Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

rituximab, 100mg in 10mL, 500mg in 50mL, concentrate for solution for infusion (MabThera®) SMC No. (675/11)

Roche Products Limited

14 January 2011

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

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

Indication under review: Rituximab maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

SMC restriction: for maintenance treatment in follicular lymphoma patients who have responded to induction with rituximab plus chemotherapy.

Rituximab significantly increased progression free survival following a response to induction therapy in patients with previously untreated follicular lymphoma compared with observation alone. Longer follow up is required to establish benefit in overall survival.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Rituximab maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Dosing Information

Maintenance treatment in patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression, or for a maximum period of two years.

Rituximab infusions should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available.

Product availability date

25th October 2010

Summary of evidence on comparative efficacy

Rituximab is a chimeric mouse / human monoclonal antibody that binds specifically to the trans-membrane antigen, CD20, located on pre-B and mature B lymphocytes and expressed on greater than 95% of all B-cell non Hodgkin's lymphomas. It induces cell death via apoptosis induction, complement dependent cytotoxicity and antibody dependent cellular cytotoxicity.

In September 2008, the Scottish Medicines Consortium (SMC) accepted for restricted use, rituximab in combination with chemotherapy for the treatment of previously untreated patients with stage III to IV follicular lymphoma. The marketing authorisation has recently been extended to support the use of rituximab as maintenance therapy for patients with follicular lymphoma following induction therapy. In this submission the company has requested that SMC consider the use of rituximab maintenance in the narrower population of follicular lymphoma patients who have responded to induction specifically with rituximab plus chemotherapy.

The evidence is based on one pivotal, phase lll, randomised, open-label study in 1,193 patients with previously untreated follicular lymphoma and high tumour burden. The study was in two treatment phases, an induction phase followed by a maintenance phase. All patients received standard induction treatment with rituximab plus either: cyclophosphamide, vincristine and prednisone (R-CVP), cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) or fludarabine, cyclophosphamide and mitoxantrone (R-FCM). Patients who achieved a complete response (CR), or CR unconfirmed (CRu), or partial response (PR), after induction treatment were randomised to rituximab maintenance (375mg/m^2 every 8 weeks after the last induction treatment for up to 12 doses, n=505) or observation but no treatment (n=513) for two years or until disease progression. Randomisation was stratified according to induction regimen (R-CHOP, R-CVP, or R-FCM), centre, region and response to induction treatment (CR/CRu or PR).

The primary outcome was progression free survival (PFS) in the maintenance phase, defined as the time from randomisation to this phase, to the date of first documented disease progression,

relapse, or death from any cause (i.e. a progression event) in the maintenance intention to treat (MITT) population. A two-sided stratified log-rank test was used to test the difference between groups and a Cox regression to adjust for prognostic factors. Secondary outcomes included quality of life (QoL) and overall survival (OS), measured from the date of randomisation to the maintenance phase, to the date of death regardless of cause. The first pre-specified interim analysis was planned after 258 progression events had taken place.

At the first pre-specified interim analysis, median follow up was 25 months and 174 (34%) patients in the observation group and 93 (18%) patients in the rituximab maintenance group had experienced a progression event. Rituximab treatment significantly reduced the risk of a progression event compared with observation (stratified Hazard Ratio [HR] 0.50, 95% CI; 0.39 to 0.64). Kaplan–Meier estimates for median PFS times could not be calculated, however, the 25th percentile assessed PFS was 507 days in the observation group and 1,096 days in the rituximab group with one year PFS rates of 82% versus 89% for observation and rituximab groups, respectively. PFS rates at two years, the end of the maintenance phase, were 66% (95% CI; 0.62 to 0.71) in the observation group and 82% (95% CI; 0.79 to 0.86) in the rituximab group.

In a later analysis at median follow up of 36 months, 221(43%) patients in the observation group and 135 (27%) patients in the rituximab group had experienced a progression event. Median PFS in the observation group was 1,472 days and was not estimable in the rituximab group, giving a stratified HR of 0.55, 95% CI:0.44 to 0.68.

At the first pre-specified interim analysis (median follow-up 25 months), 34 patients had died: 18 patients in the observation group (3.5%) and 16 patients in the rituximab group (3.2%), stratified HR 0.89, 95% CI;0.45 to 1.74). At 36 months follow up a further 12 patients in the observation group and 10 patients in the rituximab group had died, stratified HR 0.87, 95% CI;0.51 to 1.47.

QoL was measured using the EORTC QLQ-C30 and the Functional Assessment of Cancer Therapy–General (FACT-G) patient-reported questionnaires. No difference in quality of life was demonstrated between the groups using either measure.

Summary of evidence on comparative safety

No new safety concerns were reported. Overall, rituximab maintenance therapy was well tolerated.

The difference in the incidence of adverse events, 37% in the observation group and 52% in the rituximab group, was mainly due to infections and infestations (22% of observation patients and 37% of rituximab patients).

Summary of clinical effectiveness issues

In the pivotal study rituximab significantly increased PFS following a response to induction therapy in patients with previously untreated follicular lymphoma compared with observation alone. No benefit in overall survival was established at a median follow up of 36 months. Much longer follow up is required to assess the benefit in overall survival conferred by rituximab and

this low number of deaths reported is not unexpected as the median survival for patients with follicular lymphoma is >10 years. Second line treatments used on disease progression following rituximab maintenance treatment may also have affected overall survival outcomes. The number of patients treated with rituximab on progression was 84% in the observation group and 35% in the rituximab maintenance group. There is no information on comparative overall survival outcomes in these two patient groups.

The median age for diagnosis of follicular lymphoma is 60 to 65 years. The mean age of the patients randomised to the maintenance phase of the study was 56 years and around a third of the patients entering the induction phase were less than 50 years of age. The majority of patients recruited to the study had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1. This is a younger and fitter population than might be expected to be eligible for treatment in Scotland. Pre-specified subgroup analysis in the study, conducted in patients ≥60 years and in patients <60 years, showed no significant difference in the primary outcome although there was a more favourable HR in the patients <60. The updated SPC notes that exploratory analyses of the benefit of maintenance treatment showed a less pronounced effect in elderly patients (>70 years of age), however sample sizes were small.

Clinical experts in Scotland have suggested that the predominant rituximab induction therapy in Scotland is R-CVP, although R-CHOP is also used. In the pivotal study, 75% of patients received R-CHOP as induction therapy and 22% R-CVP.

The study protocol specified an interim analysis once 258 events had been reported. At this cut off, less than a fifth of patients on rituximab maintenance therapy had progressed, therefore the 25% percentile was estimated from a Kaplan Meier extrapolation and the median times to progression in both groups were not able to be estimated. Such early analysis, in a disease with a long survival, risks an optimistic estimate of effect.

Details of a systematic review/meta-analysis of studies of rituximab maintenance compared with observation were presented and these analyses support the increase in PFS demonstrated in the pivotal study.

Summary of comparative health economic evidence

The manufacturer presented a lifetime cost-utility Markov model. This compared rituximab maintenance therapy with observation during maintenance, which was appropriate. Progression-free survival during maintenance was estimated from the pivotal trial and extrapolated using a Gompertz survival function but with hazard rates being equalised between the two arms from month 72.

When disease progressed during maintenance, second-line chemotherapy was assumed to be prescribed. The likelihood of achieving a response from 2nd line chemotherapies and re-entering progression free survival was estimated from another rituximab trial comparing R-CHOP with CHOP 2nd line chemotherapies. The likelihood of receiving R-CHOP or CHOP was differentiated by treatment arm because patients progressing from maintenance within one year of having received rituximab were ineligible for R-CHOP; however patients who received rituximab maintenance and did not progress within a year were eligible for R-CHOP. This led to 88.1% receiving the more effective R-CHOP 2nd line in the rituximab maintenance arm as

compared to 80.7% in the observation maintenance arm. Effectiveness of second-line chemotherapy did not depend on previous treatment.

Utility values were taken from an unpublished survey commissioned by the manufacturer. Quality of life in progression-free survival during maintenance was valued around 10% higher at 0.88 than the quality of life for those in progression free survival subsequent to 2nd line chemotherapies at 0.79.

Costs were estimated assuming a common surveillance schedule for both maintenance arms, but rituximab administrations would each require an extra day case visit plus some pharmacy preparation costs. The average number of doses of 10.52 for rituximab maintenance (over 2 years) was drawn from the pivotal trial.

The base case estimated a gain of around 1.5 years in progression-free survival during maintenance and around 1.3 years overall survival. This translated into a gain of 1.17 quality adjusted life years (QALYs) at a cost of £18,861 to yield an incremental cost effectiveness ratio of £15,978 per QALY.

A sensitivity analysis equalising hazard rates for progression during maintenance from month 47 worsened the cost effectiveness estimate to £21,151 per QALY. A further sensitivity analysis, applying more pessimistic utility values of 0.79 for progression free during maintenance and 0.77 for progression free subsequent to 2nd line therapy, worsened the cost effectiveness to £18,102 per QALY. A range of additional sensitivity analyses around the effectiveness assumed for 2nd line treatments suggested that differentiating the rates of these between arms was not a model driver.

The main weaknesses of the analysis were:

- the calculation of the average 10.52 rituximab administrations including 4% of patients who had yet to complete rituximab maintenance therapy;
- no attempt was made to map from QLQ-C30 in the PRIMA and EORTC trials to EQ-5D data which might provide a cohesive data set and resolve many of the uncertainties around quality of life values; in addition, the literature review on quality of life methods dfailed to identify a potential mapping function which could have been used;
- adverse events did not impact on quality of life.

In spite of these weaknesses and in the light of the sensitivity analyses, the manufacturer presented a sufficiently robust case to gain acceptance by the SMC.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: comparators

Rituximab given as a second line treatment in patients who have progressed after a response to induction therapy with rituximab in combination with chemotherapy would be an appropriate alternative treatment strategy.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Rituximab	**375mg/m^2 body surface area once every 2 months**	**7,334**

Doses are for general comparison and do not imply therapeutic equivalence. Doses were based on a BSA of 1.8m^2, the use of full vials and six rituximab maintenance treatments in one year. Costs from eVadis on 8 November 2010.

Additional information: budget impact

Based upon an eligible annual incidence of around 150 patients and a market share of 20% in the first year rising to 90% in the fifth year, the manufacturer estimated a gross drug and administration cost of £330k in year 1 rising to £2.1m by year 5. SMC experts have indicated that uptake is likely to be higher than is estimated by the manufacturer in the initial years of introduction however the overall net budget impact may be lower as the prescribing costs for rituximab may be shifted from use later in the treatment pathway as occurs at present.

References

The undernoted references were supplied with the submission.

Rituximab for the first-line treatment of stage lll-IV follicular lymphoma (Review of TA110) National Institute of Health and Clinical Excellence (2008) TA138

Clinical Study Report. A multicentre, phase lll, open-label, randomised study in patients with advanced follicular lymphoma evaluating the benefit of maintenance therapy with rituxumab after induction of response with chemotherapy plus rituxumab in comparison with no maintenance therapy, March 2010.

Salles GA et al Rituximab maintenance for 2 years in patients with untreated high tumour burden follicular lymphoma after response to immunochemotherapy. J Clin Oncol 2010; 28(15_suppl): Abstract 8004

This assessment is based on data submitted by the applicant company up to and including 10 December 2010.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.