submitted to support the wider use of rituximab in combination with other cytotoxic agents and regimens.

Patients with a life expectancy >6 months, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1, and who had previously been treated with either chlorambucil (±prednisolone), single agent fludarabine (or other nucleoside analogue) or an alkylator-containing regimen were randomised. Patients who had previously received fludarabine (or other nucleoside analogue) had to have had a complete or partial response that lasted at least 6 months. Response requirements for other previous therapy were less stringent, and patients refractory to alkylator-based therapy could be enrolled. Two hundred and seventy-six patients were randomised to receive six cycles of iv fludarabine 25 mg/m^2 plus iv cyclophosphamide 250 mg/m^2 on days 1, 2 and 3 of the 28 day cycle (FC), whilst another 276 received iv rituximab 375 mg/m^2 on day 0 of cycle 1 then 500 mg/m^2 on day 1 of cycles 2 to 6 plus the fludarabine and cyclophosphamide regimen already described (R-FC). Patients were followed for up to eight years.

The median age of patients was 63 years, 67% were male, the majority (59%) had Binet stage B disease and 60% had an ECOG PS of 0. One hundred and sixty-seven patients in the FC group completed all 6 cycles, whilst 181 of those receiving R-FC did so.

The primary endpoint was progression-free survival (PFS), defined as the time between randomisation and the first documented disease progression, relapse after response or death from any cause, in the intention-to treat (ITT) population which included all randomised patients. Secondary endpoints included overall survival (OS) rate, event-free survival (EFS), duration of response and response rates.

At the time of analysis, and with a median follow-up of 25.3 months, there had been 290 PFS events (158 patients (57%) in the FC group and 132 patients (48%) in the R-FC group). Of these, 133 patients in the FC group and 102 patients in the R-FC group had progressed and 25 patients in the FC group and 30 patients in the R-FC group had died. Efficacy outcomes for this analysis are presented in Table 1. At two years, 44% of patients in the FC group and 60% of those in the R-FC group were progression-free.

Table 1: Summary of progression free survival and duration of response (ITT population)

	FC (n=276)	**R-FC (n=276)**
Progression free survival		
median (months) (Kaplan-Meier estimate)	20.6	30.6
p value (Log-Rank test)	0.0002	
HR (95% CI) non-stratified (unadjusted)	0.65 (0.51, 0.82)	
Duration of response in patients with complete or partial response as best response		
median (months) (Kaplan-Meier estimate)	27.6	39.6
p value (Log-Rank test)	0.0252	
HR (95% CI) non-stratified (unadjusted)	0.69 (0.50, 0.96)	

ITT = intention to treat; FC = fludarabine and cyclophosphamide; R-FC = rituximab, fludarabine and cyclophosphamide; HR = hazard ratio; CI = confidence interval

Results of the secondary endpoints supported the primary outcome. Significantly more patients in the R-FC arm than in the FC arm had a best overall response of partial or complete response (overall response rate - 58% FC versus 70% R-FC), and this was mostly due to a significantly higher complete response rate (13% FC versus 24% R-FC). A higher proportion of patients in the FC arm (59%) experienced an EFS event (disease progression, relapse after response, death or new treatment for CLL) in comparison with the R-FC arm (49%). The median EFS was significantly increased by 9.5 months from 19.2 months in the FC arm to 28.7 months in the R-FC arm (risk reduction of 36%). At the time of analysis, with a median observation time of 25.3 months, the OS data were immature. Sixty-eight patients (25%) in the FC arm and 62 patients (23%) in the R-FC arm had died. The median for OS in the FC arm was 51.9 months and had not yet been reached for the R-FC arm. This data did not demonstrate a statistically significant advantage in OS when rituximab was added to FC (risk of death reduction of 17%).

Phase II studies were submitted to support the use of rituximab in combination with other chemotherapy regimens.

Summary of evidence on comparative safety

The safety profile of rituximab in CLL was consistent with the known safety profile of rituximab used in combination with chemotherapy in other indications, with no new safety concerns reported in the phase lll study.

The incidence of all Grade adverse events (AEs), Grade 3/4 AEs and serious AEs was slightly higher in the R-FC arm compared to the FC arm (99% versus 96%; 80% versus 74% and 50% versus 48% respectively).

Grade 3 and 4 neutropenia, febrile neutropenia and granulocytopenia occurred in at least 2% more patients in the R-FC arm, suggesting a potential relationship to rituximab treatment. Although the incidence of Grade 3/4 infections or infestations (including opportunist infections) was comparable between the treatment arms, Grade 3/4 hepatitis B infection occurred uniquely in the R-FC arm (5 patients). Due to small numbers, firm conclusions about causality cannot be drawn.

The proportion of patients who discontinued therapy due to an AE was similar in each treatment arm (25% FC versus 26% R-FC). At the time of clinical data cut-off, more patients in the FC arm had died; 25% compared with 23% in the R-FC arm. The incidence of treatment-related deaths was slightly higher in the R-FC arm (7% R-FC versus 5% FC). The number of patients experiencing an AE with an outcome of death was higher in the R-FC than in the FC arm (13% in R-FC versus 10% in FC). Most fatal AEs were due to infections or infestations.

Summary of clinical effectiveness issues

This submission seeks to extend the marketing authorisation of rituximab, for the treatment of CLL, in combination with chemotherapy, to treat those patients who have relapsed or are refractory to previous treatment. Evidence from one randomised phase III study, adding rituximab to fludarabine and cyclophosphamide, shows that this combination prolongs median progression free survival by 10 months. Studies using other chemotherapy regimens were all phase II and nearly all single arm, meaning that results are harder to interpret.

Patients who had previously been treated with rituximab or who were fludarabine refractory were excluded from the phase III study, mainly because at the time of the study these patients were considered rare. Since then, data have become available to support both of these patient groups being re-treated and these patients are covered in the extension to the marketing authorisation.

The phase III study was open-label, however because the assessment of CLL post-treatment is objective, it is unlikely that this will have biased results. In addition, independent assessments of the data were performed.

The median age in the phase lll study was 63 years: the majority (57%) were less than 65 years, 26% were ≥ 65 and ≤ 70 years and 17% were over 70 years. Therefore patients were a younger population than generally seen in practice, where the median presenting age is 70 years. The patients included in the study were also fit with an ECOG PS of 0 or 1. Due to the relatively small patient numbers, subgroup analysis was not powered to show results for patients over 70 years of age.

Although in the phase III study all components of the regimen were given intravenously, fludarabine and cyclophosphamide are frequently given orally. This means, therefore, that the addition of rituximab to this regimen may require an additional once-monthly hospital visit for administration of the intravenous infusion, as well as an increased workload for staff involved in aseptic preparation.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis focusing on the addition of rituximab (R) to fludarabine-plus-cyclophosphamide (FC). Other treatment regimes are used in Scotland, but the comparator selected was acceptable. A Markov model was used based on data from the pivotal clinical study, with PFS and OS being extrapolated into the future using parametric techniques. Utility values were taken from a previous NICE HTA submission in the same disease area. Resource use was based on data from the pivotal clinical study, supplemented by assumptions.

The manufacturer identified three key clinical assumptions in their approach as follows:

(i) rituximab delays progression but does not affect survival once progression has occurred
(ii) following failure of FC or R-FC patients have identical treatment
(iii) orally administered FC is as effective as intravenous FC.

On this basis, the incremental cost per QALY gained for R-FC over FC was £15,593 based on a difference in costs of £9,128 and a QALY gain of 0.585.

Sensitivity analysis suggested the added benefit could fall to 50% of the predicted level and the cost per QALY would still be below £30,000 per QALY gained.

Several assumptions were required:

- There was only robust data for an evaluation of adding rituximab to FC. However, further information was provided on the robustness of the results to changes in the assumed benefit to help assess the cost-effectiveness against other chemotherapy regimens.
- Extrapolation was required to estimate the full benefit. However, the manufacturer showed that this was based on 2.1 years of data and the parametric form had a good fit to the observed data.

Despite these issues, the economic case was considered demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: Chronic Lymphocytic Leukaemia Support Association (CLLSA).

Additional information: guidelines and protocols

The British Committee for Standards in Haematology published guidelines in 2004 entitled "Guidelines on the diagnosis and management of chronic lymphocytic leukaemia." Recommendations for second line treatment include the statements that rituximab monotherapy is not recommended for previously treated CLL but that rituximab combined with fludarabine (with or without cyclophosphamide) may be effective in refractory CLL and warrants further evaluation in this setting. These guidelines are being updated.

The European Society for Medical Oncology published guidelines in 2008 entitled "Chronic lymphocytic leukaemia: ESMO clinical recommendations for diagnosis, treatment and follow-up." Second line chemotherapy options include fludarabine combinations [with cyclophosphamide (FC) and/or mitoxantrone (FCM)] ± monoclonal antibodies (FR, FCR, FA) in fludarabine-refractory patients or relapse after fludarabine-based therapy.

The National Comprehensive Cancer Network in the United States published updated clinical practice guidelines for Non-Hodgkin's Lymphomas in 2008. These include recommending chemotherapy ± rituximab or alemtuzumab as second line therapy in CLL patients.

Additional information: comparators

Rituximab for this indication is add on treatment and as such has no direct comparator. Other regimens are available for use and the most common ones are included below. Costs have been calculated for intravenous and oral preparations (where appropriate), as used in Scottish practice.

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost per 6 cycles (£)
rituximab and intravenous fludarabine and cyclophosphamide	**375mg/m^2 D 0 of cycle 1, then 500mg/m^2 D 1 of cycles 2-6, intravenously** 25mg/m^2 D 1-3 of each cycle, intravenously 500mg/m^2 D 1-3 of each cycle, intravenously	**cycle 1: 1,699** **cycles 2-6: 2,048**	**11,939**
rituximab and oral fludarabine and cyclophosphamide	**375 mg/m^2 D 0 of cycle 1, then 500mg/m^2 D 1 of cycles 2-6, intravenously** 24mg/m^2 D 1-5 of each cycle, orally 150mg/m^2 D 1-5 of each cycle, orally	**cycle 1: 1,583** **cycles 2-6: 1,932**	**11,242**
intravenous fludarabine and cyclophosphamide	25mg/m^2 D 1-3 of each cycle, intravenously 500mg/m^2 D 1-3 of each cycle, intravenously	476	2,859
oral fludarabine and cyclophosphamide	24mg/m^2 D 1-5 of each cycle, orally 150mg/m^2 D 1-5 of each cycle, orally	360	2,161
chlorambucil	10mg/m^2 D 1-7 of each cycle, orally	21	up to 253*

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 8 October 2009. D = day.
Doses are based on a body surface area of 1.8m^2. The dosing regimens and length of treatment are taken from the pivotal trial or expert opinion. * this treatment is given for up to 12 cycles

Additional information: budget impact

The estimated net budget impact was £1.1m per year, including administration costs; this was the maximum cost because it is based on 100% uptake among the estimated 100 eligible patients. The net drugs budget impact alone was £905k in year 1 rising to £916k in year 5.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 13 November 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.