# Factors predictive for response of follicular and mantle cell lymphoma to rituximab

Michael Pfreundschuh*

A recent analysis of prognostic factors may help identify which follicular and mantle cell lymphoma patients should be excluded from trials of single-agent rituximab therapy.

The major merit of a recent study of Ghielmini et al. (see opposite) is that it provides the first evaluation of prognostic factors emerging after rituximab monotherapy. Moreover, it is reassuring that, while prolonged rituximab therapy results in sustained immune suppression, it does not cause an increased rate of infections. There are, however, considerable problems with the interpretation of the study. The study population included both untreated and pretreated patients, and the current analysis of predictive factors combined the results from two subtrials in follicular lymphoma (FL) and mantle cell lymphoma (MCL).[1,2] Quite importantly, it is unclear how many patients who really needed therapy were included in the trial.

The results of the univariate analysis of prognostic factors must be interpreted with caution. With 33 factors included in the analysis and with no adjustment made for multiple testing, some factors might have emerged as having prognostic value merely by chance. These shortcomings might also explain some puzzling results. For example, histology (follicular vs mantle cell) did not emerge as a factor prognostic for event-free survival (EFS). Similarly, it is unclear why a lower baseline lymphocyte count predicted good response, but a higher lymphocyte count after induction therapy was associated with a better EFS. Whether this result is due to the smaller number of patients included in the EFS analysis, or the different processes used for patient selection, remains open to speculation.

For patients with indolent lymphoma, for whom an aggressive treatment would not be suitable, single-agent rituximab might be a valid option. This study shows that rituximab might be particularly worthwhile in patients with a low tumour load and normal blood counts; however, it is exactly this patient population that might as well be followed using a 'wait-and-watch therapy'. Indeed, studies comparing the single-agent rituximab and watch-and-wait treatment strategies in this favourable subpopulation of patients are ongoing. The prediction score suggested by Ghielmini et al. might be useful for identifying patients who should not be treated with single-agent rituximab, but it does not provide information on how to treat symptom-free patients who have low tumour burden.

While the results obtained with prolonged treatment with rituximab are regarded by the authors as promising, the interpretation of the clinical relevance of the study is difficult. Early treatment with single-agent rituximab aims to delay the time until chemotherapy is required, and possibly to lengthen overall survival time; however, it is unclear whether either of these goals can be achieved by prolonged rituximab treatment. Most importantly, from a clinical point of view, both the previous[1,2] and current paper on the two subtrials suffer from a relatively short observation time and a lack of data reported regarding overall survival.

*Michael Pfreundschuh is Professor of Internal Medicine at Saarland University Medical School, Homburg, Germany. *Competing interests*: Pfreundschuh is a member of the advisory board for Mabthera (Roche). This article was first published in *Nature Clinical Practice Oncology* 2006 vol. 3 no. 4, and is reproduced with permission. www.nature.com/clinicalpractice doi:10.1038/ncponc0457, 

In conclusion, while adding rituximab to conventional chemotherapy resulted in a significant increase in remission rates, remission duration and, in some trials,[3,4] lengthened overall survival, the value of single-agent rituximab with respect to these endpoints remains to be determined. Currently, the most urgent clinical dilemmas relating to FL are whether we can prolong survival further, and whether we can do so by earlier or more aggressive treatment, or both? Unfortunately, none of these issues are answered by this paper.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld

# Synopsis

*M Ghielmini, K Rufibach, G Salles, et al. (2005)* **Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK).** *Ann Oncol* 16:1675–1682

**Background.** Follicular lymphoma (FL) and mantle cell lymphoma (MCL) are generally considered incurable, so treatment is aimed at improving symptoms in most cases. Single-agent rituximab is an option in this setting, because it causes little toxicity and with prolonged treatment produces remissions in some patients. Factors predictive of response of FL and MCL to single-agent rituximab are ill-defined.

**Objective.** To identify characteristics potentially associated with event-free survival (EFS), response and toxicity of therapy among patients receiving single-agent rituximab for FL or MCL.

**Design and intervention.** This randomised trial used data from two subtrials, one for FL patients and one for MCL. Between January 1998 and January 2002, 29 institutions enrolled adult patients for induction therapy with rituximab for 4 weeks (375 mg/m$^2$ weekly). Patients who had partial or complete response or stable disease at week 12 were randomised to no further treatment (standard treatment) or treatment with infusions of rituximab (375 mg/m$^2$) at week 12 and months 5, 7 and 9 (prolonged treatment).

**Outcome measures.** Factors predictive of response rate and EFS were identified using preliminary univariate analyses (logistic regression for response and Cox regression for EFS), followed by a stepwise regression and multivariate analysis without adjustment for multiple testing. A scoring system to predict benefit of therapy was constructed and tested.

**Results.** At a median follow-up of 4.5 years, patients who received maintenance rituximab therapy had a significantly longer EFS than those who received no further treatment (17.9 months vs 11.2 months; $P$=0.005). Independent predictive factors for response were disease bulk <5 cm, follicular histology, normal haemoglobin and low lymphocyte count. Factors predicting prolonged EFS were response to induction therapy, a maximum of one previous cycle of chemotherapy, Ann Arbor stage* I–III, high lymphocyte count, disease bulk <5 cm, Fcγ receptor genotype VV and prolonged rituximab treatment. Using a prediction score constructed on the basis of MCL histology, bulky disease, previous chemotherapy and low haemoglobin, patients could be divided into groups expected to experience high, intermediate and low benefit of therapy, according to the number of predictive factors they presented with (0–1, 2–3 and 4–5, respectively). Median levels of circulating B lymphocytes were reduced to 20% of baseline during treatment ($P$<0.0001), but their numbers partially recovered after a median of 12 and 18 months following standard and prolonged treatment, respectively. More prolonged suppression of serum IgM occurred with extended as opposed to standard rituximab treatment. Incidences of adverse effects were similar in the two arms of the study. Serious adverse events considered to be related to rituximab included 13 infections, six cardiac events and five intestinal complications. There were seven deaths due to adverse events, consisting of four cardiac, two infectious and one intestinal event.

**Conclusions.** Clinical baseline characteristics that predicted response to single-agent rituximab therapy in FL and MCL were defined.

*Acknowledgement:* The synopsis was written by Michael Pfreundschuh, Professor of Internal Medicine at Saarland University Medical School, Homburg, Germany

** Classification of lymphoma into four stages based on the involvement of anatomic groups of lymph nodes; stage I indicates localised nodal involvement and stage IV indicates disseminated disease*