To the editor:

Maintenance rituximab every 2 months is more toxic than every 3 months in patients with non-Hodgkin lymphoma

The phase III PRIMA study of patients with previously untreated follicular lymphoma randomly assigned to maintenance rituximab (MR; every 8 weeks for 2 years) vs observation following rituximab-based immunochemotherapy (rituximab plus cyclophosphamide, vincristine, and prednisone [R-CVP], rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP], or rituximab plus fludarabine, cyclophosphamide, and mitoxantrone [R-FCM]) demonstrated an improvement of 16.5% in 6-year progression-free survival (PFS) with MR (59.2% vs 42.7%; $P < .001$) as well as increased frequency of grade 3 to 4 adverse events (24% vs 17%; most commonly infections).[1,2] These results established MR as a standard-of-care option in such patients, and MR is now empirically generalized to accompany other rituximab-based induction regimens in treating indolent non-Hodgkin lymphomas and mantle cell lymphoma. For example, the increasingly popular regimen of bendamustine and rituximab (BR) is often followed by MR every 2 months for 2 years. In our recent experience with BR, we noticed an apparently increased incidence of toxicities during maintenance that required delay or discontinuation of MR. We conducted a retrospective study to determine the predictors of MR toxicity. We hypothesized that the use of BR (vs R-CHOP/R-CVP) for induction and/or MR administered every 2 months (vs every 3 months) are associated with increased MR toxicity.

We reviewed the medical records of all patients with B-cell indolent non-Hodgkin lymphoma or mantle cell lymphoma treated at our institution with R-CHOP/R-CVP or BR as first-line induction followed by MR (375 mg/m^2) every 2 months or every 3 months for a maximum of 2 years. A total of 148 patients who received their first dose of induction after January 1, 2006, and either completed or discontinued the planned maintenance were included (Table 1). The most common diagnosis was follicular lymphoma (82%), and approximately half the patients (44%) received BR. The planned maintenance schedule was every 2 months in 28% of patients and every 3 months in the remaining patients. The decision to offer one schedule of MR vs another was largely based on whether patients were treated before or after the PRIMA study.

Toxicities attributed to MR occurred in 33 patients (22%) (76% grade 3-4, 18% grade 1-2, 6% grade unknown). Neutropenia (7%), infection (6%), or both (7%) accounted for 88% of all toxicities (supplemental Table 1). A delay/omission of at least 1 dose of MR (but not discontinuation of treatment) was required in 18 patients (12%), with MR toxicity being the reason for delay/omission in 16 (89%). MR was prematurely discontinued in 40 patients (58% of those with and 18% of those without MR toxicity; $P < .001$), most commonly as a result of toxicity (45%; n = 18) or disease progression (30%; n = 12). A variety of other uncommon reasons (eg, intravenous access, transportation difficulties, fatigue) led to discontinuation in the remaining minority.

In univariate analysis, both the induction regimen and maintenance schedule were significantly associated with MR toxicity. Of the patients treated with BR, 31% experienced toxicity during MR compared with 16% of those who received R-CHOP/R-CVP ($P = .046$). Similarly, toxicity was observed in 41% of patients in the every-2-months cohort vs 15% in the every-3-months cohort ($P = .002$). In multivariate binary logistic regression using the maintenance schedule and induction regimen as predictors, only the every-2-months schedule remained statistically significant (odds ratio, 3.42; 95% confidence interval, 1.36-8.60; $P = .009$). The univariate association between BR and MR toxicity likely reflects an increase in BR use that coincided with adoption of every-2-months MR. With a median follow-up of 53 months, the median PFS has not been reached. PFS was not significantly associated with MR toxicity ($P = .54$) or induction regimen ($P = .34$). However, there was a trend toward higher 3-year PFS in the every-3-months compared with the every-2-months cohort (91% vs 83%, respectively; $P = .09$) and in the group who completed MR compared with those who discontinued MR for reasons other than progression (97% vs 86%, respectively; $P = .09$). There were no significant differences between the every-2-months and every-3-months cohorts other than the higher frequency of BR in the former (80% vs 30%; $P < .001$).

This study is the first comparison, albeit retrospective, of every-2-months vs every-3-months MR. Patients in the every-2-months cohort were 3.4 times more likely to experience toxicity and showed a trend toward shorter PFS, which may be the result of more dose delays/omissions and, ultimately, early treatment discontinuation. A randomized prospective study comparing the 2 schedules in terms of toxicity and PFS is warranted.

Table 1. Patient characteristics in groups with and without MR toxicity

Variable	Total (n = 148)		No toxicity (n = 115)		Toxicity* (n = 33)		P
	No.	%	No.	%	No.	%	
Mean age at diagnosis, y (± SD)	60 ± 13		61 ± 13		57 ± 15		.19
Male sex	69	47	56	49	13	39	.43
Diagnosis							.09
Follicular lymphoma	122	82	95	82	27	82	
Mantle cell lymphoma	14	10	8	7	6	18	
Marginal zone lymphoma	9	6	9	8	0		
Lymphoplasmacytic lymphoma	3	2	3	3	0		
Ann Arbor stage							.40
Limited (I-II)	21	14	15	13	6	18	
Advanced (III-IV)	127	86	100	87	27	82	
B symptoms	19	13	17	15	2	6	.25
Extranodal involvement	96	65	73	63	23	70	.54
Transformed	21	14	17	15	4	12	1.00
Induction regimen							.046
R-CHOP/R-CVP	83	56	70	61	13	39	
BR	65	44	45	39	20	61	
No. of induction cycles							.13
4	6	4	3	3	3	9	
5	7	5	5	4	2	6	
6	135	91	107	93	28	85	
Response to induction							.21
Complete response	102	69	76	67	26	79	
Partial response/stable disease	45	31	38	33	7	21	
Maintenance schedule							.002
Every 2 mo	41	28	24	21	17	52	
Every 3 mo	107	72	91	79	16	49	

Proportions were compared by using the χ^2 method (and Fisher's exact test) and continuous variables were compared by using the Student t test.

SD, standard deviation.

*Any grade toxicity (see supplemental Table 1).

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To the editor:

No association between the presence of killer-cell immunoglobulin-like receptor genes and susceptibility to childhood ALL

Killer-cell immunoglobulin-like receptors (KIRs) play a pivotal role in immunosurveillance and reduction of relapse after hematopoietic stem cell transplantation in acute leukemia.[1,2] Outside the setting of hematopoietic stem cell transplantation, it was recently reported by Almalte et al that inherited KIR genes might be associated with susceptibility or resistance to childhood acute lymphoblastic leukemia (ALL).[3] They determined 6 activating KIRs (KIR2DS1-5 and KIR3DS1) in a cohort of 145 children with B-cell leukemia (B-ALL) and 30 children with T-cell leukemia (T-ALL) and compared it with a healthy control group of 245 children of French-Canadian ethnicity. Children with more activating KIR genes had a lower risk for ALL.[3] A subsequent study by Babor et al analyzed the presence of stimulatory KIRs in a similar cohort of children with B-ALL (n = 185) and T-ALL (n = 33).[4] In contrast, they did not find a reduction of stimulatory KIRs in childhood ALL patients, although allele frequencies of stimulatory KIRs between the Canadian and the European study did not differ significantly.[4]

Given these observations, we determined KIR genotypes of the 17 known KIR genes of 328 pediatric patients (203 male and 125 female) with ALL (86 B-ALL, 179 common ALL, and 63 T-ALL) treated according to the AIEOP-BFM-ALL 2000 protocol. The majority of patients were of European origin with a frequency being in line with Babor's work.[4] The control group consisted of 339 healthy blood donors with a median age of 25 and self-reported Caucasian ethnicity. We used a DNA-based quantitative real-time polymerase chain reaction–based method according to Vilches et al and Alves et al.[5,6]

Analyzing prognostic factors often reveals different and potentially coincidental results in different analyses, often because of the fact that no adjustment for multiple testing was done. Therefore, we carefully accounted for this problem in calculating our sample size and in interpreting our analyses. Power calculation was based on a 2-sample test for proportions using proportions for the 6 KIR genes of main interest given in Almalte et al.[3] Adjusting for multiple testing of 6 genes, the level of significance was set to .008 to reach a global significance level of .05 (with a power of .8). Therefore, a minimum of 256 patients and 256 controls had to be included, and the end point of all analyses was the presence of ALL (control vs patient). A possible association between occurrence of KIR genes and age, sex, DNA index, or genetics was not observed (data not shown).

Univariate logistic regression did not reveal any significant difference in frequency distribution of KIR alleles and genotypes in children with ALL compared with healthy controls (Table 1). We also analyzed receptor distributions of the 6 activating receptors among the different leukemic risk categories (low, 35%; intermediate, 46%; and high, 19%). No significant difference in receptor combinations could be found between controls and these 3 subgroups (data not shown). Furthermore, KIR genes were assigned to either KIR haplotype A or B. The distribution of these 2 haplotypes among ALL patients and the healthy reference group was 26.8% vs 30.4% for haplotype A and 73.2% vs 69.6% for haplotype B, respectively. These data are in line with published KIR gene frequencies in a Caucasian population.[7] We next determined KIR B-content scores for patients and controls and found similar score distributions between the 2 groups. Furthermore, involvement of the central nervous system was independent of activating KIRs, KIR haplotype, and B-content score. An increasing risk for ALL with an increasing number of activating KIR genes was also excluded ($P = .173$).

Our results are in sharp contrast to the findings of Almalte et al.[3] Diversity of KIR gene expression among different ethnic groups has to be taken into account as an explanation for the discrepancy of results. For instance, an increased KIR A/A genotype was found in Hispanic children with ALL, but not in non-Hispanic children.[8] Moreover, the possibility of coincidental results in statistical analyses might have to be excluded.

In summary, we did not find a significant difference in KIR gene expression between pediatric patients with ALL and healthy controls, and our results do not support the hypothesis that the number of activating KIR genes confers susceptibility or resistance to pediatric ALL. Further research is necessary to elucidate genetic factors involved in the development of ALL in children.