HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

27 January 2010

MABTHERA 100 mg, concentrate for solution for infusion
B/2 (CIP: 560 600-3)
MABTHERA 500 mg, concentrate for solution for infusion
B/1 (CIP: 560 602-6)

Applicant: ROCHE

rituximab

List I
Medicine for hospital prescription only. Prescription restricted to oncology or haematology specialists or doctors with cancer training, as well as rheumatology or internal medicine specialists. Medicinal product requiring special supervision during treatment.
Initial administration must be carried out in a hospital environment.

Date of marketing authorisation (centralised European procedure) and modifications: 2 June 1998 - 21 March 2002 - 2 August 2004 - 6 July 2006 - 18/01/2008

Reason for request: inclusion on the list of medicines approved for hospital use in the extension of indication “for first-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy".

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
rituximab

1.2. Originality
Rituximab is a genetically engineered chimeric mouse/human monoclonal anti-CD20 antibody.

1.3. Indications

"Non-Hodgkin's lymphomas (NHL)
MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

MabThera maintenance therapy is indicated for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera.

MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia
MabThera in combination with chemotherapy is indicated for the first-line treatment of patients with chronic lymphocytic leukaemia.

Rheumatoid polyarthritis
MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid polyarthritis who have had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARD), including one or more tumour necrosis factor (TNF) inhibitortherapies."

1.4. Dosage

"Chronic lymphocytic leukaemia
Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for all CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/l it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with MabThera to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.
The recommended dosage of MabThera in combination with chemotherapy is 375 mg/m^2 body surface area administered on day 0 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after MabThera infusion."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XC	Monoclonal antibodies
L01XC02	rituximab

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

- FLUDARA (fludarabine)
- ENDOXAN (cyclophosphamide);
- CHLORAMINOPHENE (chlorambucil)
- MABCAMPATH (alemtuzumab) only for patients for whom polychemotherapy involving fludarabine is not appropriate;

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CVP (cyclophosphamide, vincristine, prednisone) polychemotherapy regimens, etc.

3. ANALYSIS OF AVAILABLE DATA

The dossier submitted includes four phase II studies and one phase III comparative study (ML17102). Only the phase III study is analysed below.

3.1. Efficacy

Phase III randomised open-label study (ML17102) comparing MABTHERA in combination with an FC (fludarabine plus cyclophosphamide) chemotherapy protocol versus an FC protocol alone in 817 patients with previously untreated chronic lymphocytic leukaemia.

The study treatments:
- FC protocol (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, days 1 to 3) every 4 weeks, for a total of 6 cycles.
- MABTHERA in combination with FC chemotherapy (R-FC) was administered at a dose of 375 mg/m^2 in the first cycle, the day before chemotherapy, then at a dose of 500 mg/m^2 on the first day of subsequent cycles.

The primary efficacy endpoint was progression-free survival, defined as the time between randomisation and the date of the first documented disease progression , relapse, or death by any cause, whichever came first.

The secondary endpoints were:
- overall survival, defined as the time between randomisation and the date of death due to any cause;
- event-free survival, defined as the time between randomisation and the date of disease progression , relapse, administration of a new CLL treatment, or death by any cause;
- the overall response rate: patients were defined as responders if they have a complete response or a nodular partial response or a confirmed partial response (according to the NCI-WG CLL criteria adopted in 1996). Patients without response assessment (for whatever reason) were considered as non-responders;
- the duration of response, defined as the time between the first confirmed and documented response (complete response, nodular partial response, partial response) and the disease progression or death by any cause;
- disease-free survival, defined as the time between the first documentation of the confirmed complete response and documentation of relapse or death by any cause;
- time until use of an alternative treatment, defined as the time between the randomisation and the date of starting a new CLL treatment ;
- safety

Results:
The intention-to-treat population included 810 patients, as seven patients were excluded from analysis because no signed consent was available.
The average age of the patients was 59.5 years (median 61 years), with 70% of the patients aged <65, 23% between 65 and 70, and 7% over 70.
Sixty-four percent of patients were in Binet stage B and 31% in stage C. N.B.: 5% of patients in Binet stage A, initially included in the study, were excluded after the first amendment of the protocol.

The efficacy data presented are based on an intermediate analysis scheduled in the protocol after median follow-up of 20.7 months. This analysis showed a significant difference in respect of the primary efficacy endpoint, which led to the study being terminated. A second analysis was carried out after 4.7 months additional follow-up, i.e. a median follow-up of 25.4 months. This focused on the primary efficacy endpoint and overall survival.

The estimated median progression-free survival (primary efficacy endpoint)[1] was 39.8 months in the R-FC group vs. 32.2 months in the FC group, i.e. an absolute gain of 7.6 months (HR = 0.56 [95% CI: 0.43; 0.72]; p < 0.0001).
The analysis carried out at 25.4 months confirmed the advantage in respect of the primary efficacy endpoint observed during the first analysis (42.8 months in the R-FC group vs. 32.5 months, i.e. an absolute gain of 10.3 months).

Secondary endpoint results:
- overall survival
The median overall survival figure had not been reached in either group at the time of the principal analysis.
A total of 81 deaths were recorded: 48 patients (11.8%) in the FC group and 33 patients (8.2%) in the R-FC group (HR = 0.64 [95% CI: 0.41; 1.00]; p = 0.0487).
The analysis with 4.7 months of additional follow-up did not reveal any difference between the two groups in terms of overall survival.

- event-free survival
The median event-free survival time was 39.8 months in the R-FC group as against 31.1 months in the FC arm, i.e. an absolute gain of 8.7 months in favour of the R-FC treatment (HR = 0.55 [95% CI: 0.43; 0.70]; p < 0.0001).

- overall response rate and duration of response
The overall response rate (complete response + partial response) was 86.1% in the R-FC group vs. 72.7% in the FC group (p < 0.0001).
The complete response rate was 36.0% in the R-FC group vs. 17.2% in the FC group (p < 0.0001).
Molecular remission[2] was analysed only for a small proportion of responders: 37% in the FC group (110/296) and 21% in the R-FC group (74/347). This does not allow any conclusions to be drawn as to residual disease.
The median response time was 40.2 months in the R-FC group vs. 34.7 months in the FC group (p = 0.004).

- disease-free survival
There was no difference between the two groups in terms of disease-free survival: few events (relapse or death) occurred among patients who had a complete response: 12.4% in the R-FC group vs. 12.1% in the FC group).

- time until use of an alternative treatment
In the R-FC group 10.9% of patients and in the FC group 14.5% of patients were prescribed another treatment for their CLL. (HR = 0.65 [95% CI: 0.47; 0.90]; p = 0.0082).
The median time until use of an alternative treatment was not reached in both group.

1 The result available is derived from an estimate based on the Kaplan-Meier curve rather than on an observation
2 Molecular remission corresponds to an absence of signs of residual disease. It can be measured by flow cytometry in particular

Sub-group analysis:
Efficacy was analysed in terms of progression-free survival and overall survival according to age, Binet stage, patient characteristics on inclusion (ECOG score, date of diagnosis, B symptoms), cytogenetic abnormalities and ZAP-70, CD38 + and IgVH mutation status.
MABTHERA was observed to produce a clinical advantage in terms of progression-free survival in most of the sub-groups analysed, except for patients aged over 70 at inclusion in the study and for patients diagnosed between six and 12 months prior to inclusion in the study.
In the sub-groups analysed according to Binet stage, the addition of MABTHERA to FC chemotherapy versus FC alone improved progression-free survival in stage B but not in stage C:

- patients in Binet stage B (n=516): HR = 0.45 [95% CI: 0.32; 0.63]; p = 0.0001
- patients in Binet stage C (n=251): HR = 0.88 [95% CI: 0.58; 1.33]; p = 0.5406.

A reduction in the risk of death in favour of R-FC was observed in most of the sub-groups analysed, except for the 56 to 64 age group and patients in Binet stage C.

The committee notes that the average age of patients was 59.5, with 23% between 65 and 70 and only 7% over 70. The average age of patients with CLL in France in 2000 was 69, and 37% of new cases were diagnosed in patients aged over 75[3].

3.2. Adverse events

The proportions of patients who stopped treatment because of adverse events of any degree of severity were similar in each group (18% in both groups).
The following adverse events frequently led to suspension of treatment:
- haematological complications (12% in the R-FC group and 10% in the FC group) such as neutropenia (4% in the R-FC group and 2% in the FC group), thrombocytopenia (2% in the R-FC group and 3% in the FC group), leucopoenia (2% in the R-FC group and less than 1% in the FC group);
- infections (2% in both groups), such as pneumonia (less than 1% in the R-FC group and 1% in the FC group);
- general disorders and pain at the injection site (1% in both groups).

3.3. Conclusion

The efficacy and safety of MABTHERA in combination with an FC protocol (fludarabine plus cyclophosphamide) as first-line treatment for CLL have been assessed in an open-label randomised phase III study versus FC alone, in which 817 patients took part. The average age on diagnosis of the included patients was lower than that of patients suffering from CLL in France (59.5 versus 69).
After a 20.7 month monitoring period, the estimated median progression-free survival (primary efficacy endpoint) was 39.8 months in the R-FC group vs. 32.2 months in the FC group, i.e. an absolute gain of 7.6 months (HR = 0.56 [95% CI: 0.43; 0.72]; p < 0.0001).
The analysis carried out at 25.4 months confirmed this advantage in respect of the median progression-free survival (42.8 months in the R-FC group vs. 32.5 months, i.e. an absolute gain of 10.3 months).
The complete response rate was 36.0% in the R-FC group vs. 17.2% in the FC group (p < 0.0001).
Molecular remission was analysed only for a small proportion of responders: 37% in the FC group (110/296) and 21% in the R-FC group (74/347). This does not allow any conclusions to be drawn as to residual disease.
There was no difference between the two groups in terms of disease-free survival: few events (relapse or death) occurred among patients who had a complete response: 12.4% in the R-FC group vs. 12.1% in the FC group.

[3] Troussard et coll. Incidence et survie des hémopathies malignes : données générales et situation chez les plus de 75 ans, France, 1989-1997. Bulletin épidémiologique hebdomadaire BEH thématique 9-10, 13 March 2007, 76-79

The median overall survival was not achieved in both groups at the time of the principal analysis. A total of 81 deaths were recorded: 48 patients (11.8%) in the FC group and 33 patients (8.2%) in the R-FC group (HR = 0.64 [95% CI: 0.41; 1.00]; p = 0.0487). However, the analysis carried out after 4.7 months additional monitoring (i.e. a total duration of 25.4 months) showed no difference between the two groups in terms of overall survival.
In the sub-groups analysed according to Binet stage, the addition of MABTHERA to FC chemotherapy versus FC alone improved progression-free survival in stage B but not in stage C.
There is no quality of life data.

The proportions of patients stopping treatment because of adverse events of any degree of severity were similar in each group (18% in both groups), and were mostly due to haematological toxicity.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Chronic lymphocytic leukaemia (Binet stages B and C) is a life-threatening condition;
This medicine is intended for use as part of curative therapy;
The efficacy/adverse effects ratio in this indication is high;
It is a first-line treatment;
There are medicinal and non-medicinal alternatives (graft of haematopoietic stem cells);

Public health benefit:

Chronic lymphocytic leukaemia (CLL) constitutes a moderate public health burden. Improving its therapeutic management is a public health need falling within the scope of the fight against cancer.

The data from the pivotal study indicates that the expected impact on CLL-associated morbidity and mortality of adding MABTHERA to chemotherapy comprising fludarabine and cyclophosphamide can be regarded as moderate. The length of time that patients were monitored during this trial, which is relatively short in the light of the slow progression of this disease, does not allow the long-term effect of MABTHERA on morbidity and mortality to be assessed. Furthermore, there is no data allowing evaluation of the impact of MABTHERA on the quality of life of patients undergoing treatment.

Consequently, MABTHERA is expected to have a low public health benefit.

The actual benefit is substantial.

4.2. Improvement in actual benefit (IAB)

MABTHERA in combination with chemotherapy involving fludarabine plus cyclophosphamide offers a minor IAB (level IV) in terms of efficacy compared to that chemotherapy alone in the first-line treatment of chronic lymphocytic leukaemia.

4.3. Therapeutic use

The decision as to whether to treat the patient (or wait) depends first on the patient's general condition (age and comorbidities), then on the stage of the disease and presence of factors pointing to a poor prognosis (time for doubling of peripheral lymphocytes less than 12 months, elevated β2-μglobulin, p53 mutation, etc.). The most common cases of the disease, i.e. Binet stage A or Rai stages 0, I and II, are asymptomatic and do not justify any specific treatment.

First-line treatment of CLL involves:

- alkylating agents: chlorambucil either alone or in combination with corticosteroids, cyclophosphamide
- purine analogues, particularly fludarabine phosphate (alone or in combination), which can be used as a first-line or second-line treatment. A recent study showed that treatment with fludarabine alone did not offer any additional advantage in terms of overall survival compared with chlorambucil monotherapy in patients over 65[4].
- COP or CVP (cyclophosphamide, vincristine, prednisone) and CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) combination regimens
- monoclonal antibodies (such as MabCampath in third-line treatment).

[4] Eichhorst BF, Busch R, Stilgenbauer S, Stauch M, Bergmann MA, Ritgen M, Kranzhöfer N, Rohrberg R, Söling U, Burkhard O, Westermann A, Goede V, Schweighofer CD, Fischer K, Fink AM, Wendtner CM, Brittinger G, Döhner H, Emmerich B, Hallek M; German CLL Study Group (GCLLSG). First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood. 2009 ;114(16):3382-91.

Stem cell autograft is a treatment option especially for young patients. It requires stem cells to be collected from patients in complete remission.
The 2008 ESMO guidelines recommended fludarabine + cyclophosphamide (FC) as the first-line treatment for patients in good general health (with few comorbidities). The updated version of these guidelines, issued in 2009,[5] (and those of the SFH[6]) suggest adding rituximab in the context of an R- FC regimen.
MABTHERA in combination with FC chemotherapy therefore constitutes a new first-line approach to the management of patients suffering from chronic lymphocytic leukaemia.

4.4. Target population

The target population for MABTHERA in this extension of indication comprises patients suffering from Binet stage B or C CLL undergoing first-line treatment.
The incidence of CLL in 2005[7] in France was estimated at 3,224.
Stages B and C account for almost 45% of cases[8].
Consequently, the target population for MABTHERA in this extension of indication is estimated at 1,450 patients a year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in this extension of indication.

[5] Eichhorst B, Hallek M, Dreyling M: Chronic lymphocytic leukemia : ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology, 20, May 2009
[6] Société Française d'Hématologie [French Society of Haematology]
[7] Presentation of the most recent data on cancer incidence and mortality in France and the trends over the past 25 years (1980-2005) - Press conference held on 21 February 2008. INVS/Hôpitaux de Lyon/FRANCIM/INCA
[8] Binet J.L et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981; 48:198-206.