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ORIGINAL ARTICLE

Rituximab, bendamustine, and lenalidomide in patients with aggressive B cell lymphoma not eligible for high-dose chemotherapy or anthracycline-based therapy: phase I results of the SAKK 38/08 trial

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Abstract This phase I trial was designed to develop a new effective and well-tolerated regimen for patients with aggressive B cell lymphoma not eligible for front-line anthracycline-based chemotherapy or aggressive second-line treatment strategies. The combination of rituximab (375 mg/m^2 on day 1), bendamustine (70 mg/m^2 on days 1 and 2), and lenalidomide was tested with a dose escalation of lenalidomide at three dose levels (10, 15, or 20 mg/day) using a 3+3 design. Courses were repeated every 4 weeks. The recommended dose was defined as one level below the dose level identifying ≥2/6 patients with a dose-limiting toxicity (DLT) during the first cycle. Thirteen patients were eligible for analysis. Median age was 77 years. WHO performance status was 0 or 1 in 12 patients. The Charlson Comorbidity Index showed relevant comorbidities in all patients. Two DLTs occurred at the second dose level (15 mg/day) within the first cycle: one patient had prolonged grade 3 neutropenia, and one patient experienced grade 4 cardiac adverse event (myocardial infarction). Additional grade 3 and 4 toxicities were as follows: neutropenia (31 %), thrombocytopenia (23 %), cardiac toxicity (31 %), fatigue (15 %), and rash (15 %). The dose of lenalidomide of 10 mg/day was recommended for a subsequent phase II in combination with rituximab 375 mg/m^2 on day 1 and bendamustine 70 mg/m^2 on days 1 and 2.

Keywords Aggressive B cell lymphoma · Relapse · Elderly · Rituximab · Bendamustine · Lenalidomide

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Introduction

Non-Hodgkin's lymphoma (NHL) has the highest incidence among patients older than 60 years of age [1, 2]. The 5-year overall survival of this elderly group of patients is 58 % following upfront treatment with the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen [3]. However, approximately 25 % of patients will not achieve complete remission or will experience relapse after R-CHOP-like treatments. A substantial proportion of these patients can be cured even in relapsed/refractory disease with intensive salvage chemotherapy regimens and autologous stem cell transplantation [4].

Pre-existing comorbidities constitute the most important factors influencing treatment regimen and treatment failure

rates, and more than half of the very elderly patients (older than 80 years) are not fit enough to receive front-line anthracycline-based standard therapy for a newly diagnosed aggressive B cell lymphoma [5–7]. Moreover, no standard therapy is available for relapsing patients if they are not eligible for intensive salvage regimens. Therefore, new efficacious and more tolerable treatment regimens are needed for elderly and frail patients with aggressive B cell lymphoma who are not candidates for intensive treatments.

We tested a three-drug regimen of rituximab, bendamustine, and lenalidomide (RBL) as a new combination for the treatment of aggressive B cell lymphoma in elderly/frail patients. Bendamustine retains activity in rituximab-refractory indolent lymphoma and in transformed indolent lymphomas [8, 9]. In patients with indolent or mantle cell lymphoma, the bendamustine–rituximab combination achieved at least comparable remission rates in a large randomized trial and led to a statistically significant longer PFS when compared with the R-CHOP standard regimen [10]. Tolerability was better with R-bendamustine than with R-CHOP [11]. Activity has also been shown in aggressive lymphoma subtypes and very elderly patients [12–15].

The rationale for adding lenalidomide to R-bendamustine is a hypothesized synergistic effect of the combination with the other two drugs. Single-agent lenalidomide has been shown to produce durable responses in patients with relapsed or refractory aggressive lymphoma [16, 17]. The combination of lenalidomide with rituximab is active in elderly patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL) with a high proportion of patients achieving a complete remission (CR) with lenalidomide maintenance [18].

Given the predictable pharmacokinetic properties of bendamustine and lenalidomide that allow for dose adjustments based on changes in renal function, this combination is thereby qualified as an appropriate treatment regimen for elderly patients with comorbidities or younger patients not suitable for a salvage treatment because of limited organ function (e.g., cardiac toxicity from previous therapy) [19]. We here report on the results of a dose-finding phase I multicenter trial examining the feasibility and tolerability of the combination of RBL in patients with aggressive B cell lymphoma not eligible for high-dose chemotherapy or anthracycline-based therapy.

Methods

Study population

The study was activated in December 2009. According to the SAKK 38/08 protocol, this analysis is based on all patients enrolled in the phase I part of the trial including the first five patients in phase II having completed the first cycle of therapy as an extension cohort.

Patients with aggressive B cell NHL relapsed/refractory disease not suitable for intensive salvage regimens or for anthracycline-based first-line chemotherapy were eligible. No specific criteria were predefined for ineligibility for intensive salvage therapy or anthracycline-based standard first-line therapy. The decision on whether patients were not considered fit enough to receive intensive salvage therapy or anthracycline-based first-line therapy was left to the treating physician. DLBCL and subtypes of DLBCL according to WHO 2008, follicular lymphoma grade 3b (FL3b) and transformed follicular lymphoma (tFL), were included.

Further patient requirements were as follows: WHO performance status of 0–2, cardiac function with ejection fraction of more than 40 %, calculated creatinine clearance >50 mL/min, and adequate liver function and blood values [20]. Patients with immunohistological evidence of bone marrow involvement ≥25 %, known CNS involvement, and unstable cardiovascular disease were excluded.

Study design

This single-arm multicenter phase I/II trial was carried out in seven Swiss cancer centers. The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices. Ethical approval was obtained from the ethics committee and institutional review board for each site, and patients provided written informed consent.

Four dose levels were predefined for phase I according to a 3+3 dose escalation design. One additional dose level (dose level −1) of three patients was allowed in the event that dose level 1 was considered too toxic. Dose finding for lenalidomide in combination with rituximab and bendamustine was performed with increasing doses of lenalidomide starting from 10 mg/day up to a maximum of 20 mg/day. At the highest dose level, an additional dose escalation for bendamustine from 70 to 90 mg/m^2 was scheduled (Table 1).

Rituximab was given at a standard dose of 375 mg/m^2 i.v. on day 1 of each cycle. Bendamustine was administered i.v. on days 1 and 2, and lenalidomide was taken orally daily for

Table 1 Dose escalation schedule

Dose level	Rituximab (mg/m^2)	Bendamustine (mg/m^2)	Lenalidomide (mg)
−1	375	70	5
1	375	70	10
2	375	70	15
3	375	70	20
4	375	90	20

21 days on a 28-day treatment cycle. Treatment was scheduled for six cycles or until the occurrence of unacceptable toxicity or progressive disease, whichever occurred first.

To assess the safety of the recommended dose (RD), five additional patients were analyzed as an extension cohort. Premedication with 1 g paracetamol and an antihistamine had to be administered 1 h before each rituximab infusion, followed by bendamustine and lenalidomide. With the aim of properly assessing hematologic toxicities, the administration of granulocyte colony-stimulating factor (G-CSF) in cycle 1 was not allowed.

Adverse events (AEs) and laboratory values were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Relationship of serious adverse events (SAEs) to the study drug was determined by the investigator and was reviewed by an independent expert group. Dose-limiting toxicities (DLTs) were assessed as possibly, probably, or definitely related to the study drug. DLT was defined as one of the following events occurring within the first cycle: therapy-related death, six or more missed doses of lenalidomide due to trial drug-related toxicity, delay of >2 weeks of cycle 2 due to trial drug-related toxicity, any grade 3 or 4 non-hematological AE related to trial treatment, neutrophils $\leq 0.5 \times 10^9$/L for ≥6 days, and platelets ≤20 or 21–50×10^9/L with major bleedings. The maximum tolerated dose (MTD) was defined as the dose level containing ≥2/6 patients with a DLT during the first cycle. The tentative RD was determined as one level below the MTD.

This study used an electronic excel-based age-adjusted Charlson Comorbidity Index (CCI) calculator that made collecting comorbidity data and calculating CCI information easier and immediately available [21]. The risk definition of comorbidities is based on the assigned relevance for diseases [22]. Three age-adjusted risk groups were defined according to the sum of the comorbidities: low risk score (2–4), intermediate risk score (5–7), and high risk score (≥8).

Statistical analysis

The primary objective of phase I was to determine the MTD (based upon first cycle DLTs) and to identify RD of the combination of rituximab, bendamustine, and lenalidomide. The number of patients that was required to establish the tentative RD in phase I ranged from 4 to 30 patients, depending on which dose level was the MTD. Together with patients from phase I, a safety analysis was performed after enrolment of five patients treated in the phase II part of this study to confirm the safety of the established RD. Categorical variables were summarized by frequencies and percentages and continuous variables by descriptive statistics. Statistical analyses were performed using SAS® 9.2.

Results

Patient characteristics

This report presents the results of the phase I analysis including a five-patient extension cohort based on data obtained from the SAKK database. A total of 14 patients were enrolled. One patient was not eligible due to inadequate blood values; thus, 13 patients remained eligible for analysis. Their main clinical characteristics are summarized in Table 2. Median age was 77 years (range 67–88); WHO performance status was 0/1 in 12 patients. CCI showed relevant comorbidities with intermediate risk score in 11 and high risk score in 2 patients. With the exception of two patients with previously untreated DLBCL, all patients had relapsed/refractory disease after R-CHOP treatment for DLBCL, tFL, or FL3b. Both tFL had refractory disease prior to study inclusion (Table 3). Median time from initial diagnosis of relapsed/refractory patients to registration was 4.89 years (range, 0.23–10.29). For eight relapsed/refractory patients, the study treatment was given as second-line treatment; the other three patients had already received two or more previous treatment lines for relapsed disease. Six relapsed/refractory patients achieved a CR, three a partial remission (PR), and one patient was progressive to previous line of treatment prior to study registration. Two patients had previously been treated with rituximab and bendamustine. Of these, one patient achieved a partial response with the RBL regimen. The second patient had only one treatment cycle and refused response evaluation. Three patients were initially treated in the pre-rituximab era with either CHOP or cyclophosphamide, vincristine, prednison (CVP) alone. Two of these patients received rituximab-based chemotherapy at the time of relapse prior to inclusion in this trial.

Treatment exposure

Five patients received only one treatment cycle due to either the occurrence of DLT ($n=2$), death ($n=1$, the cause of death remained unknown), progressive disease ($n=1$), and grade 3 cutaneous rash ($n=1$). Four patients received more than one cycle but not the complete planned treatment of six courses. Reasons for early stopping were as follows: progressive disease, patient refusal, and cutaneous toxicity. Four patients completed all six treatment cycles (Table 3). Discontinuation of lenalidomide occurred twice with a dose reduction of lenalidomide from 15 to 10 mg, as prescribed by the protocol, whereas no dose reductions or discontinuations of intravenous treatment were necessary.

MTD and RD for subsequent studies

A total of eight patients were analyzed for DLT occurring during cycle 1 of phase I. The first cohort of three patients

Table 2 Patient characteristics

	Overall (*N*=13)
Sex, *n* (%)	
F	5 (38)
M	8 (62)
Age (years), median (min, max)	77.0 (67.0, 88.0)
WHO performance status, *n* (%)	
0	7 (54)
1	5 (38)
2	1 (8)
Charlson Comorbidity Index score, *n* (%)	
5	4 (31)
6	5 (38)
7	2 (15)
8	1 (8)
10	1 (8)
Stage (Ann Arbor staging), *n* (%)	
Stage I	2 (15)
Stage II	4 (31)
Stage III	5 (38)
Stage IV	2 (15)
B symptoms, *n* (%)	
No	11 (85)
Yes	2 (15)
Number of extranodal sites involved, *n* (%)	
0	4 (31)
1	6 (46)
2	1 (8)
4	2 (15)
IPI, *n* (%)	
1	4 (31)
2	6 (46)
3	3 (23)
Primary diagnosis	
DLBCL	9 (69)
tFL	2 (15)
FL3b	2 (15)
Prior treatments[a]	
R-CHOP	10 (77)
CHOP	2 (15)
R-CVP	2 (15)
CVP	1 (8)
R-bendamustine	2 (15)
Radiotherapy	4 (31)
Number of prior chemotherapy regimens, *n* (%)	
0	2 (15)
1	8 (62)
2	1 (8)
3	1 (8)
4	1 (8)

IPI International Prognostic Index [32]

[a] A patient may have received several prior treatments

with a daily dose of 10 mg lenalidomide of phase I dose escalation showed no DLT. In the second cohort with 15 mg lenalidomide, the occurrence of a delay of cycle 2 due to prolonged grade 3 neutropenia defined the first DLT. With the extension of the cohort by another three patients, an ischemic cardiac event with elevated troponin occurred at the same dose level, defining a serious non-hematologic AE. This last event was rated possibly related to trial treatment and thereby judged as the second DLT according to protocol. As a consequence, the lenalidomide dose for patient number 8 was reduced from dose level (DL) 2 to DL 1 on day 9 of cycle 1 (i.e., 15 mg for 8 days and 10 mg for 13 days). Thus, the recommended daily dose for a subsequent phase II was established as oral lenalidomide 10 mg on days 1–21 in combination with rituximab 375 mg/m^2 on day 1 and bendamustine 70 mg/m^2 on days 1 and 2 every 4 weeks.

Response to treatment

Two out of the eight patients in the phase I part experienced a progressive disease. Five patients were included in the extension phase part: one patient had an unconfirmed CR and was in remission at the follow-up visit 9 months after inclusion into the trial. Two patients achieved a PR. One patient had progressive disease after 1 cycle, and one patient died of unknown cause after a first cycle of study treatment before any evaluation of response was performed.

Safety analysis

Safety and toxicity analysis was performed for all treatment cycles of the first 13 patients (Table 4). Eight patients experienced at least one serious grade 2, 3, or 4 AE during treatment.

Of the five patients in the extension cohort, one patient died of unknown cause at the end of cycle 1; autopsy was not performed. This patient experienced grade 3 fatigue, possibly related to the study treatment, but grade 2 fatigue was already present at baseline. A second patient had more than six missed doses of lenalidomide within the first cycle due to rash and pruritus (grade 3). One further patient experienced a grade 3 supraventricular arrhythmia during the first cycle.

In summary, the most common grade 3 and 4 AEs related to trial treatment over all administered cycles were neutropenia (*n*=4, 31 %) with febrile neutropenia in a single patient and thrombocytopenia (*n*=3, 23 %). The following grade 3 and 4 non-hematologic AEs were the most often experienced: cardiac events (*n*=4, 31 %), rash (*n*=2, 15 %), and fatigue (*n*=2, 15 %).

A second patient died from pneumonia 36 days after the last drug administration in cycle 3. Some of the AEs (sensory neuropathy, dysphagia, anorexia, arachnoiditis, muscle weakness, headache) were rated unrelated to treatment by the responsible physician. All of the mentioned unrelated AEs

Table 3 Summary of treatment by patient

Patient	Diagnosis	Total cycles	Dose level	Reasons for stopping treatment	DLT
1	DLBCL, r	6	DL 1	6 cycles completed	
2	tFL, R	4	DL 1	Progressive disease	
3	DLBCL, r	6	DL 1	6 cycles completed	
4	FL3b, r	6	DL 2	6 cycles completed	
5	DLBCL, r	2	DL 2	Progressive disease	
6	tFL, R	1	DL 2	DLT	Prolonged neutropenia
7	DLBCL, r	1	DL 2	DLT	Cardiac event (myocardial infarction)
8	DLBCL	6	DL 2/ DL 1	6 cycles completed	
9	DLBCL	1	RD	Death	
10	DLBCL, r	1	RD	Progressive disease	
11	FL3b, r	5	RD	Patient refusal	
12	DLBCL, r	1	RD	Unacceptable toxicity: grade 3 rash	
13	DLBCL, r	3	RD	Unacceptable toxicity: various AE led to delay more than 2 weeks	

DLBCL diffuse large B cell lymphoma primary diagnosis, *r* relapsed, *R* refractory to previous treatment, *tFL* transformed follicular lymphoma, *FL3b* follicular lymphoma 3b relapsed/refractory, *DLT* dose-limiting toxicity, *RD* recommended dose

were grade 3 with the exception of dysphagia rated as grade 4 toxicity. Importantly many of the AEs were already present at baseline.

Discussion

Most often (elderly) patients with aggressive lymphoma and significant comorbidities cannot be treated with a curative intent, neither front line nor at relapse, and the outcome of patients not suitable for intensive regimens is poor with a median survival of less than 6 months [3, 6, 23]. For these patients, an ideal treatment regimen would provide high anti-lymphoma efficacy while maintaining an acceptable quality of life.

Based on the potential synergistic effect of lenalidomide in combination with rituximab, we designed the RBL regimen (rituximab, bendamustine, and lenalidomide) to possibly provide a new active and tolerable regimen for elderly and frail patients [24]. An acceptable toxicity profile of the rituximab and bendamustine combination in old patients (median age of 85 years) with aggressive lymphoma was already reported by a small German phase II study, which also showed a good clinical activity (complete remission rate 54 %) with bendamustine given at 120 mg/m^2/day on two consecutive days [18].

Despite a much lower bendamustine dose in comparison with the abovementioned German study, our phase I trial of the RBL combination established a lenalidomide dose (10 mg/day) much lower than the usual monotherapy dose of 25 mg/day [25]. In line with our results, a phase I/II trial of relapsed/refractory multiple myeloma (MM) patients established a recommended bendamustine dose of 75 mg/m^2/day on two consecutive days in combination with lenalidomide 10 mg/day for 21 days every 4 weeks [26].

We observed two DLTs: one hematologic and one non-hematologic AE. The most common and expected AEs for the total trial population were neutropenia, grade 3 and 4 thrombocytopenia, and cardiac events. No hematologic grade 3 toxicities occurred with lenalidomide 10 mg/day during the first cycle neither in phase I or in the first five patients of phase II. However, in later treatment cycles, more severe neutropenia occurred leading to treatment delays and the use of G-CSF. Hematologic toxicities were also the most common grade 3 and 4 AEs occurring in the abovementioned myeloma trial [26].

A variety of non-hematologic AEs were mostly related to pre-existing comorbidities; some of them difficult to be discriminated from study drug-related events. This was especially true for constitutional symptoms like fatigue. The RBL seems to cause more skin-related toxicity than reported for each drug alone in lymphoma patients.

Grade 3 and 4 cardiac events were the most important non-hematologic AEs in our study. The cause of death of an 87-year-old woman after the first cycle during phase II remains unexplained as no preceding symptoms with the exception of fatigue were reported. Although the cause of death remains open, a sudden cardiovascular event is the most probable explanation. The number of cardiac events in this frail patient group is not surprising. The risk of cardiovascular death or events related to atherosclerotic disease is markedly increased after 75 years of age [27]. Grade 3 cardiac arrhythmia and a prolonged QT interval were the only reported cardiac events for the same drug combination in relapsed/refractory MM patients [26]. A much lower

Table 4 Summary of grade 3, 4, or 5 adverse events including DLT (after baseline)

		Overall (*N*=13)			
AE category	AE	Grade 3 *n* (%)	Grade 4 *n* (%)	Grade 5 *n* (%)	Total *n* (%)
Blood/bone marrow	Hemoglobin	1 (8)			1 (8)
	Leukocytes	1 (8)			1 (8)
	Neutrophils	1 (8)	2 (15)		3 (23)
	Platelets	2 (15)			2 (15)
	Platelets[a]	1 (8)			1 (8)
Cardiac arrhythmia	Atrial fibrillation[a]	1 (8)			1 (8)
	Atrial flutter	1 (8)			1 (8)
	Sinus tachycardia	1 (8)			1 (8)
Cardiac general	Elevated troponin[a]		1 (8)		1 (8)
Constitutional symptoms	Fatigue[a]	2 (15)			2 (15)
Death	Death NOS[b]			1 (8)	1 (8)
Dermatology/skin	Pruritus	1 (8)			1 (8)
	Rash	2 (15)			2 (15)
Gastrointestinal	Anorexia[b, a]	1 (8)			1 (8)
	Dysphagia[b, a]		1 (8)		1 (8)
	Nausea	1 (8)			1 (8)
Infection	Febrile neutropenia	1 (8)			1 (8)
	Pneumonia	1 (8)			1 (8)
	Urinary infection	1 (8)			1 (8)
Musculoskeletal/soft tissue	Muscle weakness of lower extremity[b]	1 (8)			1 (8)
Neurology	Arachnoiditis[b]	1 (8)			1 (8)
	Sensory neuropathy[b, a]	1 (8)			1 (8)
Pain	Sternal, thoracic	1 (8)			1 (8)
	Headache[b]	1 (8)			1 (8)
Pulmonary/upper respiratory	Pneumonia			1 (8)	1 (8)

[a] AE already present at baseline

[b] AE unrelated to trial treatment (relationship assessed as unrelated or unlikely)

median age of 63 years in the MM study compared to 77 years in our trial might explain the difference in frequency. Therefore, the arrhythmogenic potential of the regimen has to be carefully observed in the ongoing phase II trial.

A second death was recorded in our study due to pneumonia. A direct causality of the study treatment with the fatal event could not be established nor excluded, but it is plausible because of the immunosuppressive effect of the treatment. Nevertheless, a fatal infection is a well-known risk of cancer chemotherapy in elderly frail patients, which should be weighted considering the expected benefit of treatment of chemosensitive (and potentially curable) diseases such as B cell lymphomas. In this study, we evaluated the RBL regimen in patients not eligible for either anthracycline-based front-line chemotherapy or intensive salvage regimens. WHO performance status of the majority of our patients was only minimally impaired, but the CCI risk score was indicative of additional relevant comorbidities for most patients (Table 2). The CCI provides a summary score of burden of illness and has predictive value of cancer treatment tolerance [28–31]. Serious adverse events in this predefined comorbid age group are much more likely and expected than in trials with a younger patient population.

According to protocol, formal assessment of response was not scheduled for phase I patients. Nevertheless, objective remissions were observed in three out of four evaluable patients (one CR and two PR) of the extension cohort. Based on these results, further accrual of the ongoing phase II trial is warranted.

Conclusion

A dose of lenalidomide 10 mg daily on days 1–21 in combination with rituximab 375 mg/m^2 on day 1 and bendamustine 70 mg/m^2/day on days 1 and 2 has shown to be feasible in this

frail and mostly pretreated patients. The safety of the regimen has to be addressed further in the currently ongoing phase II part of the trial. Special attention will be given to the selection of patients with cardiac risk factors and to supportive care in this elderly patient population.

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Conflict of interest EZ has participation in the Roche and Celgene advisory boards. All other authors declare no conflict of interest.

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