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A Multicenter Phase II Study of Twice-Weekly Bortezomib plus Rituximab in Patients with Relapsed Follicular Lymphoma: Long-Term Follow-Up

Alessia Bari[a] Raffaella Marcheselli[a] Luigi Marcheselli[a] Isabel Alvarez[b] Samantha Pozzi[a] Paola Ferri[a] Antonio Lazzaro[c] Alberto Fragasso[d] Santo Neri[e] Luca Baldini[f] Angelo Michele Carella[g] Francesco Angrilli[h] Roberto Guariglia[i] Gabriele Buda[j] Caterina Stelitano[k] Stefano Sacchi[a] on behalf of the Gruppo Italiano Studio Linfomi (GISL)

[a]Program of Innovative Therapy in Oncology and Hematology, Department of Diagnostic, Clinical Medicine and Public Health, University of Modena and Reggio Emilia, Modena, [b]Hematology Unit, Azienda Ospedaliera Arcispedale Santa Maria Nuova, IRCCS, Reggio Emilia, [c]Hematology Unit, Guglielmo da Saliceto Hospital, Piacenza, [d]Hematology Unit, Madonna delle Grazie Hospital, Matera, [e]Hematology Unit, Papardo Hospital Messina, Messina, [f]Department of Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, [g]Hematology Unit, San Martino Hospital, Genoa, [h]Department of Hematology, Ospedale Santo Spirito, Pescara, [i]Hematology and SCT Unit, IRCCS-CROB, Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture, [j]Division of Hematology, Università Di Pisa, Pisa, and [k]Hematology Unit, Bianchi Melacrino Morelli Hospital, Reggio Calabria, Italy

Key Words

Bortezomib · Chemotherapy-free regimen · Follicular lymphoma · Relapsed/progressive disease · Rituximab

Abstract

Single-agent bortezomib (B) has shown activity in heavily pretreated patients with relapsed/refractory indolent lymphoma. On the basis of these findings, we performed a phase II study of B combined with rituximab (R) in patients with relapsed follicular lymphoma (FL). Forty-five patients with fairly good prognostic profiles were enrolled from 2007 to 2011 and received a total of 6 cycles of the B+R combination. The endpoints were the overall response rate (ORR), progression-free survival (PFS), duration of remission (DoR), overall survival (OS), and toxicity evaluation. When considering all the enrolled patients the ORR was 64%. At 5 years, the estimated PFS, DoR, and OS were 34, 49, and 70%, respectively. After excluding the 7 R-naïve patients, the ORR was 58%, with a PFS of 19 months. The most common grade >2 toxicities were thrombocytopenia (18%), peripheral neuropathy (13%), and neutropenia (2%). Our study shows the feasibility, long-term efficacy, and excellent tolerability of the B+R combination. We are aware that our study has specific limitations, such as the small sample size consisting of patients with a relatively good prognostic profile. However, because FL patients will be treated with subsequent chemotherapy regimens, a well-tolerated and effective chemotherapy-free therapy could be considered an additional tool for long-term disease control.

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E-Mail karger@karger.com
www.karger.com/aha

Stefano Sacchi, MD
Department of Diagnostic, Clinical Medicine and Public Health
University of Modena and Reggio Emilia, Via del Pozzo 71
IT–41123 Modena (Italy)
E-Mail stefano.sacchi@unimore.it

Introduction

Follicular lymphoma (FL) is the second most frequently occurring subtype of malignant lymphoma in western countries and accounts for approximately 22% of all adult non-Hodgkin lymphoma [1]. A variety of treatment approaches including the use of alkylating agent monotherapies, combination therapy with or without doxorubicin, and combination chemoradiotherapy have been used to treat patients. In recent years, new therapeutic approaches have been investigated. These include myeloablative chemotherapy with stem cell rescue [2], purine analogues [3, 4], and immunologic therapy with naked, radiolabeled anti-CD20 monoclonal antibodies and inhibitors of B cell receptor signaling [5–8]. With the current treatment options, complete remission rates range from 65 to 85%, the duration of the primary response is about 30 months, and the expected median survival is approximately 8–10 years [9, 10]. Although patients with FL have relatively long median survival times, they tend to relapse over time, with responses to salvage therapy of a shorter duration after every relapse, and they eventually die of their disease. Thus, innovative treatments are being explored to improve the response rate and survival outcome, and to avoid the side effects of classical chemotherapeutic regimens. FL cells express CD20, overexpress the anti-apoptotic protein Bcl2, and have a constitutively activated NF-κB. This triple marker positivity provides the biological rationale for combining rituximab (R) and bortezomib (B). Indeed, R targets CD20 and B targets NF-κB, and both strongly activate apoptosis. Furthermore, the combination demonstrated additive/synergistic activity in in vitro and in vivo murine models [11, 12], the toxicities are not overlapping, and a pharmacokinetic interaction is unlikely [13, 14]. In phase I [15] and multiple phase II studies [16–19], B as a single agent showed activity in heavily pretreated patients with relapsed/refractory indolent lymphoma, utilized on either a biweekly or weekly schedule [20, 21]. These findings encouraged several studies of different regimens combining B with R and chemotherapy in indolent lymphoma, the results of which have been published [22–24].

With this background, we performed a multicenter phase II study examining the safety and efficacy of B+R in patients with relapsed FL. Here we present the results observed after a long-term follow-up period, which show excellent survival outcomes.

Patients and Methods

Patients and Treatment

Patients were enrolled in a multicenter, open-label, nonrandomized phase II study from 2007 to 2011, which was conducted at 10 Italian institutions (FOLREC03/LYM2024, ClinicalTrials.gov No. NCT01830465; EudraCT No. 2006-002521-23).

The inclusion criteria were for patients aged 18 years or older, with histologically proven FL (grade 1–3a) based on the World Health Organization classification [25], relapsed/progressive disease, and no more than 3 lines of treatment, a Karnofsky performance status ≥50%, at least 1 measurable lesion, a life expectancy of more than 6 months, left ventricular ejection fraction >50%, and adequate renal and liver function. The exclusion criteria were CNS involvement, infection with human immunodeficiency virus, hepatitis B or C virus, another primary cancer, significant comorbidity (including preexisting neuropathy grade 2 or higher), severe impairment of bone marrow function (absolute neutrophils count $<1.5 \times 10^9$/l or platelets $<50 \times 10^9$/l unless due to lymphoma involvement), and pregnancy, breast feeding, or refusing to use an acceptable method of contraception for the duration of the study.

All patients provided written informed consent. The institutional review board at all of the participating institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki, International Conference on Harmonization, and Guidelines for Good Clinical Practice.

Patients with relapsed/progressive FL received a total of 6 cycles of B and 6 infusions of R. B (VELCADE®; Johnson & Johnson/Janssen-Cilag S.p.A) was delivered as an intravenous bolus at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 for six 21-day courses (cycles I–VI). R was administered as an intravenous infusion at the dose of 375 mg/m^2 on day 1 of cycles III, IV, V, and VI. Two additional doses were administered in weeks 3 and 6 after cycle VI. Dose modification was permitted in cases of neutropenia, thrombocytopenia, and neurotoxicity. Prophylactic antiviral agents, filgrastim, and antibiotics were permitted according to the treating physician's discretion.

Pretreatment and Safety and Efficacy Assessments

Hematological parameters, clinical chemistry, and performance status were assessed on day 1 of each cycle, at the end of treatment, and at each follow-up visit, which occurred every 3 months for the first year then every 6 months until relapse or progression. Pretreatment and efficacy assessments included a physical examination, laboratory parameters, CT scans of the chest, abdomen and pelvis, and bone marrow biopsy. During follow-up, CT scans were scheduled every 6 months until relapse or progression. Responses were evaluated at the end of cycle II, and 1 month after the end of treatment.

Outcomes

The primary endpoint was the overall response rate (ORR) at the end of treatment (6 cycles of B and 6 infusions of R) defined as the number of patients who achieved complete (CR) and partial (PR) responses. The responses were evaluated in accordance with the International Working Group Criteria for Non-Hodgkin Lymphomas [26].

The secondary endpoints were ORR after 2 cycles of treatment (only B injections) and progression-free survival (PFS), defined as

Table 1. Baseline characteristics (n = 45)

Variable	n	%	Median (range)
Age, years	45		65 (36–82)
Hb, g/dl	43		13.3 (10.2–16.0)
WBC, $\times 10^9$/l	43		5.7 (2.3–62)
Lymphocytes, $\times 10^9$/l	42		1.34 (0.14–6.27)
Age >60 years	29	64	
Male	23	51	
AA stage			
I	5	11	
II	7	16	
III	14	31	
IV	19	42	
With B-symptoms	3	7	
LDH (n = 41)			
≤ULN	29	71	
>ULN	12	29	
Nodal sites			
0–4	32	71	
>4	13	29	
Extranodal sites			
>1	5	11	
Bulky disease[1]	3	7	
BM involvement	9	20	
FLIPI (n = 41)			
0–1	17	41	
2	8	20	
3–5	16	39	
Histology			
Grade 1	21	47	
Grade 2	12	27	
Grade 3a	11	24	
NA[2]	1	2	
Prior lines[3]			
1	18	40	
2	17	38	
3	10	22	
Time from the last treatment			
<1 year	10	22	
1–3 years	17	38	
3–5 years	10	22	
>5 years	8	18	

AA = Ann Arbor; LDH = lactate dehydrogenase; UNL = upper limit of normality; BM = bone marrow.

[1] One mediastinal site with a diameter of 8 cm and 2 nonmediastinal sites with diameters of 8 and 12 cm.

[2] Patient with a diagnosis of FL not otherwise specified.

[3] Number of lines of antineoplastic treatment.

the time from study entry to the time of any documented progressive disease, relapse, or death from any cause. Duration of remission (DoR) was defined as the time from CR/PR confirmation to the time of any documented relapse/progressive disease or death from any cause. Overall survival (OS) was defined as the time from study entry to the last observation or death from any cause.

Table 2. Patient disposition and treatment exposure (safety population; n = 45)

Median cycles, n	6 (1–8)
Patients completing all 8 cycles, n	21 (47)
Patients completing at least 6 cycles, n	29 (64)
Reason for discontinuing before completing 8 cycles, n	
SD/PD	12 (27)
PN	7 (16)
AEs	2 (4)
Investigator decision/patient choice	3 (7)
Median R dose intensity, %	94
Median B dose intensity, %	97

Values in parentheses are the percentage or range. SD = Stable disease; PD = progressive disease; AEs = adverse events.

Safety was evaluated by assessing the laboratory parameters and adverse events. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 3.0).

Study Design and Statistical Analysis

The study was planned according to Simon's optimal two-stage design [27], with ORR as the primary endpoint. With a significance level of $\alpha = 0.05$ and power of 90%, we considered ORR rates of 40% as a level of no interest (P0) and 60% as a level of interest (P1). In the first stage 17 evaluable patients were enrolled and, if more than 8 responses were observed, 24 additional patients were enrolled in the second stage. The study regimen was considered ineffective with less than 22 overall responses observed at the final assessment. Given that approximately 10% of patients were expected to be deemed ineligible after registration for any reason, we planned to recruit a total of 45 patients. Sample size was determined with a one-sided test. The baseline characteristics of the patients were summarized as numbers and percentages for categorical variables and as medians and ranges for continuous variables.

The response rates were reported with the exact binomial 95% confidence intervals (CIs). Kaplan-Meier methodology was used to estimate OS, PFS, and DoR [28]. Safety was analyzed taking into consideration all patients who received at least 1 dose of a study drug. All analyses were done with Stata SE/10 package.

Results

Patient Characteristics

Between 2007 and 2011, 45 patients with relapsed FL were enrolled in the FOLREC03/LYM2024 clinical trial. The baseline clinical characteristics and prior therapies are detailed in table 1. The median age at study entry was 65 years (range 36–82), 51% were males, and 39% had a

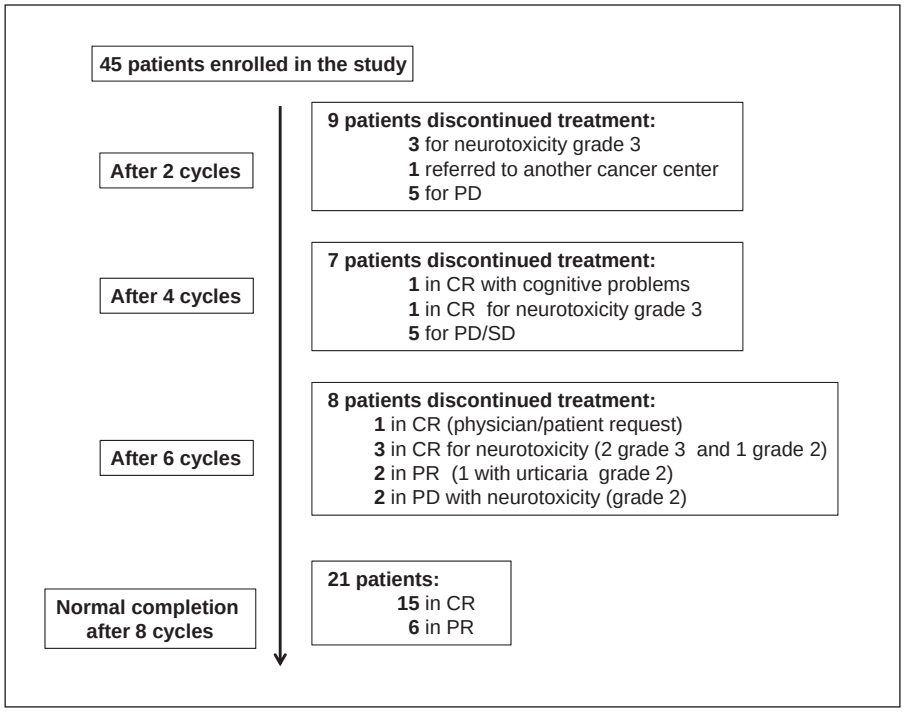

Fig. 1. Study flow chart and reasons for discontinuation. PD = Progressive disease; SD = stable disease; CR = complete response; PR = partial response.

Table 3. Response after treatment with B+R and after the first 2 cycles of therapy (B injection only) in the 45 eligible patients

	n	%	95% CI[1]
Response			
ORR	29	64	49–78
CR	21	47	32–62
PR	8	18	8–32
SD	1	2	0–12
PD	11	24	13–40
EF/W	4	9	2–21
Response after 2 cycles of therapy			
ORR	15	34	20–49
CR	3	7	1–18
PR	12	27	15–42
SD	21	47	32–62
PD	5	11	4–24
EF/W	4	9	2–21

PD = Progressive disease; SD = stable disease; EF/W = early failure/withdrawal after the first 2 cycles of treatment (3 for neurotoxicity and 1 referred to another cancer center); ORR = overall response rate; CR = complete response; PR = partial response.

[1] Based on binomial distribution.

Follicular Lymphoma International Prognostic Index (FLIPI) [29] score of 3–5. Before registering in the study, 18 (40%), 17 (38%), and 10 (22%) patients had been treated with 1, 2, and 3 prior lines of therapy, respectively. Seven (16%) of these patients were R naïve but had previously been treated with chemotherapy.

Treatment Exposure

Patients received a median of 6 cycles of B+R (range 1–8). In total, 20, 16, and 18% received 2, 4, and 6 cycles, respectively, and 47% completed the assigned treatment. The median dose intensity delivered was 0.972 and 0.939 for B and R, respectively (table 2). After 2 courses, 9 patients (20%) withdrew from the trial (fig. 1). After 4 courses, another 7 patients (16%) withdrew, and 8 patients (18%) withdrew after 6 cycles. Twenty-one patients (47%) received all 6 cycles of therapy plus the 2 additional doses of R.

Efficacy

The efficacy criteria for the first-stage analysis were met (11 of the first 17 patients achieved CR/PR), and the enrollment continued to the planned final accrual of 45 patients. The treatment responses are summarized in table 3. Twenty-nine patients achieved CR/PR for an ORR

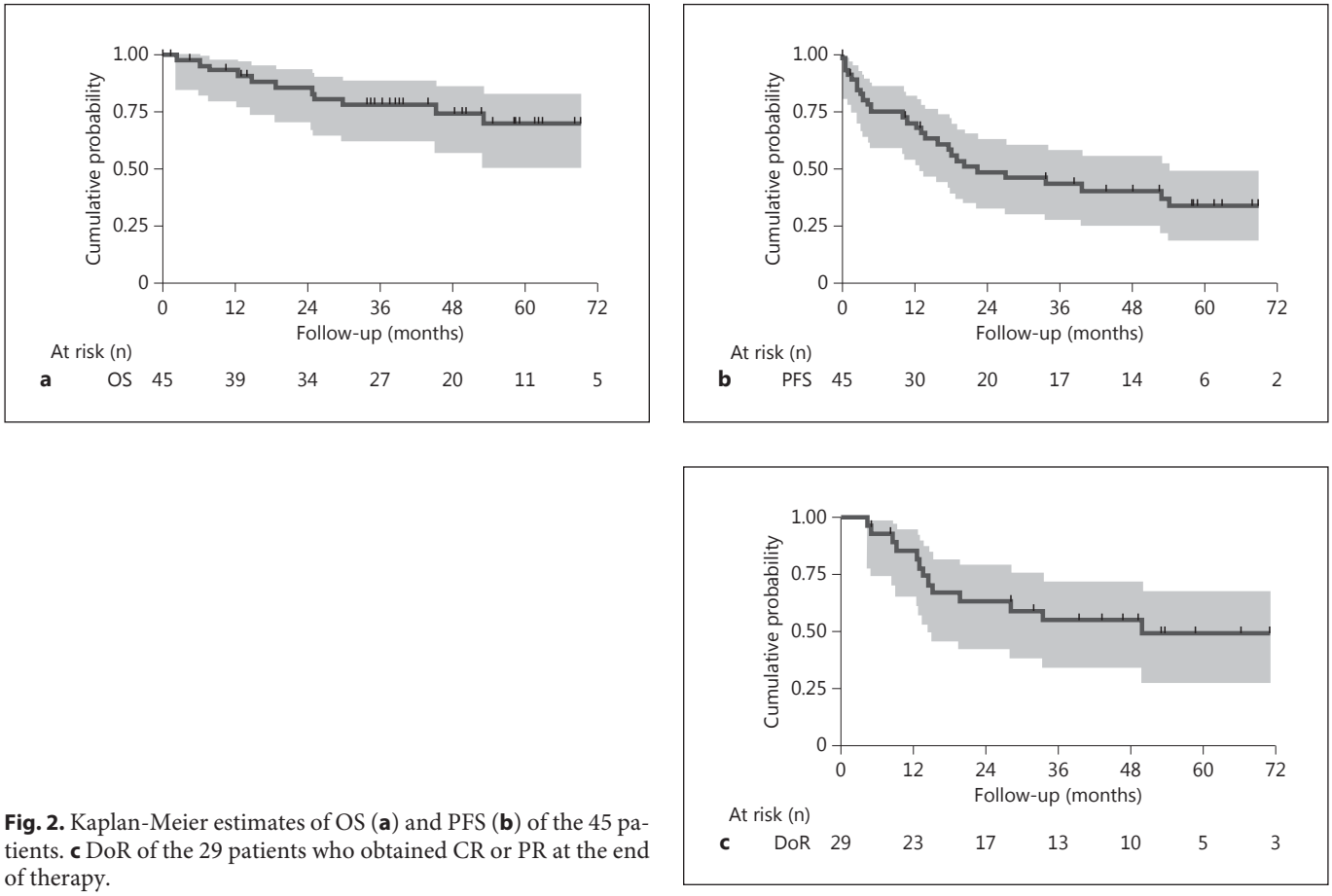

Fig. 2. Kaplan-Meier estimates of OS (**a**) and PFS (**b**) of the 45 patients. **c** DoR of the 29 patients who obtained CR or PR at the end of therapy.

of 64% (95% CI 49–78); of these patients, 21 (47%, 95% CI 49–71) and 8 (18%, 95% CI 8–32) achieved CRs and PRs, respectively. One patient (2%, 95% CI 0–12) had stable disease and 11 (24%, 95% CI 13–40) progressed. Four patients (9%, 95% CI 2–21) withdrew from the study before the first 2 cycles of therapy. The ORR after 2 cycles of therapy (i.e. after receiving only B) was 34% (95% CI 20–49) with 3 (7%) achieving CR and 12 (27%) achieving PR. After a median follow-up of 52 months (range 1–91), we observed 11 (24%) deaths: 8 from progressive disease, 1 from heart failure, 1 from sudden death, and 1 from an unknown cause. The median PFS was 22 months (95% CI 13–54) and the median DoR was 50 months (95% CI 14 to not reached). The median OS was not reached. At 5 years, the estimated PFS, DoR, and OS were 34% (95% CI 20–49%), 49% (95% CI 28–67%), and 70% (95% CI 51–82%), respectively (fig. 2). A separate analysis excluding the 7 R-naïve patients showed an ORR of 58% (37% CR and 21% PR) with a PFS of 19 months (95% CI 10–20).

Toxicity

Toxicity was evaluable in all 45 patients. The B+R combination was generally well tolerated considering that the study population was relapsed patients, and no deaths due to toxicity were observed. As detailed in table 4, most toxicities were grade 1 and 2, with a low frequency of grade 3 and 4 adverse events. The most common serious adverse events of grade >2 were thrombocytopenia (18%), peripheral neuropathy (PN) (13%), and neutropenia (2%). No cases of grade >2 anemia were reported. Overall, 6 (13%) patients experienced grade 3 PN. However, the treating physicians decided to stop the therapy due to PN in 7 patients, despite it being grade 2 in 3 of these patients. Grade ≥2 thrombocytopenia was more frequent between cycles I and IV, whereas grade ≥2 neurotoxicity was more frequent after 5 cycles of treatment.

Table 4. Side effects of B+R treatment (evaluable in all 45 patients)

	Anemia		Neutropenia		Thrombocytopenia		Infections		PN	
	n	%	n	%	n	%	n	%	n	%
Grade										
0	25	56	34	76	24	53	34	76	22	49
1	16	36	5	11	12	27			4	9
2	4	9	5	11	1	2	10	22	13	29
3			1	2	7	16	1	2	6	13
4					1	2				
Total	45		45		45		45		45	

Grades are according to the NCI Common Toxicity Criteria classification.

Discussion

Despite great progress in the treatment of FL in recent years, there is still no cure. Although patient survival is longer, the evolution of the disease has not changed and is still characterized by a succession of ever more frequent recurrences. Eventually, patients die from progressive disease or complications that are usually treatment related. The ability to use treatments other than standard chemotherapy that are still highly effective, such as the combination of B+R, is therefore extremely important.

The finding from this multicenter, open-label, nonrandomized phase II study confirmed that the combination of R with a twice-weekly injection of B was effective in relapsed FL patients. Considering all of the enrolled patients, the ORR was 64% and the CR rate was 47%. After a long-term follow-up of 52 months, we observed a median PFS of 22 months and an excellent median DoR of 50 months, while the median OS was not yet reached. At 5 years, estimated PFS, DoR, and OS were 34, 49, and 70%, respectively. The considerable length of the DoR highlights the good efficacy of the combination. After excluding the 7 R-naïve patients, we still observed a good ORR of 58% (37% CR, 21% PR), with a PFS of 19 months.

A recent randomized trial [22] comparing B+R to R alone showed a median PFS of 12.8 months (range 11.5–15.0) after a median follow-up of 33.9 months in the B+R group (n = 340), with an ORR of 63%, including 25% CRs. Comparing our results with those obtained in the B+R arm of the randomized study, we observed that the CR rate was much higher (47 vs. 25%) and the PFS longer (22 vs. 12.8 months) in our study. We also observed better outcomes in terms of CR and PFS when comparing the results of the subanalysis that excluded the 7 R-naïve patients with the results of the B+R arm of the randomized study: CR was 37 versus 25%, and PFS was 19 versus 12.8 months. The low risk profile of our study population could partially explain these good results.

In terms of toxicity, we confirmed that B+R was generally well tolerated with manageable toxicities, considering that the patients were relapsed or had progressive disease, with a low rate of grade ≥3 adverse events. The most common serious adverse events were thrombocytopenia, neurotoxicity, and neutropenia. The favorable tolerability was evidenced by the fact that 64% of the patients completed at least 6 cycles of therapy, and the median B+R dose intensity was 0.972 and 0.939, respectively. Furthermore, we did not observe late toxicities over the long-term follow-up such as second neoplasms. The 42% of patients who experienced grade 2/3 PN tended to improve over time, and 26% recovered fully.

We are aware that our study has specific limitations. First, the small sample size weakened the strength of the statistical analysis, particularly that of efficacy. Second, and for the same reason, the 95% CIs around the survival outcomes were large. Third, our study population had a relatively good prognostic profile. Indeed, only 39% of the patients were classified as FLIPI 3–5, 40% received only 1 prior line of therapy, 16% were R naïve, 20% had bone marrow involvement, 7% had bulky disease, and 29% had >4 nodal site involvements. The low risk profile of several patients enrolled in the trial may partially explain the better results we observed in comparison with the B+R arm of the randomized trial [22]. The strengths of our study include the very long follow-up (more than 5 years) and the precise and careful evaluation of side effects.

In conclusion, after a very long follow-up period our study shows the feasibility, considerable efficacy, and excellent tolerability of the B+R combination in patients with advanced-stage FL. Taking into account that FL is an incurable disease and that patients will be treated with subsequent chemotherapy regimens, the availability of an effective chemotherapy-free regimen with a relatively low toxicity provides an additional tool for the long-term control of FL.

Finally, even after considering the limitations of the study, we believe that our results provide enough clinical information for the use of the B+R combination in clinical practice and that our findings are important for the general onco-hematologist.

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Author Contributions

S.S.: conception and design of the study, interpretation of the data, final approval of the version to be published. L.M., R.M., and P.F.: statistical analysis, data collection, interpretation of data, and creation of tables and figures. S.S., R.M., A.B., and S.P. wrote the manuscript. S.S., I.A., S.P., A.L., A.F., S.N., L.B., A.M.C., F.A., R.G., G.B., C.S., and A.B. participated in the patients' care, data recording, and the interpretation of the data. All authors contributed critically to the drafting of the article and approved the final version.

Disclosure Statement

All authors report no potential conflicts of interest.

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