Scottish Medicines Consortium

rituximab 10mg/ml concentrate for infusion (MabThera®) (No.330/06)

Roche

10 November 2006

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 as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab.

In a phase lll, randomised, open-label study, rituximab maintenance treatment significantly increased the median progression-free survival from 15 months in the observation arm to 52 months in the rituximab arm with an increase in overall survival at three years. This prolonged survival requires to be confirmed in longer term follow up.

Rituximab is restricted for use only by oncologists or haematologists who have expertise in treating lymphoma.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab.

Dosing information

375mg/m^2 once every three months by intravenous infusion until disease progression or for a maximum period of two years.

Product availability date

25 September 2006

Summary of evidence on comparative efficacy

Follicular lymphoma is the second most common subtype of non Hodgkin's Lymphoma (NHL). Most patients present with advanced stage III/IV disease which is generally accepted to be incurable although patients may live with their disease for 8-10 years. Patients are usually not actively treated unless they are symptomatic. Once symptomatic, the aim of treatment is to shrink the tumours to provide symptomatic relief and improved quality of life. The response pattern to treatment is characterised by multiple remissions and relapses with successive treatments producing typically poorer and shorter responses. Rituximab is a chimeric mouse/human monoclonal antibody which binds specifically to the trans-membrane antigen, CD20, located on the pre-B and mature B lymphocytes, and expressed on >95% of all B cell NHLs. It induces cell death via apoptosis. It is already licensed for induction treatment in follicular lymphoma in both untreated and relapsed patients.

There is one pivotal, phase III study using rituximab for maintenance, in the licensed patient population at the licensed dose. Four additional supporting studies used either different dosing schedules or patient populations from those licensed and will not be discussed here.

In this open-label study of two parts (induction therapy followed by observation or maintenance therapy), 465 patients with relapsed/refractory, CD20-positive follicular lymphoma stage III-IV, were randomised centrally to six cycles of either CHOP (intravenous (IV) cyclophosphamide 750 mg/m^2, IV doxorubicin 50 mg/m^2 and IV vincristine 1.4 mg/m^2, all administered on day 1 plus prednisolone 100 mg orally on days 1 to 5 of a 21 day cycle) (n=231) or R-CHOP (CHOP plus rituximab 375 mg/m^2 as a slow IV infusion on day 1) (n=234). Randomisation was stratified by centre, previous purine analogue treatment, age, number of previous induction treatments, best previous response, time since diagnosis and bulky disease. The primary outcome measure for this induction phase was last tumour response rate. Tumour assessments were carried out after cycles three and six and those patients with stable or progressive disease were withdrawn from the study. At the end of the induction phase, the overall tumour response rate in the R-CHOP treatment arm was significantly higher than in the CHOP treatment arm, 85% and 72% ($p<0.0001$), respectively. The number of partial responses (PR) in each of the treatment arms was similar, 56% and 57% respectively, but there were significantly more complete responses (CR) in the R-CHOP arm, 30% and 16% ($p<0.0001$). Patients achieving a CR or PR of at least 4 weeks duration with induction therapy, and who had no rituximab-related toxicity necessitating stopping rituximab, whose immunoglobulin (IgG) levels were >3g/l and who had no active infection, were re-randomised to observation (n=167) or maintenance therapy with rituximab 375 mg/m^2 as a slow IV infusion once every three months (n=167) until disease progression or for a maximum of two years. Randomisation was stratified for centre, treatment allocation at first randomisation and the quality of response to induction therapy (CR/PR). Tumour assessments were made every three months during the first two years and every 4-6 months thereafter. The primary endpoint during the maintenance phase was progression-free

survival (PFS) defined as the interval between the date of second randomisation and date of relapse, progression, or death, whichever occurred first. Overall survival was a secondary outcome defined as time from second randomisation to death from any cause.

After a median follow-up of 33 months from the second randomisation, rituximab maintenance treatment significantly increased the median PFS from 15 months in the observation arm to 52 months ($p<0.0001$), an improvement of 37 months and a 70% reduction in risk of disease progression. The secondary endpoint of overall survival was significantly higher at three years in the rituximab arm compared with observation, 85% vs 77% of patients, respectively, $p=0.01$. Sub-group analysis of the impact of maintenance therapy with respect to initial induction treatment found that R-CHOP followed by rituximab maintenance therapy provided significantly longer PFS than CHOP followed by rituximab maintenance, 52 months compared with 42 months. Both maintenance groups provided significantly longer PFS than in the respective observation arms, 23 and 12 months, $p=0.0043$ and $p<0.0001$, respectively.

Summary of evidence on comparative safety

No new safety concerns were reported that were not already known from the use of rituximab as induction therapy. In the maintenance phase, neutropenia was the most common adverse event with an incidence of 11% in the rituximab group compared with 5.4% in the observation group ($p=0.07$). This may account for the significant increase in the grade 3-4 infection rate in the rituximab group compared with observation (9% vs 2.4%, $p=0.009$). There were no deaths related to rituximab maintenance treatment.

Summary of clinical effectiveness issues

The statistical analysis plan for the study allowed for three interim analyses with a threshold for statistical significance set at $p<0.001$, to allow early stopping if this threshold was crossed. After the second analysis, the Independent Data Monitoring Committee recommended, initially, stopping the first randomisation and then the second, due to both primary outcomes meeting the predetermined stopping criteria.

During the re-randomisation to maintenance therapy there were slight differences between the treatment arms in the distribution of low and high risk disease scores with slightly more patients in the rituximab maintenance arm having low risk disease (35% vs 30%) and slightly less having high-risk disease (30% vs 38%). These are not thought to have influenced the study findings.

Subgroup analysis of the different induction therapies was undertaken to confirm that the benefit seen in PFS with maintenance treatment was not due to patients who had not received rituximab during induction responding to it during maintenance therapy. This was confirmed as the best outcomes were seen in those patients who were treated with R-CHOP followed by rituximab maintenance. This may be due to the higher number of patients achieving a CR during R-CHOP induction therapy.

This is the first time a treatment has been shown to prolong survival in follicular lymphoma as no consistent long-term benefits in overall survival have been demonstrated with previous maintenance regimens, some of which are associated with significant toxicity. However, longer follow up will be required to confirm the advantage seen with rituximab, and although no effect on cumulative infections was noted during follow up, the lack of sequelae of long term suppression of IgG and B cells should also be confirmed.

Summary of comparative health economic evidence

The manufacturer presented a cost utility analysis of rituximab maintenance therapy relative to observation through a 30 year Markov model with monthly cycles and three health states: progression free, progression and dead. Clinical effectiveness data were drawn from the pivotal randomised controlled trial. The first two years' transition probabilities were drawn from trial data. The transition probabilities for years three to five were drawn from Weibull extrapolations of the relevant survival curves. For years 5+, the transition probabilities for both rituximab and observation were drawn from the observation survival curves, as the manufacturer felt it unreasonable to apply those of rituximab. Treatment with rituximab was three monthly for up to two years, though drop-out prior to the full 8 courses occurred in 42% of cases.

The manufacturer estimated that rituximab would result in a gain of 1.62 years of PFS, and 1.19 years overall survival at a gross lifetime cost of £21,600 per patient. This translated into a gain of 0.89 QALYs and a net cost of £6,886 to yield a cost effectiveness estimate of £7,721 per QALY.

Observation appears to be the appropriate comparator, given toxicity and consequent lack of use of other possible active comparators. The model structure did not incorporate adverse events, which were higher under rituximab. This biased the clinical effectiveness estimates slightly in favour of rituximab, though the extent of this is difficult to quantify. The costs of adverse events were factored into the analysis, though were outside the formal model.

While there was still some uncertainty stemming from the long-term nature of the disease course, this was dealt with adequately through sensitivity analysis.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

There are no current guidelines on the use of rituximab as maintenance therapy in follicular lymphoma. However, the National Institute for Health and Clinical Excellence published in March 2002, Technology Appraisal no 37. Lymphoma (follicular non-Hodgkin's) - rituximab. The clinical effectiveness and cost effectiveness of rituximab for follicular lymphoma. This appraisal was due for review in January 2005.

Additional information; previous SMC advice

The Scottish Medicines Consortium (SMC) previously reviewed rituximab and following a full submission, issued the following guidance, in March 2003 and December 2004.

In March 2003, the SMC recommended restricted use of rituximab in non-Hodgkins lymphoma within NHS Scotland to use by oncologists or haematologists in Scotland who have expertise in treating lymphoma. It should be administered in a hospital environment where full resuscitation facilities are available.

In December 2004, SMC recommended that rituximab is accepted for use within NHS Scotland for the treatment of previously untreated patients with stage lll-lV follicular lymphoma in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy.

Rituximab is for use only by oncologists or haematologists who have expertise in treating lymphoma. It should be administered in a hospital environment where full resuscitation facilities are available. Limited results show that rituximab plus CVP significantly increased the time to treatment failure compared with CVP alone.

Additional information: comparator medications

Possible comparators are interferon alfa in patients with high tumour burden, chlorambucil, and some combination regimens. However combination regimens studied have not shown benefit to outweigh their toxicity.

Additional information: costs

Drug	Dose	Cost for 2 years of treatment
Rituximab	**375mg/m^2 intravenously every three months for up to 2 years**	**£9779**

Costs based on a body surface area of 1.8m^2 and on prices from the eVadis database accessed on 4th September 2006.

Additional information: budget impact

The manufacturer estimated that 13% of stage III/IV patients receive second line therapy of whom 68% respond, yielding an estimate of 84 patients being eligible for rituximab. Since therapy occurs over two years, this results in a budget estimate of £410K in year one, rising to £830K by year five, though if the market penetration is less than 100% of the eligible patient population this will reduce the overall budget impact pro rata.

The 13% of stage III/IV patients receiving second line therapy is based upon undocumented market research by the manufacturer. If a greater proportion receive second line therapy, the budget impact would be proportionately greater.

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 15 October 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.