Rituximab serum concentrations during immuno-chemotherapy of follicular lymphoma correlate with patient gender, bone marrow infiltration and clinical response

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ABSTRACT

Background

Treatment of follicular lymphoma with rituximab is currently recommended at a dose of 375 mg/m^2. We aimed to provide a rationale for optimal dosing and scheduling of this anti-CD20 antibody based on pharmacokinetics.

Design and Methods

Clinical efficacy of immuno-chemotherapy with rituximab, fludarabine and mitoxantrone followed by 2-monthly rituximab maintenance was evaluated in 29 patients with previously untreated follicular lymphoma in a prospective phase II trial (AGMT-NHL9). Pharmacokinetic analysis was assessed in 17 patients.

Results

Induction treatment resulted in high clinical response rates (complete remission 66%; ORR 100%). Significantly higher complete remission rates were observed in female patients (86 *vs.* 47%; Odds Ratio 6.8, 95% CI: 1.12; 41.82; P=0.05). Rituximab pharmacokinetic analysis showed a high variability ranging over almost 1 order of magnitude at maintenance cycle 1 (area under the curve 1,540-12,025 g/L*days). Median area under the curve was lower in men (81%) and in patients with initial bone marrow infiltration (76%). Higher rituximab serum concentrations before next therapy (C_{trough}) were associated with female sex (P=0.04) as well as with absence of initial bone marrow infiltration (P=0.001). C_{trough} correlated with remission quality (complete *vs.* partial remission; P=0.005) and progression-free survival (P=0.03). A decline in rituximab C_{trough} below 25,000 ng/mL was observed 9.5 to 62 months before clinical relapse (P=0.008).

Conclusions

The results of this pilot trial suggest that more differentiated dosing schedules based on gender and bone marrow infiltration should be explored for rituximab therapy for lymphoma. *This study was registered in ClinicalTrials.gov (Identifier: NCT01560117).*

Key words: follicular lymphoma, rituximab, gender, bone marrow infiltration, clinical response.

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The online version of this article has a Supplementary Appendix.

Introduction

Immunotherapy with the monoclonal anti-CD20 antibody rituximab has become standard of care for patients with follicular lymphoma.[1] However, questions still remain regarding dosing and scheduling of rituximab, optimal type of chemotherapeutic combination partners during induction, and the best interval and length of rituximab maintenance treatment.[2-4] Fludarabine-mitoxantrone combinations have shown strong debulking activity as initial therapy followed by rituximab maintenance.[5,6] While rituximab maintenance with a standard dose of 375 mg/m^2 prolongs clinical remissions, administration schedules still vary: 3-monthly infusions for two years and 2-monthly infusions for one or two years are those most frequently used.[4,7] Some pharmacokinetic data for rituximab have been reported for induction treatment.[8-13] These studies have proposed a presumptive 'active' level of 25,000 ng/mL in anti-lymphoma treatment. However, only limited information is available about maintenance treatment in patients who are in remission and have no remaining tumor burden.[14,15]

In order to optimize management of previously untreated follicular lymphoma (FL) with rituximab, in 2003, the AGMT initiated a phase II study (NHL9) with 3 major goals: i) to investigate the effect of treatment with R-FM and rituximab maintenance on the depth of remission measured by *BCL2/IgH* PCR;[16] ii) to obtain pharmacokinetic data during induction and 2-monthly rituximab maintenance treatment in order to provide a rationale for dosing and scheduling; iii) to link prognostic markers and remission quality with pharmacokinetic (PK) data.[17,18] The results indicate a high inter-individual variability of rituximab serum levels related to gender, initial bone marrow infiltration, as well as to quality and duration of clinical response, thereby challenging a simple, body surface area-based, dosing concept for CD20 antibody therapy.

Design and Methods

The AGMT NHL9 phase II study included 29 adult patients (median age 53 years, range 33-74; 15 male, 14 female) with previously untreated advanced follicular lymphoma grade 1 or 2. The clinical characteristics of the patients are shown in Table 1. Inclusion criteria were: a positive *BCL2/IgH* rearrangement in peripheral blood (PB) and/or bone marrow (BM); clinical stage III or IV, requiring treatment (*Online Supplementary Appendix*). Treatment consisted of 6 cycles of rituximab 375 mg/m^2 i.v. Day 1, mitoxantrone 10 mg/m^2 i.v. Day 1, and fludarabine 25 mg/m^2 i.v. Days 2-4 (rituximab, fludarabine and mitoxantrone (R-FM)). Cycles were repeated every 28 days. After an interval of 4-12 weeks after initiation of the 6th cycle of R-FM, 26 patients with a complete remission (CR), unconfirmed CR (Cru), or partial remission (PR) received maintenance treatment with rituximab 375 mg/m^2 every two months for two years or until relapse (*Online Supplementary Figure S1*). The protocol was approved by the local ethics committees and informed consent was obtained from all patients. Between December 2003 and December 2007, 29 patients were enrolled. All patients were evaluated for clinical response, 17 patients for pharmacokinetics (10 of these up to maintenance cycle 6). Twenty-three patients had at least one molecular follow up for *BCL-2/IgH* response in peripheral blood (PB) (n=21) or bone marrow (BM) (n=15) or both (n=13).

Clinical response evaluation

Clinical response was evaluated at the end of induction therapy with R-FM as well as during and after maintenance treatment using the standardized response criteria for NHL of 1999 (including CT scans).[19]

BCL-2/IgH polymerase chain reaction

PCR assessment for BCL2 major and minor breakpoints was performed with DNA from PB or BM MNC with an assay using BIOMED-2 primers and a sensitivity of at least 1 abnormal in 10^3 normal cells.[20]

Rituximab pharmacokinetics

Detailed PK analysis of serum samples was carried out in cycles 1 and 6 of induction as well as maintenance (before start of infusion, at the end of infusion, Days 2, 3, 4, 8, 15 and 22). Serum trough levels before start of infusion were determined in cycles 1, 2, 4 and 6 of induction as well as maintenance. The median interval between induction cycle 6 and maintenance cycle 1 was eight weeks (range 4-12 weeks); between maintenance 1 and 2: eight weeks (range 7-12 weeks); between maintenance 2 and 4: 15.5 weeks (range 8-36); between maintenance 4 and 6: 15 weeks (range 8-36).

Rituximab serum concentrations were determined by an enzyme-linked immunosorbent assay (QPS Netherlands BV, Groningen, The Netherlands) (*Online Supplementary Appendix*).

Pharmacokinetic data were calculated by Kinetika® software version 3.0 (Innaphase, USA).

Statistical analysis

Categorical variables were described by absolute and relative frequencies and compared between groups using χ^2 tests or Fisher's exact tests where appropriate. Reported *P* values are the results of two-sided tests. *P* values 0.05 or under were considered

Table 1. Patients' characteristics and clinical outcome.

	All patients N=29	Female N=14	Male N=15
Median age (years) (range)	53 (33-74)	49 (33-66)	54 (44-74)
Bone marrow infiltration	17 (59%)	9 (64%)	8 (53%)
Bulky disease	5 (17%)	1 (7%)	4 (26%)
FLIPI 0-1 (low risk)	12	7	5
FLIPI 2 (intermediate risk)	8	1	7
FLIPI 3-4 (high risk)	9	6	3
CR	19 (66%)	12 (86%)*	7 (47)*
PR	10 (34%)	2 (14%)*	8 (53%)*
Continuous remission CCR	22 (76%) 17 (59%)	10 (71%) 10 (71%)	12 (80%) 7 (47%)
Relapse	9 (31%)	4 (29%)	3 (20%)
Sequential BCL2/IgH asessed	23	12	11
BCL-2 conversion to negative (PB or BM)	21 (91%)	11 (92%)	9 (90%)
Median observation time in months; (range)	50 (5-68)	-	-
Progression-free survival at 36 months	82%	84%	80%
Overall survival at 36 months	89%	100%	80%
PK assessment	17	9	8

*P=0.05

statistically significant. Kaplan-Meier curves were calculated for survival estimates, and a log rank test was used to determine differences between groups. Statistical calculations were performed using WinSTAT software version 3.0 or Stata Statistical Software: Release 11.ed., 2009 (StataCorp LP., College Station, TX, USA).

Linear fit was performed for correlation of AUC and serum trough (C_{trough}) values.

Results

Clinical response

All 29 patients responded to induction therapy with R-FM with a CR rate of 66% (19 of 29) and a PR rate of 34% (10 of 29) (Table 1). Twenty-six patients received further maintenance therapy with rituximab with a final CR rate of 77% (20 of 26). Nine patients relapsed (2 before maintenance, 7 during or after maintenance). After a median observation time of 50 months, 4 patients have died. Progression-free survival at three years was 82% with an overall survival (OS) rate of 89% (*Online Supplementary Figure S2A and B*).

Interestingly, female patients had a significantly higher CR rate after induction (12 of 14 (86%) *vs.* 7 of 15 (47%); *P*=0.05; Odds Ratio 6.8, 95% CI: 1.12; 41.82). Despite a high CR rate, women had at least equal initial BM involvement (64 *vs.* 53%, *P*=N.S.) and FLIPI scores suggesting that female patients responded better to induction therapy (Table 1). Furthermore, female patients showed a slightly better PFS (85% *vs.* 80% at 36 months) and OS (100% *vs.* 80% at 36 months; *P*=0.058) that was statistically not significant (Table 1 and *Online Supplementary Figures S2C and D*).

The high clinical response rate after R-FM was accompanied by a complete molecular response (MR) rate of 91% (21 of 23).

Pharmacokinetics of rituximab

Detailed pharmacokinetic profiling

Detailed rituximab serum concentrations were assessed in cycles 1 and 6 of induction and maintenance treatment, respectively (n=16). A high inter-individual variability of total area under the curve (AUC_{total}) values ranging over almost 1 log at maintenance cycle 1 (1,540-12,025 g/L*days, median 5,736) was observed (Figure 1A and *Online Supplementary Table S1*). This was accompanied by a similar variation in half-life (median 23.3 days; range 5.9-54.7) (*Online Supplementary Table S1*). The striking difference in clinical response rates prompted us to perform

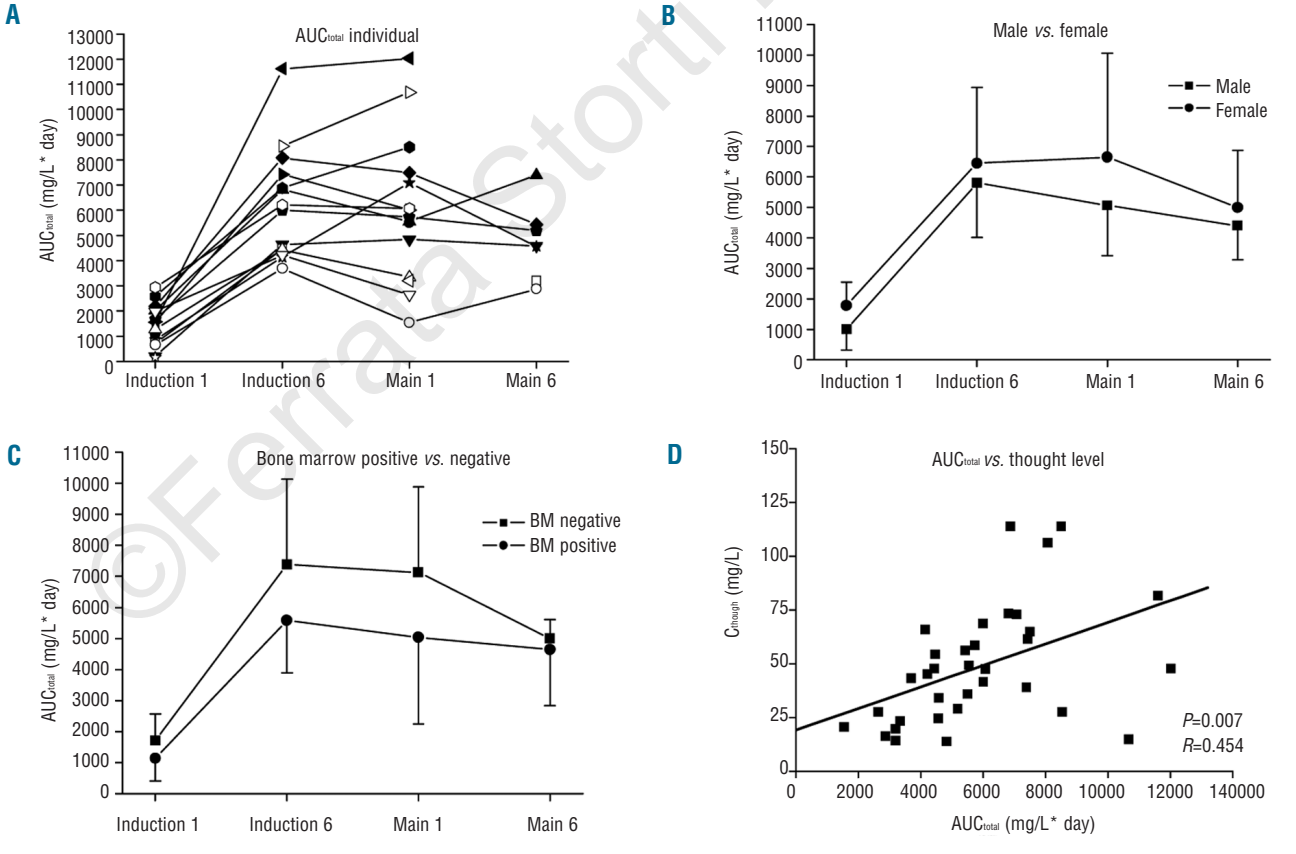

Figure 1. Detailed pharmacokinetic profiling during R-FM induction and rituximab maintenance. (A) Area under the curve (AUC_{total}) during induction cycles 1 and 6 as well as maintenance cycles 1 and 6 shows high inter-individual variability (n=16). (B) Female patients have higher median AUC_{total} throughout the study period (AUC_{total} men: 81% of that found in women). (C) Patients without bone marrow (BM) infiltration (BM negative) at diagnosis have higher median AUC_{total} (AUC_{total} in patients with BM infiltration: 76% of that found in BM negative patients). (D) Correlation between AUCtotal and serum trough levels (Ctrough) obtained before rituximab infusions.

subgroup analysis stratified by gender. Indeed, female patients had higher AUC_{total} throughout the treatment period. Overall, the median AUC_{total} in men was 81% of the values observed in women (Figure 1B and *Online Supplementary Table S1*). This finding was in agreement with the observed volume of distribution in women (induction 1: 5.2 L *vs.* 8.6 L; *Online Supplementary Table S1*). Similar findings were obtained for patients with or with-

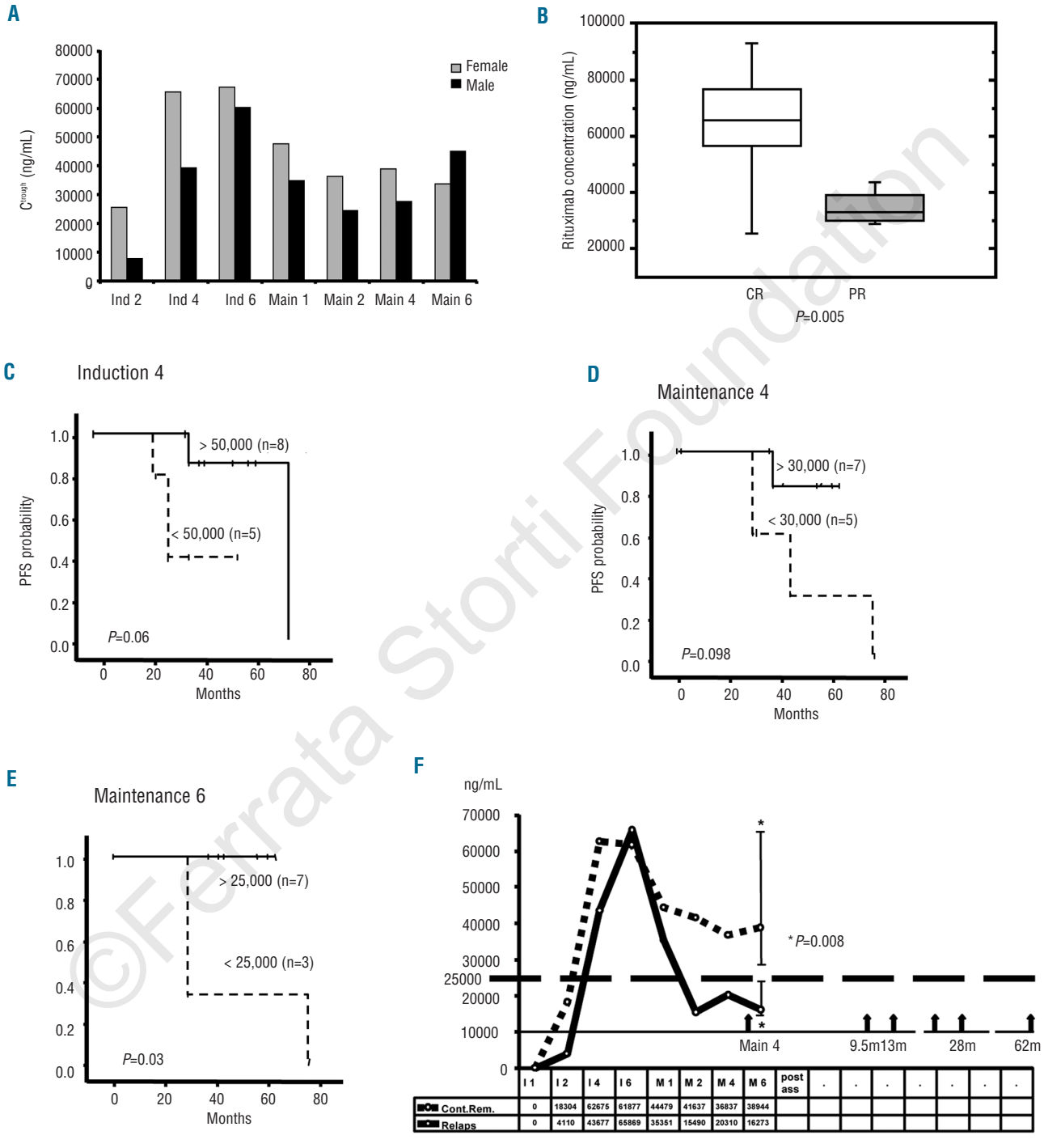

Figure 2. Association of rituximab trough levels with gender, quality of remission (complete (CR) *vs.* partial (PR)), progression-free survival (PFS) and clinical relapse. (A) Median C_{trough} in ng/mL are higher (median 29%, range 10-70%) in female patients at almost all time points during induction and maintenance treatment (for details see Table 2). (B) Higher rituximab C_{trough} correlate with CR rates at the end of R-FM induction. (C-E) Correlation of C_{trough} before induction 4, maintenance 4 and maintenance 6 with PFS. Rituximab cut-off levels are given in ng/m. (F) Median rituximab serum levels in patients with continuous CR or PR (dotted line) or clinical relapse. Clinical relapse (black arrows) is preceded by a significant decline in C_{trough} before maintenance 6 (last serum level assessment). Time of relapse is given in months after last C_{trough} assessment. Patients per time point: continuous remission 7-10, relapse 3-6. The presumptive active serum level of rituximab (25,000 ng/mL) is shown by an interrupted line.

out BM infiltration (median AUC_{total} in patients with BM infiltration was 76% of that found in patients with negative BM histology) (Figure 1C and *Online Supplementary Table S1*). While the differences in AUC_{total} between men and women, as well as between patients with or without BM infiltration, were not statistically significant, they may still be biologically important. No correlation was found between AUCtotal and age (cycle 1: R=0.34, P=0.76; cycle 6: R=0.34, P=0.57).

The correlation between AUC and serum trough levels (Ctrough) indicated that the latter could be used as surrogate for AUC_{total} in further analysis (R=0.454; P=0.007) (Figure 1D).

Association of serum trough levels (C_{trough}) with gender, initial bone marrow infiltration and clinical outcome

Serum levels before administration of rituximab were available during induction and at least once during maintenance therapy in 17 patients. Twelve of these 17 patients had a CR at the end of induction.

Median rituximab levels increased steadily during the 6 cycles of induction therapy with R-FM (Figure 2A and Table 2). During 2-monthly rituximab maintenance with 375 mg/m^2 median serum concentrations remained constantly over 25,000 ng/mL.

Median levels of female patients were higher at almost

Table 2. Median rituximab C_{trough} levels (ng/mL) according to gender, bone marrow infiltration and clinical response.

	Induction cycle 2 median (range)	N	Induction cycle 4 median (range)	N	Induction cycle 6 median (range)	N	Maintenance cycle 1 median (range)	N	Maintenance cycle 2 median (range)	N	Maintenance cycle 4 median (range)	N	Maintenance cycle 6 median (range)	N
Median all patients	12,695 (<500-44,876)	15	56,643 (25,308-93,207)	13	62,451 (43,271-113,691)	15	38,693 (13,826-113,709)	16	31,041 (6,233-72,874)	11	34,746 (1,545-54,069)	12	36,287 (14,172-66,751)	10
Female	25,647 (<500-44,876)	9	65,704 (31,132-93,207)	7	67,244 (43,271-113,691)	8	47,616 (14,701-113,709)	9	36,339 (6,233-72,874)	6	38,926 (16,018-52,426)	6	33,693 (16,273-60,848)	6
Male	7.666 (<500-17,429)	6	39,206 (25,308-78,905)	6	60,390 (46,345-106,098)	7	34,839 (13,826-64,709)	7	24,605 (6,374*-57,485)	5	27,632 (1,545-54,069)	6	45,092 (14,172-66,751)	4
BM negative	25.647 (2,808-44,876)	5	76.994 (43,677-93,207)	5	81,581 (65,869-113,691)	5	47,616 (19,692-113,709)	7	26,395 (6,233-57,485)	5	46,882 (20,310-54,069)	4	38,459 (24,595-56,070)	3
BM positive	7,666 (<500-31,557)	10	45,467 (25,308-68,249)	8	57,348 (43,271-73,366)	10	27,420 (13,826-58,521)	9	36,339 (6,374-72,874)	6	34,538 (1,545-43,314)	7	34,115 (14,172-66,761)	7
BM negative & no bulk	25,647 (2,808-44,876)	5	76,994 (43,677-93,207)	5	81,581 (56,643-113,691)	5	56,162 (35,863-113,709)	6	41,535 (6,233-57,485)	4	49,654 (26,119-54,069)	4	34,459 (24,595-56,070)	3
BM positive &/or bulky	7,666 (<500-31,557)	10	45,467 (25,308-68,249)	8	57,348 (43,271-73,366)	10	25,347 (13,826-58,521)	10	31,041 (6,374-72,874)	7	27,424 (1,545-43,314)	8	34,115 (14,172-66,751)	7
CR	19,178 (<500-44,876)	11	65,704 (25,308-93,207)	9	65,869 (45,143-113,691)	11	47,525 (13,826-113,709)	12	41,637 (6,233-72,874)	9	36,837 (14,857-54,069)	9	38,459 (24,595-60,848)	7
PR	2,883 (1,336-12,695)	4	32,934 (28,700-43,677)	4	57,348 (43,271-67,216)	4	27,690 (19,692-35,863)	4	15,489 (6,374-24,605)	2	16,018 (1,545-20,31)	3	16,273 (14,172-66,751)	3
Cont. remission	18,303 (<500-44,876)	10	62,675 (25,308-93,207)	8	61,877 (45,143-113,691)	10	44,479 (13,826-113,709)	10	41,637 (19,714-72,874)	7	36,837 (14,857-54,069)	7	38,944 (28,927-66,751)	7
Cont. CR	19,178 (<500-44,876)	9	65,704 (25,308-93,207)	7	62,451 (45,143-113,691)	9	44,479 (13,826-113,709)	10	41,637 (26,395-72,874)	7	36,837 (14,857-54,069)	7	38,701 (28,927-60,848)	6
Relapse	4,110 (1,656-25,647)	5	43,677 (31,132-76,994)	5	65,869 (43,271-81,581)	5	35,351 (19,692-72,883)	6	15,489 (6,233-56,676)	4	20.310 (1,545-46,882)	5	16,273 (14,172-24,595)	3

Table 3. Correlation with rituximab C_{trough} during induction and maintenance.

		Induction 2 (n=15)	Induction 4 (n=13)	Induction 6 (n=15)	Maintenance 1 (n=16)	Maintenance 2 (n=11)	Maintenance 4 (n=12)	Maintenance 6 (n=10)
Gender (female *vs.* male)								
	R	0.46	0.46	0.15	0.33	0.22	0.30	0.23
	P	**0.04**	0.06	0.30	0.10	0.26	0.17	0.26
BM infiltration (yes *vs.* no)								
	R	0.42	0.56	0.72	0.51	0.03	0.44	0.07
	P	0.06	**0.02**	**0.001**	**0.02**	0.46	0.08	0.43
Remission quality (CR *vs.* PR)								
	R	0.46	0.67	0.30	0.34	0.45	0.70	0.21
	P	**0.04**	**0.005**	0.13	0.09	0.08	**0.005**	0.28
Continous R *vs.* Relapse								
	R	0.32	0.26	0.14	0.13	0.43	0.52	0.74
	P	0.12	0.20	0.31	0.31	0.09	**0.04**	**0.007**

R: correlation coefficient; P: P value .

all time points during induction and maintenance (median 29%). Differences were significant in induction cycle 2 (P=0.04) (Table 3). Saturation of rituximab serum levels was achieved at cycle 4 in women but only at cycle 6 in men (Figure 2A).

Low rituximab serum levels were associated with histological BM infiltration as an indicator of tumor load (Tables 2 and 3). Median trough levels in patients with BM infiltration before induction cycles 2, 4 and 6 were only 29.8%, 59% and 70% compared to the respective levels of patients without BM involvement. These differences were statistically significant (Tables 2 and 3; P=0.02 to 0.001). C_{trough} available in 2 patients with bulky disease were also always below the median (*data not shown*). Patients with high tumor burden generally (BM infiltration and/or bulky disease) had lower levels (Table 2). Multivariate analysis was not performed due to small patient numbers. However, the effects of gender and BM infiltration seemed to be independent since women as well as men *without* BM infiltration had higher Ctrough levels compared to their respective gender *with* BM infiltration at almost all time points. For example, levels before cycle 2 (ng/mL), female: BM negative 29,672, BM positive: 19,178; male: BM negative: 12,695, BM positive: 4,110 (Table 2). In general, men with BM infiltration had the lowest levels. FLIPI subgroups were small and did not seem to correlate with PK. Nonetheless, these data indicate a considerable influence of initial tumor burden (BM infiltration) on rituximab serum concentration, particularly during induction.

We also observed an association between rituximab C_{trough} levels and response to treatment. Serum concentrations during induction cycles 2 and 4 showed significant correlation with CR rates at the end of induction (Tables 2 and 3, Figure 2B; P=0.04 to 0.005). A correlation between the quality of remission and C_{trough} levels was also found during maintenance (Table 3). We observed a trend towards longer PFS in patients with higher rituximab levels (Figure 2C and D). At maintenance 6, this reached statistical significance despite low patient numbers (P=0.03) (Figure 2E).

A dissociation in C_{trough} levels between patients remaining in continuous CR or PR and patients who later relapsed was observed during maintenance (Table 2 and Figure 2F). The decline in rituximab serum concentrations preceded clinical relapse in 5 of 6 patients. Relapses occurred 9.5 to 62 months after the last PK measurement. Interestingly, patients who later relapsed had levels below 25,000 ng/mL at maintenance 6, while all patients remaining in continuous remission had levels above 25,000 ng/mL at this time point (median 16,273 ng/mL, range 14,172-24,595 vs. 38,944, range 28,927-66,751; P=0.008). These data establish a close relationship between rituximab C_{trough} levels and clinical outcome.

Discussion

The results of this prospective phase II study in previously untreated follicular lymphoma show that rituximab serum levels correlate with patient pre-treatment characteristics and clinical outcome. High clinical efficacy was observed with the R-FM induction regimen with 100% overall response rate (ORR) and high CR rates (66%).[5,6] The study cohort was too small to observe the inferior OS recently reported by several study groups.[21-23]

Previous data on rituximab PK in follicular lymphoma were mainly generated during monotherapy.[8,11-13] Here, we report a unique, detailed analysis of the association between serum concentrations, prognostic factors and clinical outcome of FL during intensive immunochemotherapy induction and rituximab maintenance. Since our PK results are based on only 17 patients, definitive conclusions cannot be drawn. Nevertheless, this pilot PK study provides valuable clues that will help the future planning of larger clinical trials with regards to frequency and timing of C^{trough} assessment, as well as dosing and scheduling of rituximab.

One of the major findings of this study is the log-fold inter-individual variability in rituximab concentrations indicating that median levels are not representative. Rituximab PK depended on gender and on the presence or absence of bone marrow infiltration at diagnosis as a marker of tumor burden.

Female patients responded better to therapy despite equal initial risk factors. Gender is not part of the FLIPI but has been recognized as a prognostic factor in FL.[17,18] In line with these observations, gender proved to be an independent risk factor in multivariate analysis in previous trials with rituximab and recently in the PRIMA study.[7,24] Interestingly, higher rituximab serum concentrations have previously been observed in women with rheumatological diseases.[11-13,25] The NHL9 data indicate that this is due to a higher distribution volume in men. Our data suggest that female patients benefit from rituximab containing regimens more than men, possibly due to higher serum levels throughout induction and maintenance. Strong evidence for male sex being a poor prognostic factor in follicular as well as diffuse large B-cell lymphoma in the rituximab era has been provided by several studies.[24,26]

Whether tumor burden is inversely correlated with rituximab serum concentrations is still a question of debate.[8-10,12,27,28] Here, we show that BM involvement (recognized as a risk factor in the FLIPI 2 and other prognostic scores)[17] is associated with low rituximab levels. The highest initial levels were observed in patients with neither BM infiltration nor bulky disease. Patients with BM involvement had low rituximab serum in induction cycles 2-6. This indicates potential under-dosing of these patients early during induction.

Remission quality may have an impact on PFS.[29] It is, therefore, compelling that high rituximab trough levels were correlated with complete remission and even PFS. C_{trough} levels in CR *versus* PR patients differed as early as after the first cycle of therapy, again providing a rationale for intensification of rituximab treatment early in induction. An association between remission and antibody concentrations has been described in other studies.[8,15,30] Potential causes include tumor mass, amount of circulating CD20 antigen, or genetic factors like polymporphisms in the FCgamma receptor (*FCGR*) genes involved in binding and internalization of antibodies or B-cell recovery.[31,32] However, FCGR3A polymorphism did not significantly influence response or PFS in the PRIMA study, making a direct relationship to rituximab levels unlikely.[33]

Clinical relapses were preceded by a decline in antibody levels. This was probably due to a rise in CD20 positive lymphoma cells that was not readily detected by clinical response evaluation. Our data show that at maintenance cycle 6 relapsing patients had less than 25,000 ng/mL while all patients in continuous remission had more than

25,000 ng/mL.[8] These data suggest exploring rituximab serum levels as an early predictive marker of clinical outcome in prospective trials is warranted.

As far as maintenance treatment is concerned, 2-monthly rituximab administration maintained constant levels above the putative threshold (25,000 ng/mL).[4,7] Two other publications have reported rituximab levels during maintenance.[14,15] In an interesting attempt to individualize rituximab treatment, Gordan *et al.* have given rituximab to 16 patients with FL whenever serum levels decreased below 25,000 ng/mL and concluded that the optimal interval between maintenance treatments was 3-4 months.[14] The 'active' serum level was originally determined by assessing rituximab concentrations in responders and non-responders three months after induction monotherapy.[8] It seems that this threshold is still a fairly good discriminator in the setting of immune-chemotherapy followed by maintenance where clinical debulking is much more rapid and the PK is different.

The results of this pilot study suggest that rituximab is not always applied in the best way. We propose to explore C_{trough} levels in future studies in order to improve scheduling by altering dose, frequency and timing of the drug. Novel anti-CD20 antibodies are currently being developed as substitutes for rituximab. Among these are drugs given at a fixed dose, such as ofatumumab, GA-101, or the cutaneous formulation of rituximab.[34] The NHL9 data challenge the concept of dosing strategies by which 'one solution fits all'. This may be important in the planning of clinical trials and in personalized antibody-based lymphoma therapy.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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