Translated from *Rev Prescrire* May 2007; **27** (283): 337

rituximab

New Indication

Lymphoma maintenance therapy: inadequate follow-up

● **Favourable short-term results need longer-term confirmation in terms of effects on survival; they also need to be weighed against the risk of serious adverse effects (infections, cardiac and gastrointestinal disorders).**

Follicular lymphoma is the most frequent form of non Hodgkin's lymphoma (1). It is a slow-growing form of lymphoma and is therefore described as non-aggressive. Without treatment, median survival time is 8 to 10 years. In patients at advanced stage, initial treatment with rituximab (Mabthera°, Roche in the European Union) plus the CHOP chemotherapy regimen (cyclophosphamide + doxorubicin + vincristine + prednisone) or the mini-CHOP regimen (reduced-dose doxorubicin) increases recurrence-free survival time but has not been shown to improve overall survival (2).

Insufficient follow-up to evaluate overall survival. The evidence for the effectiveness of rituximab maintenance therapy is mainly based on one unblinded trial involving 465 patients with relapsed or refractory lymphoma after one or two cycles of treatment without rituximab (**a**)(3,4).

Patients were randomised to CHOP or CHOP plus rituximab regimens, for six treatment cycles at three-week intervals. Then "responders" (two-thirds of patients in both groups) were again randomised to simple monitoring without treatment or to rituximab infusions every 3 months.

Two years after the second randomisation, the median progression-free survival time was 42.2 months with rituximab versus 14.3 months without treatment (p<0.0001) (3). This survival advantage was not influenced by the initial chemotherapy regimen (i.e. CHOP alone or CHOP + rituximab) (3). However, not all lymphoma progression was symptomatic.

The overall survival rate estimated three years after the second randomisation was 85.1% with rituximab versus 77.1% without treatment (p=0.011) (4). However, the median overall survival time had not been reached in either group, and there were few deaths (4 with rituximab, 3 without treatment (3).

Serious risks. In addition to reactions occurring during infusions, severe adverse events occurred in 37% of patients treated with rituximab compared to 23% of untreated patients, including infections (9% versus 2.4%) and cardiac disorders (3% versus <1%) (3,4). Intestinal occlusion and gastrointestinal perforation occurred in a few patients, some of whom died (this issue page 201).

Reactivation or exacerbation of viral infections is another potential risk. Cases of fulminant hepatitis B have been reported, as well as two deaths from progressive multifocal leukoencephalitis associated with JC virus, a polyomavirus that is present in the latent state in more than 80% of adults (2,5).

In practice. The French Committee that assesses the therapeutic value of new drugs concluded that rituximab maintenance therapy offers major advantages compared to existing options for lymphoma maintenance therapy (6).

Nevertheless, these lymphomas progress slowly, and available short-term results, although encouraging, are insufficient to judge the impact of rituximab on overall survival. In addition, rituximab maintenance therapy exposes patients to serious adverse effects, including infections and cardiac and gastrointestinal disorders. Pending more convincing evidence of benefit, rituximab should only be used with care in follicular lymphoma.

rituximab
(Mabthera°)

Solution for intravenous infusion (after dilution)

- **100 mg** of rituximab (10 mg/ml) per vial
- **500 mg** of rituximab (10 mg/ml) per vial

■ **New indication:** *"Maintenance therapy (…) for patients with relapsed/refractory follicular lymphoma responding to induction therapy".*
[EU marketing authorisation, centralised procedure]

Cytotoxic agent; monoclonal antibodies

a- The results of the PRIMA trial of rituximab maintenance therapy after first-line chemotherapy should be available in 2009 (ref 3).

Selected references from Prescrire's literature search.

In response to our request for information, Roche only provided us with published documents.

1- Prescrire Rédaction "Les lymphomes non hodgkiniens. La malignité varie beaucoup selon les cas" *Rev Prescrire* 2003; **23** (237): 209-214.
2- Prescrire Rédaction "rituximab-Mabthera°. Lymphome folliculaire en première ligne: prolonge le délai avant rechute" *Rev Prescrire* 2006; **26** (272): 332.
3- European Medicines Agency - CHMP "European Public Assessment Report (EPAR) (rev. 10) - Scientific discussion - Mabthera": 15 pages; posted on the EMEA website on 6 November 2006.
4- van Oers MHJ et al. "Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial" *Blood* 2006; **108** (10): 3295-3301.
5- U.S. Food and Drug Administration - Center for Drug Evaluation and Research "Information for healthcare professionals. Rituximab (marketed as Rituxan)" December 2006: 3 pages.
6- Haute autorité de santé - Commission de la transparence "Avis de la Commission-Mabthera" 8 November 2006: 8 pages.