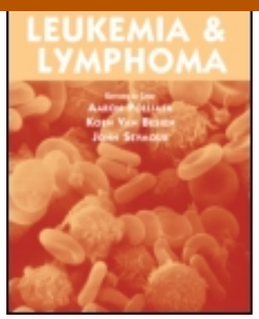

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Rituximab with cyclophosphamide, vincristine, non-pegylated liposomal doxorubicin and prednisone as first-line treatment for splenic marginal zone lymphoma: a Fondazione Italiana Linfomi phase II study

Emilio Iannitto[1], Stefano Luminari[2], Claudio Tripodo[3], Salvatrice Mancuso[1], Marina Cesaretti[2], Luigi Marcheselli[2], Francesco Merli[4], Caterina Stelitano[5], Angelo Michele Carella[6], Alberto Fragasso[7], Elisa Montechiarello[5], Giuseppina Ricciuti[8], Alessandro Pulsoni[9], Marco Paulli[10], Vito Franco[3] & Massimo Federico[2]

[1]*A.O.U. Policlinico Paolo Giaccone, Palermo, Italy,* [2]*University of Modena and Reggio Emilia, Modena, Italy,* [3]*University of Palermo, Palermo, Italy,* [4]*Arcispedale S. Maria Nuova – IRCCS, Reggio Emilia, Italy,* [5]*Azienda Ospedaliera Bianchi Melacrino Morelli, Reggio Calabria, Italy,* [6]*Azienda Ospedaliera Universitaria "San Martino", Genova, Italy,* [7]*Presidio Ospedaliero Madonna delle Grazie, Matera, Italy,* [8]*Department of Hematology, Pescara, Italy,* [9]*University La Sapienza, Roma, Italy and* [10]*University of Pavia and Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS), Fondazione Policlinico, San Matteo, Pavia, Italy*

Abstract

Rituximab ® provides high response rates and effective disease palliation in patients with splenic marginal zone lymphoma (SMZL). We conducted a phase II trial in patients with SMZL who were either untreated or were splenectomized but had shown disease progression within 1 year after splenectomy. Treatment consisted of six courses of Rituximab with cyclophosphamide, vincristine, non-pegylated liposomal doxorubicin and prednisone (R-COMP). Fifty-one patients were eligible for the analysis. The overall response rate was 84%. The 6-year progression-free survival and overall survival were 54% and 72%, respectively. Toxicity was substantial (grade $\geq$ 3 neutropenia: 26%; grade $\geq$ 3 infections: 8%). Of the 15 deaths, two occurred on treatment (one sepsis and one pneumonia). Six deaths were due to lymphoma progression, four to secondary neoplasia, one to sepsis, one to pneumonia and one to splenectomy complications. R-COMP should be restricted to patients with bulky disease associated with symptoms or to patients with possible histological transformation.

Keywords: Splenic marginal zone lymphoma, rituximab, first line

Introduction

Splenic marginal zone lymphoma (SMZL) is a well-defined, mature B-cell neoplasm [1] that mostly affects elderly individuals [2,3]. Although the lymphoma burden mainly affects the spleen, nearly all patients are in stage IV at diagnosis, due to bone marrow (BM) infiltration. Nearly 50% of cases exhibit a subtle leukemic component with a variable percentage of villous lymphocytes [4]. Signs and symptoms mainly consist of peripheral cytopenia and/or abdominal discomfort caused by splenomegaly. In most cases, SMZL pursues an indolent clinical course, and the median overall survival (OS) is approximately 10 years [5]. However, in about 20% of cases, the neoplasm progresses at a more aggressive pace with an OS of less than 5 years [6–8]. Moreover, in around 10% of cases, histologic transformation occurs toward high-grade histotypes, such as diffuse large B-cell lymphoma (DLBCL) [9–11]. Notably, this unfavorable evolution is not prevented by splenectomy [12]. It is widely accepted that patients who are asymptomatic at diagnosis should be managed with a watchful eye for progression [3–6,11]. Treatment requirements may be indicated by a number of clinical and laboratory parameters, including the presence of bulky or symptomatic splenomegaly, B-symptoms, autoimmune phenomena or significant cytopenia [13,14]. Diverse treatments, including splenectomy, rituximab (R) and chemotherapy with or without R, provide effective symptom control and recovery from cytopenias, but comparative trials are lacking [15]. Recently, a growing number of studies have shown that R immunotherapy achieved a high overall response rate (ORR) that presented a challenge to the role of palliative splenectomy as first-line therapy [16–18]. In addition, retrospective studies have suggested that a combined approach of R with chemotherapy, particularly purine analogs, could attain better results than R alone, in terms of complete response (CR) rates and progression-free survival (PFS) [15,19].

Myocet™ (Cephalon, Frazer, PA) is a liposome-encapsulated formulation of doxorubicin. This formulation provides particular pharmacokinetic properties, which result in a larger area under the curve, smaller volume of distribution and preferential distribution to the liver, spleen and lymphoid tissues, compared to conventional doxorubicin [20]. Liposomal doxorubicin was suggested as a strategy to minimize cardiac

Correspondence: Dr. E. Iannitto, Department of Oncology, Hematology Unit, University of Palermo, Via del Vespro 129, Palermo, 90127, Italy. E-mail: emilio.iannitto@gmail.com

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side effects and promote selective drug uptake by lymphoma cells [21]. Moreover, R in association with cyclophosphamide, vincristine, liposomal doxorubicin and prednisone (R-COMP) was demonstrated to effectively treat DLBCL in older and/or frail patients, with an acceptable toxicity profile [22]. Taken together, these characteristics make R-COMP a potentially effective candidate for the treatment of SMZL.

Based on the above findings, in 2005 the former Gruppo Italiano Studio Linfomi (GISL), current Fondazione Italiana Linfomi (FIL), started a prospective multicenter study to investigate the activity and toxicity of R-COMP as a first-line therapy in a series of patients with SMZL who were either ineligible for or unwilling to undergo a splenectomy.

Patients and methods

Study design and objective

This multicenter phase II trial included symptomatic patients with SMZL. The primary endpoint was ORR after administration of R-COMP as first-line treatment. Secondary endpoints included safety, CR rate, failure-free survival (FFS), OS and risk of histological transformation.

The trial (Italian OsSC number: 2005-000693-45) was approved by the ethics committees according to local rules. It was compliant with Good Clinical Practice guidelines and the October 2008 revision of the Declaration of Helsinki. All participants provided written informed consent.

Diagnosis

The diagnosis of SMZL in patients without splenectomy was based on the integration of peripheral blood (PB) lymphocyte morphology and immunophenotype, bone marrow (BM) histology and immunophenotypical analyses [13]. Specifically, the presence of a mixed nodular and intrasinusoidal pattern of infiltration by medium sized lymphoid cells with abundant clear cytoplasm with a CD19+, CD20+, CD5±, CD10−, CD23−, CD43±, FMC7±, CD103−, *bcl*-2+, cyclin D1 − immunophenotype [3] and a "chronic lymphocytic leukemia (CLL) score" of 2 or less were considered as matching diagnostic criteria for SMZL and included in the study.

In patients with splenectomy, the diagnosis was based on spleen histology according to World Health Organization (WHO) criteria [1]. For study inclusion, SMZL was diagnosed based on the histological report of the local pathologist. At the end of the study, all histological specimens were centrally reviewed by the FIL board of expert hematopathologists; any cases with unconfirmed SMZL diagnoses were removed from the final analysis.

For study eligibility, patients with SMZL had to be older than 18 years and show negative hepatitis B surface antigen (HBsAg), anti-human immunodeficiency virus (HIV) and anti-hepatitis C virus (HCV) serological analyses, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and a left ventricular ejection fraction $> 50\%$.

The prerequisite for enrollment was that patients required treatment but were ineligible for or unwilling to undergo splenectomy. The need for treatment was based on the occurrence of bulky disease status (defined as ≥ 6 cm below the left costal margin); a worsening condition; painful splenomegaly without conspicuous lymphadenopathy irrespective of concurrent cytopenia; the presence of symptomatic/progressive cytopenia (hemoglobin < 10 g/dL, platelets $< 100\,000/mm^3$, neutrophils $< 1000/mm^3$) due to any cause; or a prominent lymphadenopathy and/or involvement of extranodal sites (except for BM and spleen), irrespective of concurrent cytopenia.

Splenectomized patients with SMZL were considered eligible when they fulfilled the criteria for requiring treatment within 1 year after splenectomy.

Baseline evaluation and treatment

At baseline, after three treatment cycles and at the end of treatment, each patient underwent a full history and clinical examination: complete serum biochemistry, including lactate dehydrogenase and β_2-microglubulin determinations; peripheral blood and BM immunophenotyping; a BM biopsy and computed tomography scans of the chest, abdomen and pelvis. Cardiac function was evaluated with electrocardiography and echocardiography at baseline and at the end of treatment.

The R-COMP regimen consisted of 21-day cycles, including (day 1) cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 (cap at 2 mg), liposomal doxorubicin 50 mg/m^2 and (days 1–5) prednisone 60 mg/m^2, then (day 8 of the first cycle and day 1 for subsequent cycles) R 375 mg/m^2.

After three cycles, all patients were restaged. Those in CR received only one more cycle of R-COMP, patients who achieved a partial response (PR) received three more cycles of R-COMP and those with no response were withdrawn from the study. Dose reductions were not planned. R administration followed labeling instructions and guidelines. Granulocyte-colony stimulating factor (G-CSF) was administered according to each institution's recommendation.

Response criteria

The definition of treatment response followed the revised Matutes criteria [13]. Specifically, PR was defined as a 50% or greater improvement in SMZL manifestations; this included a resolution or decrease in spleen size, improvement of cytopenias and resolution or decrease in lymphadenopathy, when present. Also, the BM should show a decrease in lymphoid infiltration.

CR was defined as the resolution of organomegaly and normalization of blood counts (hemoglobin > 12 g/dL; platelets $> 100\,000/mm^3$; neutrophils $> 1500/mm^3$, with no evidence of circulating clonal B cells). Also, little or no BM infiltration should be detected with immunohistochemistry.

No response and progressive disease (PD) were defined, respectively, as less than 10% improvement and worsening of disease manifestations. Follow-up visits were scheduled every 3 months until progression or relapse. At the appearance of any signs of progression patients underwent restaging, and when lymphadenopathy occurred lymph nodes were biopsied. Thereafter the follow-up visits were scheduled according to the center policy or clinical needs.

Survival and toxicity

FFS was measured from the date of study entry to the date of any treatment failure, including treatment discontinuation

for toxicity, a response less than PR, progression or relapse, or to the date of death from any cause. PFS was defined as the time of study entry to the time of any documented progressive disease, relapse or death from any cause. OS was defined as the time of study entry to the last observation or death from any cause.

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

Statistical analysis

The study was planned according to Simon's optimal two-stage design [23], with ORR as primary endpoint. In the first stage, 19 evaluable patients were enrolled, and with more than 12 responses observed, 34 additional evaluable patients were enrolled in the second stage. Sample size was determined with a one-sided test. At a significance of $\alpha = 0.05$ and power of 90%, we considered ORR rates of 60% and 80% as levels of no interest (P_0) and of interest (P_1), respectively. The study regimen would be rejected with fewer than 38 overall responses at the final assessment. Given the approximate 10% of patients expected to be deemed ineligible after registration for any reason, we planned to recruit a total of 60 patients. Data were analyzed with the Stata SE/10 package. Time-to-event data were analyzed with the Kaplan–Meier method [24] and compared with the log-rank test. Results are reported with two-sided 95% confidence intervals (CIs). Proportions were compared with χ^2 and Fisher exact tests and a two-sided test was used in all tests with a level of significance of 0.05 [25].

Results

Patient characteristics

Between June 2005 and June 2009, 63 patients were prospectively recruited into the study by 21 Italian centers, and 51 were finally evaluable. Of the 12 patients excluded from the final response and survival analysis, one was due to withdrawal of consent and 11 were due to a revision of the initial histologic diagnosis (four nodal marginal zone lymphoma, four mantle cell lymphoma [MCL], two non-Hodgkin lymphoma [NHL] unspecified and one follicular lymphoma).

The median age at diagnosis was 64 years (range 30–86), and 27 (53%) patients were males; nine had undergone a splenectomy within 1 year prior to enrollment.

We carried out a *post hoc* OS analysis according to Intergruppo Italiano Linfomi [7] (IIL) and hemoglobin–platelet–lactate dehydrogenase (LDH)–extrahilar lymphadenopathy [26] (HPLL) prognostic scores, and 29% and 6% patients were classified at high risk, respectively. The demographics and baseline data of the eligible patients are summarized in Table I.

At the end of the first phase, after analysis of the first evaluable 19 patients, an objective response was observed in 15 patients (ORR 79%; 95% CI 54–94), higher than the 12 responses required.

Efficacy

Among the 51 evaluable patients, 41 (80%) completed all six cycles of treatment, two (4%) completed treatment after five cycles, six (12%) after three cycles and two (4%) after two cycles (Figure 1).

Treatment was discontinued due to adverse events ($n = 2$; one ictus cerebri and one pneumonitis, after five cycles), stable disease (SD) or PD ($n = 6$, after three cycles), infusion reaction to liposomal doxorubicin ($n = 1$, after two cycles) and death ($n = 1$ sepsis, after two cycles).

The final analysis included 51 patients; among these patients an objective response was observed in 43 patients (ORR 84%; 95% CI 71–93), higher than the 38 responses required to consider the study regimen as active. Responses included 33 CRs (65%; 95% CI 50–78) and 10 PRs (20%; 95% CI 10–33) (Table II). Among 42 non-splenectomized patients, CR was obtained in 27 patients (64%; 95% CI 48–78) and PR in nine patients (21%; 95% CI 10–37), and thus the ORR was 86% (95% CI 71–95). No patient achieved a CR within the first three cycles of therapy.

The median follow-up was 68 months (range 2–97). Regarding the definition of FFS, 27 failures were recorded, including four treatment discontinuations for toxicity, six responses less than PR, 13 relapses or progression after obtaining PR or CR and four deaths from causes not related to lymphoma (second neoplasia [$n = 3$], splenectomy complication [$n = 1$]). For the PFS endpoint, overall 18 patients had progressive disease

Table I. Patients' characteristics and active disease criteria.

Characteristic ($n = 51$)	n	%
Male gender	27	53
Age > 60	33	65
Performance status > 1	2	4
ENS > 1	46	90
Hb < 12 g/dL	22	43
β2M > UNL*	34	81
Albumin < 3.5 g/dL*	6	13
Active disease criteria		
Hb < 10 g/dL	12	23
Plt < 100 000/mm^3	11	21
Neutrophils < 1000/mm^3	3	6
LDT < 12 months	6	12
LDH > UNL	25	49
B-symptoms	12	23
Symptomatic splenomegaly	36	71
Extrasplenic involvement	24	47
BM involvement > 50%	30	59
Stage IV	51	100
Prognostic scores		
IPI score ($n = 51$)	51	
0–2	11	22
3	25	49
4–5	15	29
IIL score ($n = 45$)		
Low-risk	13	29
Intermediate-risk	19	42
High-risk	13	29
HPLL score ($n = 51$)		
A	24	47
B	24	47
C	3	6

*Missing values: β2M $n = 9$; albumin $n = 6$.
ENS, extranodal sites including bone marrow involvement; Hb, hemoglobin; β2M, β_2-microglobulin; UNL, upper normal limit; Plt, platelets; LDT, lymphocyte doubling time; LDH, lactate dehydrogenase; Extrasplenic involvement, lymph nodes with or without extranodal sites (excluding BM); BM, bone marrow; IPI, International Prognostic Index; IIL, Intergruppo Italiano Linfoma [7]; HPLL, hemoglobin − platelet − LDH − lymph node extrahilar [26].

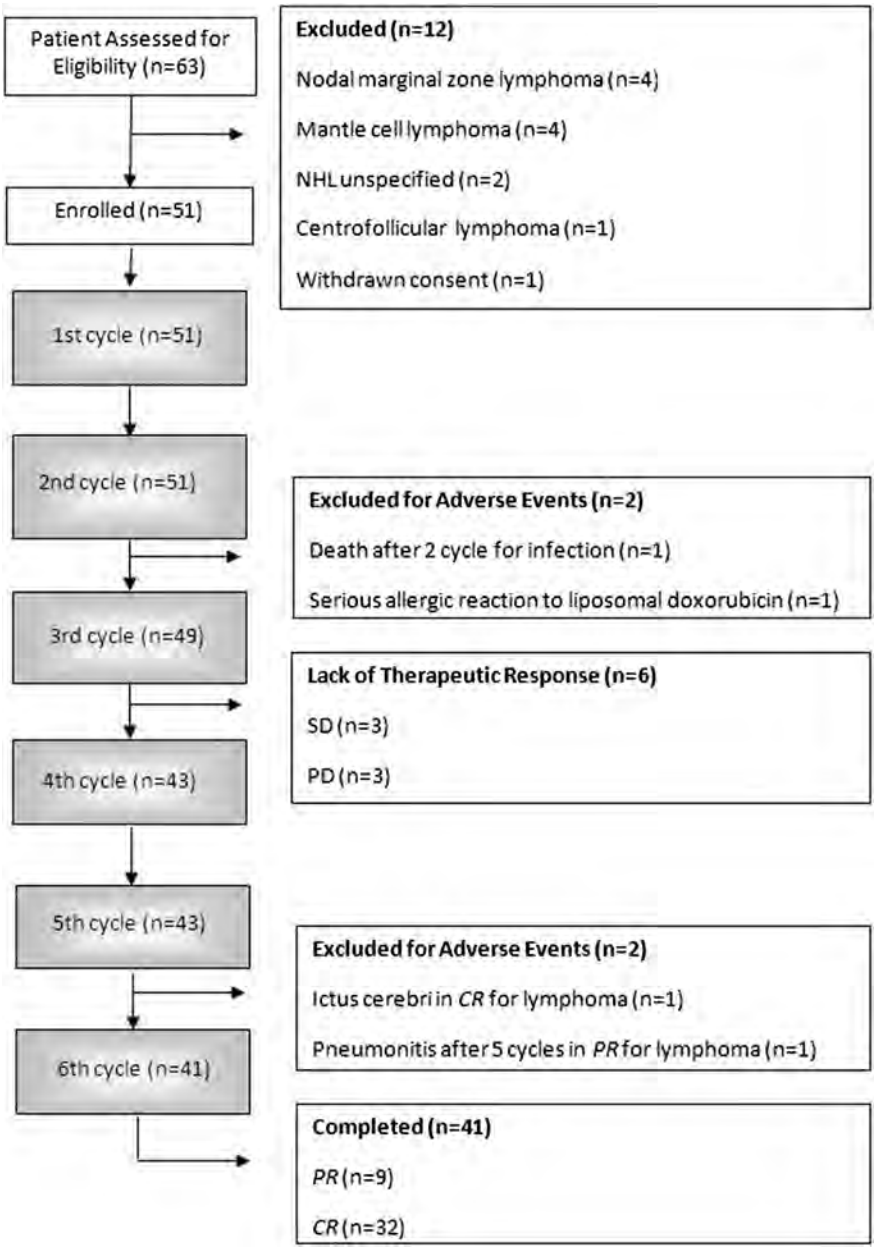

Figure 1. Flow chart of the present study, according to the Consolidated Standards of Reporting Trials (CONSORT) statement. PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

(three at the end of therapy and 15 during follow-up), and five patients died. Overall, 15 deaths were recorded in the study population. The estimated 6-year FFS, PFS and OS rates were 50% (95% CI 36–63), 54% (95% CI 40–67) and 72% (95% CI 58–83), respectively (Table II and Figure 2).

In the *post hoc* OS analysis with the two prognostic systems available, the HPLL score effectively identified patients at different risk levels (log-rank test, $p = 0.026$), but the IIL score did not show strong prognostic power (log-rank test, $p = 0.471$) (Figure 3). Notably, during the median follow-up time of 68 months (range 40–97) for surviving patients, no case of histological progression to DLBCL was observed.

Toxicity

The observed R-COMP toxicity was substantial but manageable, and mostly restricted to neutropenia (Table III and Figure 4). Thus, the median dose intensity for all drugs could be maintained up to 90% (median dose intensity, mg/m^2: 0.980, 0.977, 0.981, 0.938 and 0.982 for cyclophosphamide, vincristine, liposome-encapsulated doxorubicin, prednisone and R, respectively). Thirteen (26%) of patients developed severe (grade ≥ 3) neutropenia and four (8%) developed severe infections (grade ≥ 3). Of these, two patients died during treatment (sepsis after the second cycle and pneumonia after the third cycle) and two went off study (one after the third cycle for pseudomonas sepsis and one after the fifth cycle for pneumonia).

Non-hematological grade ≥ 3 toxicity occurred in four cases (8%) (one ictus cerebri; one R allergic reaction; one liposomal doxorubicin allergic reaction; one intestinal occlusion). Second malignancies occurred in eight cases (15%) (three myelodysplastic syndrome [MDS], one bladder cancer, one prostate cancer, one melanoma, one Hodgkin

Table II. Treatment results ($n = 51$).

	n	%	95% CI
Response to chemotherapy			
CR	33	65	50–78
PR	10	20	10–33
ORR	43	84	71–93
SD	3	6	
PD	3	6	
EW	2	3	
6-Year survival			
OS		72.5	58.0–82.7
PFS		54.3	39.6–66.9
FFS		50.5	36.0–63.3

CR, complete response; PR, partial response; ORR, overall response rate; SD, stable disease; PD, progressive disease; EW, early withdrawal; OS, overall survival; PFS, progression-free survival; FFS, failure-free survival; CI, confidence interval.

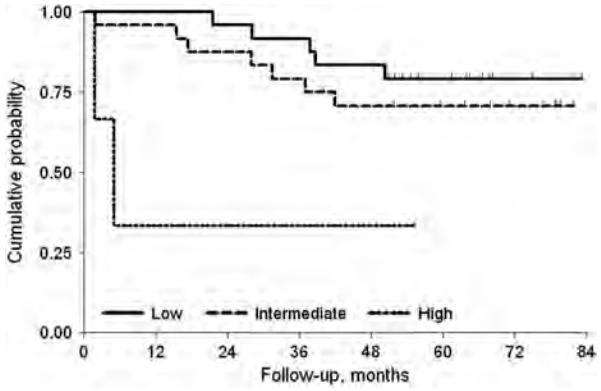

Figure 3. Overall survival stratified by HPLL score.

lymphoma and one MCL); one MDS subsequently evolved to full-blown acute myeloid leukemia. The median time between the end of treatment and the diagnosis of second malignancy was 51 months (range 23–85).

Causes of death

At the time of the analysis, 15 patients had died. The deaths were due to disease progression ($n = 6$, 40%), infection ($n = 4$, 26%; two in the course of R-COMP and two during rescue treatment after progression), second malignancy ($n = 4$, 27%) and splenectomy complication ($n = 1$, 7%). All deaths, excepted two, were recorded after the completion of R-COMP treatment.

Discussion

This trial showed that R-COMP was an effective first-line treatment for patients with symptomatic SMZL who had not received splenectomy. The ORR and CR rates were 84% and 65%, respectively.

The observed toxicity is worth highlighting, but it proved to be manageable. Indeed, the treatment was discontinued owing to toxicity in four patients and deaths related to treatment were recorded in two of these patients. In previous phase II trials in elderly patients with NHL, neutropenia and infections were the most common toxicities [22,27,28]. Accordingly, in the present study, neutropenia was the most common (26%) grade ≥ 3 toxicity, and severe infections accounted for 8% of cases. The median dose intensity was greater than 90% for all associated drugs; however, we have no data on the use of G-CSF, which was left to the clinician's judgement.

Most deaths in this study were due to causes indirectly related to the lymphoma: 27% were due to second malignancy and 27% were due to infections, two that developed in the course of R-COMP therapy and two during salvage treatment for relapsed or progressive disease.

The mortality rate may appear high for a rather indolent disease such as SMZL; nevertheless the inclusion criteria required the presence of symptomatic disease, and more than one-third of the enrolled cases had a high International Prognostic Index (IPI) and IIL score [7]. Notably, the 6-year OS of this series compares favorably to that reported in a large series of patients treated with chemotherapy ± Mabthera [19].

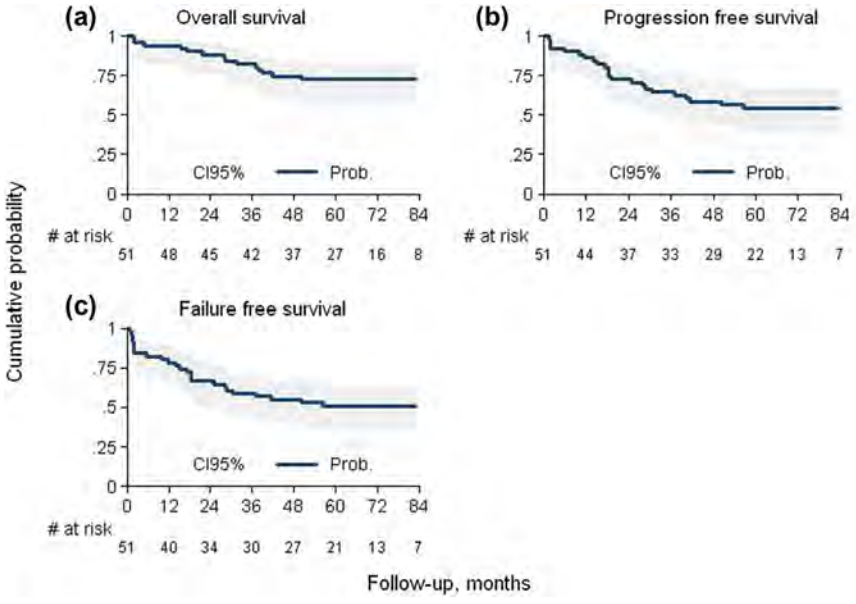

Figure 2. Kaplan–Meier analysis of the probability of (a) overall survival (OS), (b) progression-free survival (PFS) and (c) failure-free survival (FFS).

Table III. Hematologic toxicities, NCI CTCAE criteria.

	Anemia		Neutropenia		Thrombocytopenia		Infections	
Grade	*n*	%	*n*	%	*n*	%	*n*	%
0	32	62	29	57	39	76	40	78
1	14	27	6	12	5	10	3	6
2	5	10	3	6	7	14	4	8
3			7	14			2	4
4			6	12			2	4
Total	51		51		51		51	

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Regarding long-term toxicity, the overall incidence of second malignancies was markedly high (15% at 5 years). Previous studies reported a high frequency of additional cancers in patients with SMZL [8,9,11]. A multicenter, retrospective analysis on patients largely treated with systemic purine analogs reported 12 secondary cancers and a 5-year cumulative incidence rate of 18.3%; moreover, the incidences of urinary and lung malignancies were significantly higher than those expected [29].

A recent, large monocentric retrospective analysis of 100 patients who underwent splenectomy with a median follow-up of 5.15 years reported an 11% incidence of transformation to high grade NHL and two deaths secondary to epithelial cancer (one hepatocarcinoma and one lung cancer). The overall incidence of secondary neoplasia was 13% [12]. However, it was not clear whether other non-fatal neoplasia were recorded.

We would emphasize that, in the present study, we recorded three cases of secondary MDS, but no cases of histological transformation toward high-grade lymphoma (i.e. DLBCL). In the literature, the reported rates of DLBCL secondary to SMZL range between 10 and 19% with a median time to transformation of around 2 years [10,12]. Conversely, no cases of secondary MDS have been reported to date.

When this study was designed, splenectomy was considered the preferred first-line treatment for SMZL, based on heterogeneous historical series, which mostly included patients who were splenectomized for diagnostic purposes; however, data were scarce on the efficacy of systemic therapy. Subsequently, some small retrospective studies suggested that R monotherapy was very effective and could safely replace a splenectomy as the first-line treatment [16–18,30]. In these series, the reported OR and CR rates after R monotherapy were 88–100% and 31–45%, respectively. However, R monotherapy achieved CR in only 35% of treatment-naive patients without splenectomy, despite the CR in almost all patients with splenectomy. These results suggested that R had limited efficacy in clearing the lymphomatous burden provided by the spleen reservoir, and/or that the splenic environment provided resistance to the established clone. The PFS rate in a retrospective analysis of a large series of consecutive patients with a long follow-up was 75% at 5 years, which is better than that we obtained in the present study with a more aggressive and toxic treatment; however, it is worth noting, that, after four weekly doses for induction, a maintenance R dose was administered every 2 months for up to 2 years, and that any comparison of prospective with retrospective studies should be viewed cautiously. In patients without splenectomy, even better results were reported for R associated with chemotherapy, mostly purine analogs. The CR rates were 62–79%, and the PFS was 80% at 5 years [19,31]. However, it is difficult to make comparisons with retrospective monocentric studies.

Most retrospective series that evaluated SMZL treatment had a potentially severe flaw, apart from the selection bias: they usually lacked homogeneous criteria for starting treatment, which made comparisons problematic. Furthermore, particularly among patients who had not been splenectomized, without a central histological review, it is difficult to rule out the possibility that some patients with diverse diseases were included [32].

The results of the present study in patients with symptomatic SMZL without splenectomy and a median observation time of 68 months showed high levels of CR (64%), PFS (54%) and OS (72%) at 6 years, compared with results from other studies on chemoimmunotherapy. Thus, we demonstrated the efficacy and safety of a new chemoimmunotherapy protocol for SMZL.

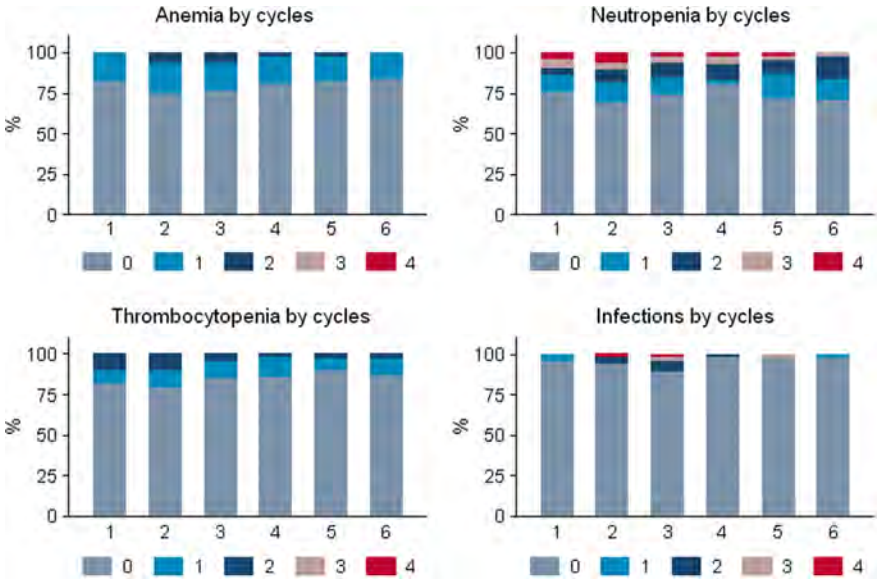

Figure 4. Distribution of hematological toxicities (CTCAE version 3.0 grade) by cycles of treatment.

A major novelty of this phase II study was the diagnostic approach adopted, which did not include a diagnostic splenectomy [14]. Indeed, in all cases, the SMZL diagnosis was based on the integration of PB and BM morphology, and phenotype. The consistency of these diagnoses was verified *ad interim* by a board of expert hematopathologists, who reported 81% concordance. Thus, despite the multicenter design of the protocol, the data confirmed that an integrated diagnostic approach is suitable for prospective trials investigating a first-line therapy.

In conclusion, R-COMP could be considered an effective therapeutic alternative for SMZL, when an association with chemoimmunotherapy is considered. The toxicity was substantial, and certainly higher than that of R monotherapy. The occurrence of MDS should be monitored. Although R-COMP achieved higher PFS than R monotherapy, at present, in our opinion, R-COMP treatment is most suited to patients with SMZL symptoms that have a documented or possible histological transformation toward a more aggressive histotype due to widespread involvement of abdominal lymph nodes or other extranodal sites, apart from the spleen and BM. An effective treatment with low toxicity remains a therapeutic need. To address this therapeutic need, another trial (BRISMA IELSG-36) is in progress, with the same setting as the present study, but with the aim of exploring the efficacy and toxicity of bendamustine combined with R.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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