Original article

Annals of Oncology 16: 1675–1682, 2005
doi:10.1093/annonc/mdi320
Published online 19 July 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)

M. Ghielmini[1]*, K. Rufibach[1], G. Salles[3], L. Leoncini-Franscini[1], C. Léger-Falandry[3], S. Cogliatti[1], M. Fey[1], G. Martinelli[2], R. Stahel[1], A. Lohri[1], N. Ketterer[1], M. Wernli[1], T. Cerny[1] & S.-F. Hsu Schmitz[1]

[1]*Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland;* [2]*Istituto Europeo di Oncologia, Milano, Italy;* [3]*Centre Hospitalier Lyon-Sud, Lyon, France*

Received 9 June 2005; accepted 10 June 2005

Background: Predictive factors of rituximab efficacy and its effect on the immune system are still not defined.

Patients and methods: Three hundred and six patients with follicular or mantle cell lymphoma received four weekly doses of rituximab (induction) and no further treatment (arm A) or four more doses at 2-month intervals (arm B).

Results: Response rate to induction was 44%. Independent predictive factors for response were disease bulk <5 cm, follicular histology, normal hemoglobin and low lymphocyte count. Factors associated with event-free survival (EFS) were having responded to induction, having received not more than one line of therapy, Ann Arbor stage I–III, high lymphocyte count, disease bulk <5 cm, Fc-gamma receptor genotype VV and receiving prolonged treatment. B cells were suppressed by treatment but recovered after a median of 12 months in arm A and 18 months in arm B. The median IgM level after 1 year was normal in arm A but was decreased to 73% of baseline in arm B. We observed 24 serious adverse events, equally distributed between arms. Ten patients receiving induction only and six patients receiving prolonged treatment developed a second tumor.

Conclusions: We defined the characteristics predicting response and EFS to rituximab. Prolonged treatment results in longer EFS at the cost of a longer reduction in B cell and IgM levels, but without additional clinical toxicity.

Key words: rituximab, predictive factors, toxicity, Fc-γ receptor, follicular lymphoma, mantle cell lymphoma

Introduction

Follicular (FL) and mantle cell lymphomas (MCL) are usually considered incurable diseases. Even though aggressive interventions such as autologous or allogeneic transplantation may prolong survival or eventually cure some patients [1, 2], in the majority of cases treatment is aimed at relieving or preventing symptoms [3, 4]. Many treatment options are now available, ranging from relatively simple and well tolerated single agent regimens to complex and possibly toxic combination chemo(immuno)therapies. In this mainly palliative setting, many physicians believe that the optimal treatment is one producing the least side-effects while obtaining a long time without symptoms of disease.

Single agent rituximab is one of these options, having been shown to cause little toxicity and to obtain, given at a prolonged schedule and in some patient subsets, remissions that are comparable to what is obtained with multi-agent regimens [5, 6]. However, many are still reluctant in applying single-agent immunotherapy, fearing an insufficient activity compared with other more traditional schemes.

The efficacy of antibody treatment was shown to differ among lymphoma subtypes, but the reason why some histologies respond better than others has not been clarified. Due to the different mechanisms of action of monoclonal antibodies, it is possible that some mechanisms are more effective against some tumor types than against others, but it could as well be that certain histologies are more associated with biological or clinical characteristics of the patient that influence treatment

Correspondence to: Dr M. Ghielmini, Oncology Institute of Southern Switzerland, Ospedale San Giovanni 6500 Bellinzona.
Tel: +41-91-811-79-15; Fax +41-91-811-79-16;
E-mail: mghielmini@ticino.com

response. Furthermore, a prospective and prolonged observation of relevant clinical and immunological side-effects in a large cohort of patients treated with the single agent has not been reported.

We therefore analyzed an important number of characteristics of 306 patients with FL or MCL and of their disease that could predict benefit from treatment with single-agent rituximab, based on data of the SAKK trial 35/98. We also describe the observed short and long-term major side-effects. This exploratory analysis intended to identify potential factors that are associated with response, event-free survival (EFS) and toxicity.

Patients and methods

Trial design

This trial consisted of two subtrials: one for FL and one for MCL patients. The trial treatment and assessment schedule were identical in both subtrials. Patients were enrolled from January 1998 to January 2002 in 29 institutions. The trial was approved by the local ethics committee of each participating institution and conducted in accordance with the Declaration of Helsinki and currently applicable amendments. All patients gave written informed consent.

Patients were initially treated with rituximab 375 mg/m^2 per week for 4 weeks ('induction' phase). Patients with stable disease or in partial or complete response at week 12 (from treatment start) were randomized in a 1:1 ratio into two groups: no further treatment (arm A, 'standard treatment') or treatment with a single infusion of rituximab 375 mg/m^2 at week 12, and again at months 5, 7 and 9 (arm B, 'prolonged treatment'). The randomization was stratified according to status of disease at trial entry (first presentation versus refractory or relapsed), response to induction treatment (stable disease versus response) and center. Patients were centrally randomized by the minimization method via fax at the SAKK Coordinating Center in Bern. Upon disease progression or relapse, further treatment was at the treating physician's discretion.

EFS time was the primary end point and calculated as the time from first induction infusion to progression, relapse, second tumor or death from any cause. For the randomized phase of the two subtrials, a group sequential design with two interim analyses and one final analysis was adopted. Both subtrials reached the final stage.

Patients

Inclusion criteria were a biopsy-proven follicular or mantle cell lymphoma, age ≥18 years and measurable disease defined as the presence of at least one previously unirradiated lesion with two measurable perpendicular diameters of which at least one should be of 2 cm. The interval between the last systemic anticancer treatment and trial entry should not be less than 28 days. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and, after observing unexpected cardiac events in the first 10 months of the trial [7], a cardiac ejection fraction (EF) ≥50% by echocardiography. Exclusion criteria included symptomatic central nervous system (CNS) disease, a history of significant medical conditions, including previous malignancies within 5 years, a reduced renal function (creatinine >2× the upper limit of normal [ULN]) or liver function (bilirubin >2× ULN). Pregnant or lactating females, patients with active opportunistic infections or patients with known HIV, hepatitis B or C infections were also excluded. Previous treatment with rituximab was not allowed. A central histology review was performed for all cases before randomization.

Trial assessments

The detailed examinations required by the trials are described elsewhere [5, 6]. Briefly, patients underwent a complete staging at trial entry, which was repeated at 12 weeks, and at 7, 12, 18 and 24 months, then yearly or when clinically required. Re-evaluation of the bone marrow (BM) was required only at week 12 and month 12 if involved at trial entry. Routine blood counts and chemistries were assessed at baseline, before each rituximab administration and at months 2, 3, 5, 7, 9 and 12. Serum immunoglobulins (IgG, IgA, IgM) were measured at baseline and again at months 3, 7 and 12, while blood samples for immunophenotyping were taken at baseline, week 12 and months 9, 12, 18 and 24. Analysis of lymphocyte subsets was performed as described before [5].

Statistical methods

To identify factors predictive of response to rituximab induction and EFS, we first performed preliminary univariate analyses (logistic regression for response and Cox regression for EFS) on the factors listed in Table 1. For EFS (only randomized patients were considered), further models including an additional covariate for treatment arm, with or without treatment-factor interaction, were also explored as suggested in [8]. We then selected among the factors and interactions via a stepwise procedure with entry criterion P value = 0.1 and stay criterion P value = 0.05. Finally we refit the models using data from all patients seen with non-missing values for the selected variables. Due to correlations between some variables (e.g. disease bulk at baseline and disease bulk at randomization) and numerous missing values, some factors were excluded prior to the selection procedure in order to increase model stability. The pre and post differences of lymphocyte subset counts were analyzed by the Wilcoxon signed rank test. The between-arm differences of immunoglobulin levels were compared by the Wilcoxon rank sum test. No adjustment for multiple testing was performed, therefore the reported P values should be interpreted with caution.

Prediction score

To construct a prediction score that could help clinicians select the right candidates for single-agent rituximab, we randomly selected 206 ('training set') out of the pooled cohort of 306 patients and repeated the above model-building procedure to select predictive baseline clinical characteristics. The selected significant variables were then used to construct a score classifying the patients into groups with different expected benefits from rituximab treatment. The reproducibility of such a score and grouping was validated using the data of the remaining 100 patients of the trial ('validation set').

Results

Patient characteristics

The main characteristics of the 306 patients enrolled and of their disease are summarized in Table 1. Thirty-two patients were retrospectively judged ineligible: 27 because the pathology review could not confirm the follicular or the mantle cell histology and five because the disease was not measurable according to protocol criteria. One patient was not evaluable because he died before the trial treatment could be initiated.

Of the 273 eligible and evaluable patients, 61 were not randomized to the second phase of the study because of disease progression or major toxicity during the induction phase.

Table 1. Main characteristics of eligible and evaluable patients and *P* values from preliminary univariate regression analyses

		N	%	Effect on response *P* value[b]	Effect on EFS *P* value[b,c]
Age	<59/≥59	140/133	51/49		
Sex	M/F	135/138	49/51	0.008	
Performance status	0/1/2	187/69/17	69/25/6		
B-symptoms	No/yes	186/83	69/31	0.03	0.02
Hemoglobin	Grade 0/grade >0	188/85	69/31	0.0001	0.01
Platelets	Grade 0/grade >0	236/36	87/13	0.03	0.002
WBC	Grade 0/grade >0	224/49	82/18		
ANC	≤3.7/>3.7	135/136	50/50		
Neutrophiles	Grade 0/grade >0	235/36	87/13		
Lymphocytes	Grade 0+1/grade >1	97/174	36/64	0.01	
B lymphocytes	≤96.7/>96.7 10^6/l	84/107	44/56		
T lymphocytes	≤675/>675 10^6/l	89/103	46/54		
T-helper	≤353/>353 10^6/l	88/103	46/54		0.03
T-suppressor	≤236/>236 10^6/l	92/100	48/52		
Natural killer	≤154/>154 10^6/l	88/104	46/54	0.03	
Monocytes	≤0.4/>0.4 10^9/l	130/139	48/52		
LDH	≤1× ULN/>1× ULN	168/100	63/37		
IgG	≤8.4/>8.4 mg/ml	110/105	51/49		
IgA	≤1.2/>1.2 mg/ml	106/109	49/51		
IgM	≤0.6/>0.6 mg/ml	117/99	54/46		
Ann Arbor stage	I–III/IV	107/164	39/61		0.0002
Disease bulk	<5/≥5 cm	130/143	48/52	0.0002	0.001
BM involvement	No/yes	101/156	39/61	0.04	0.01
Histology	FL/MCL	185/88	68/32	< 0.0001	0.0002
Growth pattern	Other/diffuse	219/31	88/12	0.03	0.04
CD 43	Negative/positive	157/76	67/33	0.0008	
MIB-1	<30%/≥30%	140/111	56/44		
Previous chemotherapy	No/yes	91/182	33/66	0.05	0.002
No. of previous chemotherapies	≤1/≥2	151/122	55/45	0.05	0.002
No. of previous chemo cycles	≤10/>11	87/90	49/51		
Previous radiotherapy	No/yes	228/45	84/16		0.04
Best previous response	CR/PR/SD+PD	74/91/20	40/49/11		
Fc-γ receptor genotype	FF/FV/VV	85/105/32	38/47/14		FV: 0.60 VV: 0.005
Characteristics at randomization (N = 212)					
Performance status	0/1	161/51	76/24		
Hemoglobin grade	0/grade >0	161/51	76/24		0.003
Platelets grade	0/grade >0	188/23	89/11		
WBC grade	0/grade >0	171/41	81/19		
ANC	≤3.7/>3.7	107/104	51/49		
Lymphocytes grade	0+1/grade>1	73/138	35/65		0.002
Monocytes	≤0.4/>0.4 10^9/l	109/100	52/48		
LDH	≤1×ULN/>1× ULN	150/61	71/29		
IgG	≤8.4/>8.4 mg/ml	83/87	49/51		
IgA	≤1.2/>1.2 mg/ml	76/94	45/55		

Table 1. (*Continued*)

		N	%	Effect on response *P* value[b]	Effect on EFS *P* value[b,c]
IgM	≤0.6/>0.6 mg/ml	85/86	50/50		
Disease bulk	<5/≥5 cm	110/102	52/48		<0.0001
BM involvement	No/yes	88/113	44/56		0.004
Histology	FL/MCL	151/61	71/29		0.002
Response to induction rituximab	No/yes	92/120	43/57		<0.0001

[a]All continuous variables were dichotomized at their median values among all patients.
[b]Only *P* values ≤0.05 are reported.
[c]The *P* values for EFS came from Cox regression model including a covariate for treatment arm, with or without a further covariate for interaction.

Predictive factors for response

The response rate to rituximab induction in the 273 eligible and evaluable cases was 44% (38% partial response and 6% complete response). Among 33 factors assessed, 15 were found potentially predictive for response (Table 1). The favorable factors finally selected by the stepwise procedure were disease bulk <5 cm, follicular histology, normal hemoglobin and low blood lymphocyte count (CTC toxicity grade >1), all determined at treatment start (Table 2).

Table 2. Independent predictive factors for response to induction treatment selected by a stepwise procedure (n = 271)

Factor		*P* value	Odds ratio	Confidence interval
Histology	FL/MCL	0.003	2.4	(1.4–4.4)
Hemoglobin	Grade 0/grade >0	0.003	2.4	(1.3–4.4)
Lymphocytes	Grade >1/0+1	0.02	2.0	(1.1–3.5)
Disease bulk	<5/≥5 cm	0.0006	2.5	(1.5–4.3)

Factors associated with event free survival

At a median follow-up of 4.5 years, the EFS for the 212 randomized patients was 11.2 months in arm A and 17.9 months in arm B (P = 0.005) (Figure 1). The preliminary univariate analyses showed that 14 baseline characteristics and five characteristics at randomization have a potentially significant impact on EFS (Table 1). Favorable factors finally selected by the stepwise procedure, after taking treatment arm into account, were: having responded to rituximab induction, Ann Arbor stage I–III, having received not more than one previous line of therapy, disease bulk <5 cm and high blood lymphocyte count (CTC toxicity grade ≤1) at randomization (Table 3; the final model was based on 197 patients). None of the lymphocyte subtypes alone was found to be responsible for this latter effect. Repeating the model selection procedure in patients whose Fc-γ receptor genotype was known revealed that Fc-γ receptor with a VV genotype is an additional independent favorable factor for EFS (Table 4; the model was based on 171 patients). Figure 2 suggests that the effect is possibly only present in FL patients. However, a histology–genotype interaction was not selected by the stepwise procedure, although a log-rank *P* value of 0.004 was observed in a comparison between different genotypes in FL patients (in MCL: P = 0.2).

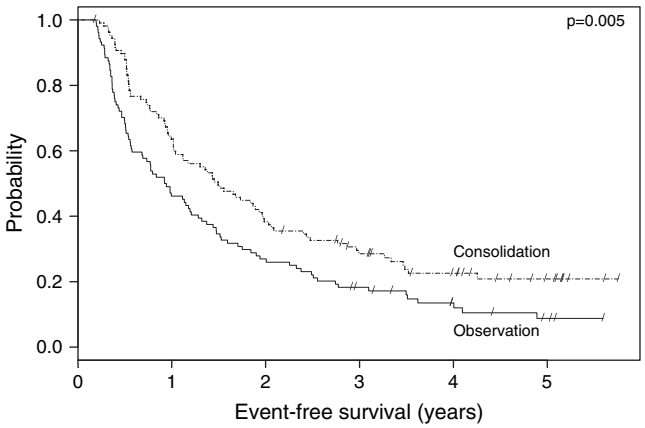

Figure 1. EFS of 212 patients with FL or MCL randomized to receive rituximab at the standard (arm A) or the prolonged schedule (arm B). The prolonged schedule yields significantly longer EFS.

Prediction score for EFS after rituximab

The unfavorable baseline clinical characteristics selected by a stepwise procedure in the training set of 206 patients were: MCL histology, stage IV, bulky disease, previous chemotherapy and low hemoglobin (CTC toxicity grade >0). The prediction score was then constructed as the number of unfavorable characteristics present within each patient, with the score ranging from 0 to 5. The EFS curves stratified by prediction score for patients in the training set were very similar to those for patients in the validation set (Figure 3). The similarity suggested validity of the score. As suggested by the EFS curves, patients could be classified into three groups: high-benefit group with score 0–1, intermediate-benefit group with score 2–3 and low-benefit group with score 4–5. By applying such grouping to the whole population of 212 randomized patients, the median EFS in arm A was 19.8 months in the high-benefit group, 11.0 months in the intermediate-benefit group and 5.1 months in the

Table 3. Independent predictive factors for EFS selected by a stepwise procedure (n = 197)

Factor		P value	Hazard ratio	Confidence interval
Response at week 12	CR+PR/SD+PD	<0.0001	0.4	0.3–0.5
No. of previous chemo regimens	≤1/≥2	0.01	0.7	0.5–0.9
Ann Arbor stage	I–III/IV	<0.0001	0.4	0.3–0.6
Lymphocytes at randomization	Grade 0+1/>1	0.02	0.6	0.4–0.9
Disease bulk at baseline	<5/≥5 cm	0.05	0.7	0.5–1.0
Treatment	Consolidation/ observation	0.0004	0.6	0.4–0.8

Table 4. Independent predictive factors for EFS when including Fc-γ receptor genotype selected by a stepwise procedure (n = 171)

Factor		P value	Hazard ratio	Confidence interval
Response at week 12	CR+PR/SD+PD	<0.0001	0.4	0.3–0.5
No. of previous chemo regimens	≤1/≥2	0.01	0.6	0.4–0.9
Ann Arbor stage	I–III/IV	0.0001	0.5	0.4–0.7
Treatment	Consolidation/ observation	0.0012	0.6	0.4–0.8
Fc-γ receptor genotype	VV/not VV	0.01	0.5	0.3–0.9

low-benefit groups. For arm B the corresponding median values were 42.3, 17.2 and 7.3 months (Figure 4). The benefit of prolonged rituximab treatment seems to be noticeable only in patients with fewer unfavorable characteristics.

Effects on the immune system

Data on lymphocyte subsets at baseline are available on 129 of 212 randomized patients, and on fewer cases at later time points during the study. The baseline levels of T-helper, T-suppressor, NK and B lymphocytes were lower than the normal ranges in almost half of the patients. T-helper, T-suppressor and NK cells remained stable all along the study in both arms, while circulating B cells showed a reduction to median level 20% of baseline after 8–12 weeks from treatment start (P <0.0001). After 1 year, the tendency of B-cell recovery was seen in arm A (median level 81% of baseline, n = 22) but not in arm B (median level 50% of baseline, n = 35); this latter group took 6 months longer to recover to baseline values (Figure 5).

Data on immunoglobulin levels at baseline are available on 90 of 212 randomized patients, and the number of available observations decreased as the follow-up proceeded. Because immunoglobulins were measured locally in each institution, with different methods and normal values, the variation in their levels was evaluated as a ratio to the baseline value. IgG and IgA remained stable in both arms during treatment, while the IgM levels evolved with a different pattern in the two treatment arms: after 1 year the median IgM level had decreased to 73% of baseline in arm B (n = 50) whereas in arm A the median level had recovered to 100% (n = 30, P = 0.007) (Figure 5).

Infections and second tumors

In the 306 patients treated, serious adverse events possibly or probably related to rituximab treatment were 13 infections, six cardiac events and five intestinal complications, resulting in seven deaths (four cardiac, two infectious, one intestinal). Further 11 serious adverse events were all non-fatal and of various nature (infusion reaction, cytopenias, renal, neurologic, metabolic). The incidence of these reactions was similar in arms A and B.

Of the 306 patients treated, 47 developed an infection: 27 during the induction phase and 20 during the post-randomization phase (eight in arm A and 12 in arm B). Of these 20 infections seven were severe (life-threatening or requiring hospitalization): two in arm A (pneumonia and candida stomatitis) and five in arm B (two pneumonia, one viral hepatitis, one cholecystitis and one severe paradontosis). The recovery of B cells and IgM tended to be slower in patients who experienced an infection compared with patients without infections (difference not significant).

There were 16 cases of second tumor (five MDS/AML and 11 solid tumours): 10/202 in patients receiving induction only, 6 of 104 in patients receiving prolonged treatment.

Discussion

This is the largest study on clinical and biological predictive factors for activity of single-agent rituximab. Besides being based on a large patient set, the analyzed factors include not only the classical clinical patient characteristics, but also an important number of pathology data, baseline and after-treatment lymphocyte subsets, Fc-γ receptor genotype and prospectively collected data on toxicity with a long follow-up.

Some of our predictive factors are common predictive factors in all cancer patients undergoing chemotherapy: parameters associated with the amount of disease (stage and disease bulk), with the impact of the disease on patient homeostasis (hemoglobin level) or with the extent of previous treatment (number of previous therapy regimens). The lower chance of response in MCL patients compared with FL patients also reflects what is known for chemotherapy in general, and the observation that responders do better than non-responders is common as well.

Compared with other studies of single-agent rituximab, including enough cases to allow a multivariate analysis, we confirm the favorable role of FL histology for response as in the study by McLaughlin [9]. Parameters describing previous treatment history or disease extension were also found to have predictive influence by others, although the significant descriptive parameters were not the same as in our analysis [9, 10].

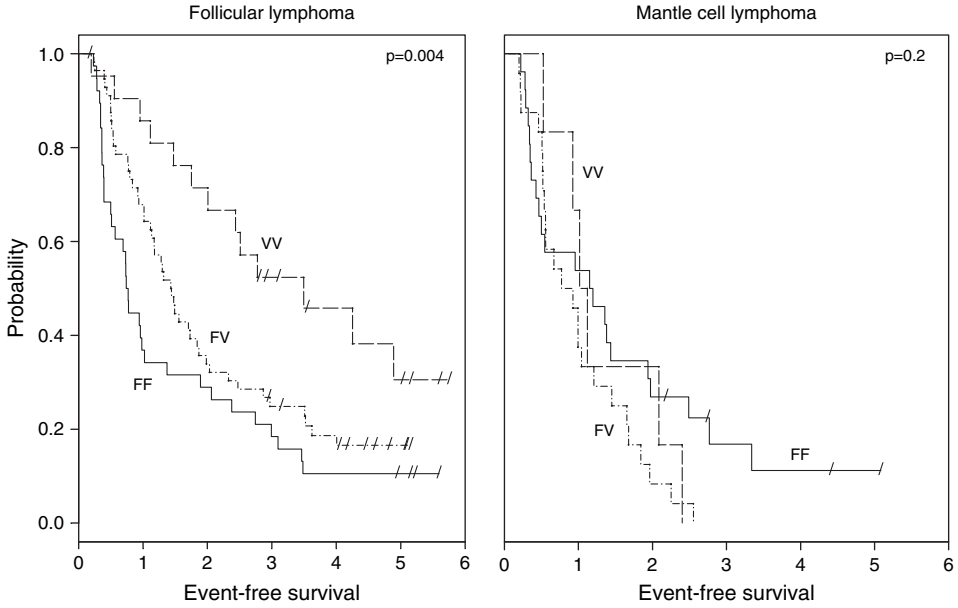

Figure 2. Effect of patient's Fc-γ III receptor genotype on EFS. A VV genotype seems to be favorable in FL patients, but irrelevant in MCL patients.

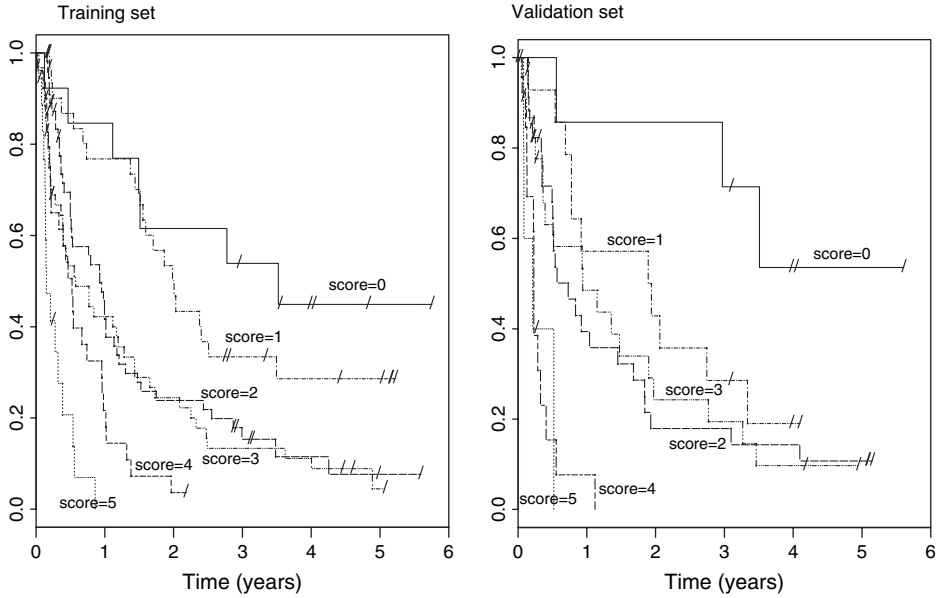

Figure 3. EFS stratified by prediction score, in the randomly selected 'training' and 'validation' sets of patients. The score is given for each patient as the number of present unfavorable characteristics among: MCL histology, stage IV, bulky disease, previous chemotherapy or hemoglobin level lower than normal.

Other results from our study are more puzzling. First, it seems surprising that factors influencing response and factors affecting EFS are not the same. For instance, lymphomas with follicular histology have a higher chance of responding to rituximab, but histology was not included in the selected multivariate model for EFS. Possible explanations are: (1) different patient sets—more patients were included for response analyses than for EFS analyses (limited to randomized patients who did not progress under induction treatment); (2) confounding effect—since histology plays an important role on response to induction treatment, its impact on EFS might be partially confounded by the effect of response to induction treatment that was selected in the multivariate EFS model; (3) selection procedure—applying different selection procedures might result in different models, hence the models presented in this report should not be considered as 100% definitive. Overall, the fact that histology was not selected in the EFS model does not mean that it does not exert influence on EFS. One piece of evidence is that histology was selected in the prediction score model in which non-randomized patients were also included.

On the other hand, patient's genotype for the Fc-γ III receptor influences EFS (only in FL) but not the chance of responding.

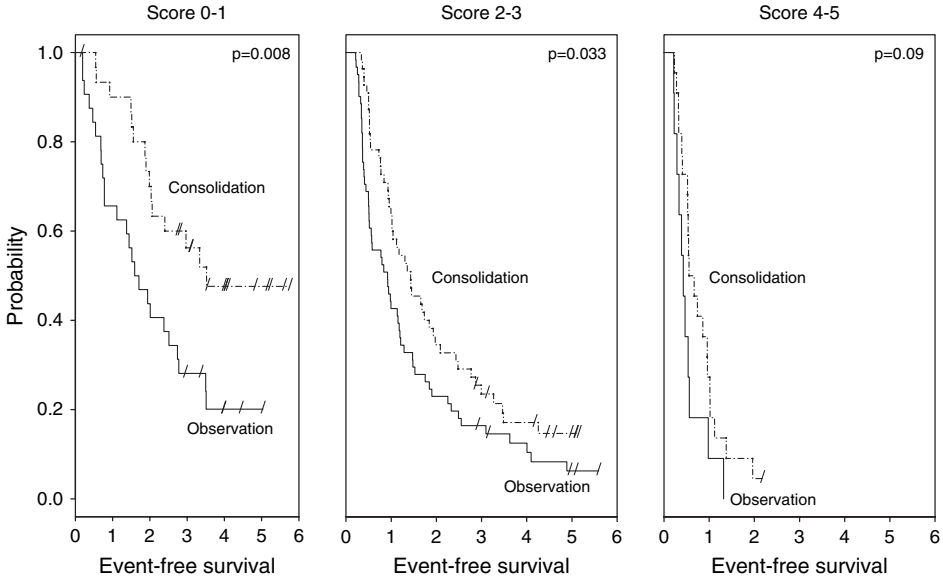

Figure 4. EFS stratified by treatment, separately for each benefit group derived from prediction score. Prolonged treatment with rituximab appears more effective in patients presenting with a lower number of adverse factors.

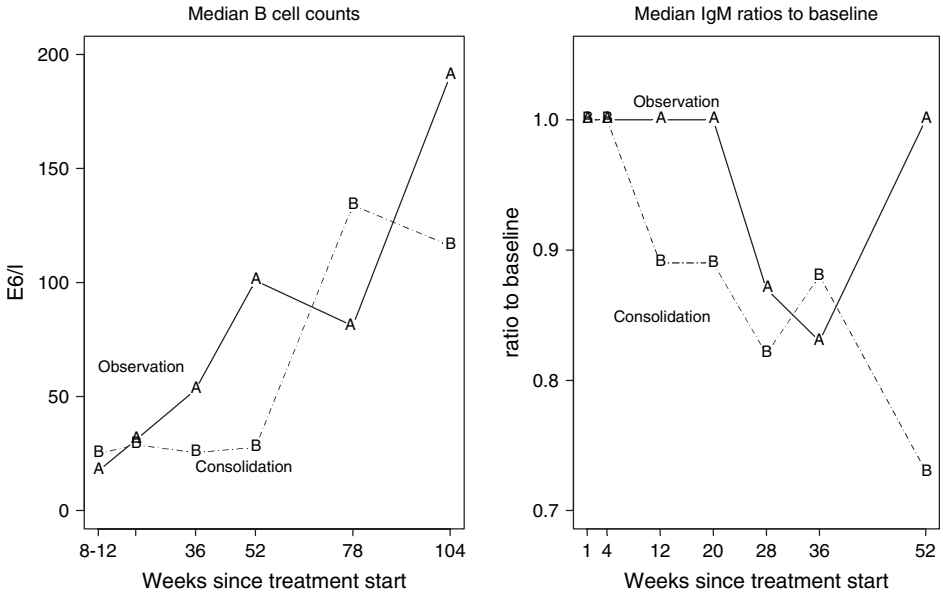

Figure 5. Effect of rituximab on the immune system. Patients treated with the prolonged schedule experienced a longer B-cell depletion and a longer IgM reduction.

Finally, a lower baseline lymphocyte count predicts response, but a higher lymphocyte count after induction is associated with better EFS. Analogy to the three explanations above could also be applied here. In addition, a tentative biological explanation for these apparent contradictions could be that of the several mechanisms of action of rituximab, one (activation of the complement) is predominant during the induction phase and another one (the more lymphocyte- and Fc-γ dependent ADCC [antibody dependent cell cytotoxicity]) is more active during the observation/prolonged phase. If this was true, the failure of prolonged rituximab to extend EFS in MCL [6] could be attributed to the lack of Fc-γ mediated ADCC, as our data suggests that Fc-γ genotype is not a predictive factor in MCL. The observation that the effect of rituximab is Fc-γ dependent in some lymphomas (as FL or lymphoplasmocytic) and not in others (as MCL or chronic lymphocitic leukemia, CLL) was made by other authors as well [11–13].

Our data also exhibited a relatively long immunosuppression caused by the prolonged schedule of rituximab, but not associated with an increase of clinically relevant immunosuppression-associated pathologies as infections or second tumors.

In conclusion, for patients with follicular lymphoma and not suitable for an aggressive treatment, single-agent rituximab is confirmed to be a valid option, particularly if patients present

with a low tumor load and normal blood counts. In these cases prolonged treatment results in significantly longer EFS. Some of these patients may, in some centres, be managed by a watch and wait policy, and studies are ongoing comparing these two strategies in this favorable population.

Even though the extended schedule causes a more prolonged reduction of B cell and IgM levels, no additional toxicity is seen. Because the response rate to rituximab is not dependent on the presence of lymphocytes and on Fc-γ receptor genotype, while on the other hand EFS is dependent on them, we raise the hypothesis that the mechanism of action of rituximab may differ during treatment: cytotoxic cell-*in*dependent during the early phase and cytotoxic cell-dependent during the later phase.

References

1. Tse WW, Lazarus HM, Van Besien K. Stem cell transplantation in follicular lymphoma: progress at last? Bone Marrow Transplant 2004; 34: 929–938.
2. Fisher RI. Mantle cell lymphoma: at last, some hope for successful innovative treatment strategies. J Clin Oncol 2005; 23: 657–658.
3. Horning DJ. Follicular lymphoma: have we made any progress? Ann Oncol 2000; 11 (Suppl 1): S23–S27.
4. Bertoni F, Zucca E, Cavalli F. Mantle cell lymphoma. Curr Opin Hematol 2004; 11: 411–418.
5. Ghielmini M, Hsu Schmitz SF, Cogliatti S et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly ×4 schedule. Blood 2004; 103: 4416–4423.
6. Ghielmini M, Hsu Schmitz SF, Cogliatti SB et al. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). J Clin Oncol 2005; 23: 705–711.
7. Ghielmini M, Hsu Schmitz SF, Bürki K et al. The effect of rituximab on patients with follicular and mantle-cell lymphoma. Ann Oncol 2000; 11 (Suppl 1): S123–S126.
8. Klein JP, Moeschberger ML. *Survival Analysis*. New York: Springer 2003.
9. McLaughlin P, Grillo-Lopez AJ, White CA et al. Prognostic factors for non-Hodgkin's lymphoma patients treated with chemotherapy may not predict response duration in patients treated with immunotherapy; rituximab experience. Proc AACR 1999; 40: 718 (4746).
10. Foran JM, Cunningham D, Coiffier B et al. Treatment of mantle-cell lymphoma with rituximab (chimeric monoclonal anti-CD20 antibody): analysis of factors associated with response. Ann Oncol 2000; 11 (Suppl 1): S117–S121.
11. Treon SP, Hansen M, Branagan AR et al. Polymorphism in FcγRIIIA (CD16) receptor expression are associated with clinical response to rituximab in Waldenström's macroglobulinemia. J Clin Oncol 2005; 23: 474–481.
12. Farag SS, Flinn IW, Modali R et al. FcγRIIIa and FcγRIIA polymorphism do not predict response to rituximab in B-cell chronic lymphocitic leukemia. Blood 2004; 103: 1472–1474.
13. Cartron G, Dacheux L, Salles G et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor Fc-gamma RIIIa gene. Blood 2002; 99: 754–758.