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Successful Alemtuzumab Retreatment in Progressive B-Cell Chronic Lymphocytic Leukemia: A Multicenter Survey in 30 Patients

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ABSTRACT

Although retreatment with alemtuzumab in relapsing B-cell chronic lymphocytic leukemia (CLL) may be beneficial, there has thus far been no thorough analysis available on this topic. Data were collected from 30 chemotherapy-pretreated patients with progressive CLL who had received alemtuzumab twice in consecutive, distinct therapy lines. The median dose of alemtuzumab retreatment was 402 mg (range, 43 – 1090 mg). Retreatment with alemtuzumab induced an overall response rate of 47%. From the start of alemtuzumab retreatment, median progression-free survival (PFS) and overall survival (OS) were 6.3 months and 20.0 months, respectively. Response rates, PFS and OS upon alemtuzumab retreatment were correlated with response to initial alemtuzumab treatment, the time interval between the initial course of alemtuzumab and start of retreatment, and the hemoglobin concentration prior to retreatment. Reported toxicities from 24 cases included infections (50%), febrile reactions upon alemtuzumab administration (38%), exanthema (21%) and grade 4 neutropenia (13%) and thrombocytopenia (17%). We conclude that alemtuzumab retreatment represents an effective and tolerable therapeutic option for selected patients with CLL.

Keywords: alemtuzumab, retreatment, chronic lymphocytic leukemia, CLL

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Introduction

Chronic lymphocytic leukemia (CLL) can be treated with various therapies in a sequential manner. The selection of standard therapies depends on patient characteristics and disease features. For younger (<60) and physically fit patients, a combination of fludarabine, cyclophosphamid and rituximab (FCR regimen) has proven highly effective as first- and second line treatment option [1, 2], whereas for elderly and frail patients, chlorambucil is still a good choice [3]. For CLL patients with 17p deletion, alemtuzumab-based regimens are recommended as first line therapy [4, 5]. In addition, treatment with alemtuzumab is an established option for salvage therapy, particularly for patients who have failed alkylating agents and fludarabine. Alemtuzumab (MabCampath®, Genzyme) is a humanized monoclonal antibody that targets the CD52 cell surface glycoprotein, which is abundantly expressed on normal and malignant B- and T-lymphocytes. The therapeutic benefit of alemtuzumab has been demonstrated in phase II studies with pretreated CLL patients [6-11], in a phase II study with chemo-naïve CLL patients [12], and was confirmed in a phase III trial (CAM307) with chemo-naïve CLL patients [4]. Routine use of alemtuzumab in clinical practice is feasible and relatively safe, as shown by the retrospective reports on pretreated CLL patients from our Austrian-Czech CLL Alemtuzumab Registry [13-15].

Currently, there is little data on how to treat CLL patients with disease progression after alemtuzumab treatment. In our previous Alemtuzumab Registry report, we noted that a remarkable number of patients with progressive disease having received a first course of alemtuzumab were fit enough to receive a second course of alemtuzumab. Intriguingly, long lasting responses were observed among patients retreated with alemtuzumab. To date, there are no clinical trials published on the efficacy and safety of alemtuzumab retreatment. Only single case reports [7, 16, 17] and series of six [18] and seven CLL patients [19] have been published indicating clinical benefits from alemtuzumab retreatment.

In this survey, we retrospectively investigated the efficacy and toxicity of alemtuzumab retreatment in 30 patients with CLL. All cases had received a second course of alemtuzumab as monotherapy due to progressive disease (PD) after a treatment-free interval following the first alemtuzumab treatment. Patients'

characteristics and clinical features predicting clinical benefit of alemtuzumab retreatment were analysed.

Patients and Methods

Patients

This retrospective survey was conducted retrieving clinical data from a large data base of 196 pretreated patients with CLL who received alemtuzumab as monotherapy. The kind and sequence of prior therapy regimens is detailed in **Table 2**. Thirty patients selected for this analysis had received a second course of alemtuzumab as the next therapy ("alemtuzumab retreatment"). The indication to re-induce alemtuzumab was considered by the treating physician; arguments for choosing alemtuzumab rechallenge might have been lasting response upon alemtuzumab, good tolerability and massive pre-treatments with chemotherapy **(Table 2).** The data set included patient characteristics, pretreatment modalities, cumulative doses of alemtuzumab, response, reported toxicities and disease course. Data were collected from 16 clinical centers in Austria, one hospital in South Tyrol (Italy), and a center in Brno (Czech Republic). In this survey, alemtuzumab retreatment was initiated between May 15, 2002 and December 27, 2007. Final follow-up data available for this analysis were obtained on May 25, 2010. The median observation time for this patient cohort was 20.9 months. Approval of the survey was obtained from the Ethics Committee at the Medical University of Innsbruck.

Treatment

Usually, the alemtuzumab dose was escalated during the first week of therapy by intravenous (IV) administration of 3 mg on day 1, 10 mg on day 2, and 30 mg on day 3. Subsequent doses of 30 mg were administered ordinarily three times per week for a projected 12 weeks, either intravenously (IV) (n = 5) or subcutaneously (SC) (n = 22). In 3 cases, mode of application was not reported. Policies regarding dosages of

alemtuzumab varied widely and were left to the discretion of clinicians from participating centers. Anti-infective prophylaxis, with valacyclovir and trimethoprim-sulfamethoxazole, was given in accordance with accepted guidelines [20].

Response Evaluation

Patients who received at least one dose of alemtuzumab for retreatment were considered evaluable for safety and efficacy. Response or disease progression was evaluated according to the National Cancer Institute Working Group (NCI-WG) criteria [21] immediately after the last alemtuzumab administration, 2 months after the last antibody administration, and subsequently, in case of a delayed response. For documentation of CR, PR, or stable disease (SD), the clinical benefit had to persist for at least 2 months. PFS was defined as time from first dose of alemtuzumab retreatment to disease progression or death, whichever occurred first. OS was measured from initiation of alemtuzumab retreatment.

Statistical Considerations

Comparison of response rates between patient subgroups (based on cytogenetic categories and other baseline characteristics prior to alemtuzumab) was carried out using Pearson's chi-square test. Event-related data (PFS and OS) were estimated using the Kaplan-Meier method, and comparison of outcomes between categorical subgroups was made using the log-rank test. Univariate analysis was performed to determine correlations between baseline characteristics and PFS or OS. The significance level was set at $P < 0.05$, in two-sided tests.

Results

Patient Characteristics

Out of 196 patients followed in our registry, who had been treated first-line with chemotherapy and later with alemtuzumab in second or higher line, 30 patients (15%) received retreatment with single-agent alemtuzumab and were therefore included in this study. Importantly, between the two lines of alemtuzumab therapy, no other CLL treatment was administered. Patient demographics, baseline characteristics and therapy modalities at the start of alemtuzumab retreatment are detailed in **Table 1**. For all individual cases, the cumulative alemtuzumab doses, treatment responses and time intervals between both alemtuzumab series are detailed in **Table 2.** Briefly, 22 patients were male (73%), and their median age was 66 years (range 50 – 81 years). The majority of the cases (63%) were refractory towards fludarabine, and presented with stage Rai 4 (53%). The median number of previous treatment lines (including the initial alemtuzumab course) was 4 (range, 2 - 12). The median interval between the last dose of alemtuzumab course I and start of alemtuzumab course II was 10.9 months (range, 0.9 - 39.6 months). For the 30 patients, the median dose of alemtuzumab course I was 552 mg (range 123 – 1093 mg) and in course II, 402 mg (range, 43 – 1090 mg). Various clinical parameters with potential impact on the results of alemtuzumab retreatment with respect to response, clinical benefit, PFS and OS were tested for their predictive value **(Table 1)**. Results of this data analysis are presented in **Table 3.**

Response upon alemtuzumab retreatment

Individual responses upon alemtuzumab treatment I and II are summarized in **Table 2.** Briefly, 14 patients (47%) achieved a PR by alemtuzumab retreatment. Six patients (20%) manifested SD and 9 patients (30%) PD. One patient was not evualuable for response since he died during alemtuzumab retreatment for unknown reasons. Notably, 11 out of 13 patients (85%) who responded to the first alemtuzumab course responded again to the second course. The remaining two patients showed long-lasting SD (with PR at the blood level but persistent splenomegaly). Of note, 3 out of 11 patients (27%) with SD upon alemtuzumab course I showed PR upon alemtuzumab course II. Six out of six patients (100%) who were retreated with alemtuzumab although having progressed during or shortly after the first alemtuzumab course again experienced PD **(Tables 2 and 3).** Response to

alemtuzumab retreatment was correlated with the following characteristics at start of retreatment: Rai stage, presence or absence of bulky lymphadenopathy, peripheral blood leukocyte count, hemoglobin level, response to the initial alemtuzumab course, and the time interval between the alemtuzumab courses **(Table 3).** In this case series, response to alemtuzumab retreatment was not dependent on gender, age, platelet count or $ß_2$-microglobulin level, and most remarkably not on cytogenetic risk category, number of prior therapies, and refractoriness toward fludarabine. Regarding cases categorized by cytogenetic risk (n = 20), response to alemtuzumab retreatment was achieved in 1/2 (50%), 5/7 (71%), 0/3 (0%), 1/3 (33%) and 2/5 (40%) of patients with 13q deletion, normal interphase karyotype, trisomy 12, 11q deletion, and 17p deletion, respectively.

Progression-free survival after alemtuzumab retreatment

Disease progression of CLL was documented at the time when the first signs of PD were recognized. During the follow-up period of this survey, all patients with alemtuzumab retreatment progressed, with the exception of one who was censored due to early death (see above). The median PFS after start of alemtuzumab retreatment was 6.3 months (range, 0.9 months to 26.9 months) **(Figure 1).** Short PFS was related to the following clinical characterstics at start of alemtuzumab retreatment **(Table 3)**: higher age; presence of anemia **(Figure 2A)** and bulky lymphadenopathy; lack of response upon initial alemtuzumab therapy, and a short time interval between the finish of the initial alemtuzumab therapy and start of alemtuzumab retreatment **(Figure 2B)**. As expected, PFS was significantly associated with the cumulative alemtuzumab dose applied and the clinical response achieved **(Table 3).**

Next, we investigated whether PFS, after starting alemtuzumab course I and II, differed when calculated for the cohort of these 30 patients. The median PFS after alemtuzumab course I was 8.9 months and after course II still 6.3 months. (p = 0.150) **(Figure 1).** In the subset of responders (n = 13) to the initial alemtuzumab course **(Table 2)**, median PFS was 9.4 months after alemtuzumab course I and 11.9

months after course II (P = 0.312). However, also non-responders to alemtuzumab course I (n = 17) benefited with a median PFS of 7.5 months, although this patient group showed a PFS of only of 3.3 months upon alemtuzumab retreatment (P = 0.002).

Overall survival after alemtuzumab retreatment

Median OS after initiation of alemtuzumab retreatment was 20.0 months for the total cohort of 30 CLL patients. Poor OS was associated with following clinical parameters present at start of alemtuzumab retreatment: higher age, presence of bulky lymphadenopathy, presence of anemia, lack of response upon initial alemtuzumab therapy; and short time interval between the alemtuzumab courses **(Table 3).** On the contrary, an improved OS was seen in responders to alemtuzumab retreatment.

Disease Progression

Patients with disease progression during or shortly after alemtuzumab therapy presented primarily with increasing peripheral blood lymphocyte counts (n=16; 53%), progressive lymphadenopathy (n=7; 23%), increasing splenomegaly (n=2; 7%), and other clinical or laboratory features (rising LDH, cachexia, or other non specified signs) (n= 5; 17%).

Toxicity

Data on toxicities upon alemtuzumab retreatment were available from 24 cases. Two patients experienced no side effects. Frequently documented toxicities were, in falling order: infections (n = 12 [50%]; including fever of unknown origin [n=7], sinusitis [n=2], pneumonia [n=1], endocarditis [n=1] and enteritis [n=1]); febrile reaction with shaking chills during or shortly after alemtuzumab administration (n = 9 [38%]), and exanthema (n = 5 [21%]). Thrombocytopenia and neutropenia of grade IV were observed in 4 (17%) and 3 cases (13%), respectively. Of note, severe

thrombocytopenia and neutropenia was comparably low also during first course of alemtuzumab in these 24 patients (thrombocytopenia grade IV, n = 3 [13%]; neutropenia grade IV, n = 2 [8%]). One patient died shortly after start of alemtuzumab retreatment, and the cause remains unknown.

CLL treatment following alemtuzumab retreatment

Twenty-two of the thirty cases received one or more further systemic therapies due to progressive disease after alemtuzumab retreatment **(Table 2).** The following therapies were chosen: a third course of alemtuzumab in 8 patients, of whom 6 had a PR to the second alemtuzumab therapy; rituximab-containing chemo-immuno therapy (n = 8); rituximab monotherapy (n = 2); chemotherapy (n = 3); and dexamethasone plus rituximab (n = 1). In the 8 patients receiving a third alemtuzumab therapy, a PR was achieved in one and SD in two cases. Alemtuzumab administration was cessated in one case due to septicemia **(Table 2).** One patient received combination therapy with cyclophosphamide, fludarabine, alemtuzumab and rituximab and achieved an ongoing CR.

Discussion

In our previous retrospective reports [13-15], we demonstrated that routine use of alemtuzumab in CLL patients was beneficial and safe, in line with prospective clinical studies [6-12]. Interestingly, it became evident that a considerable portion of patients received alemtuzumab retratment subsequently. A prospective clinical study addressing the role of alemtuzumab retreatment in CLL is unlikely to be performed in the foreseeable future. Thus, we aimed at investigating the utility of alemtuzumab retreatment in retrospect and at identifying factors that can be used for adequate patient selection.

Who were the patients subjected to alemtuzumab rechallenge? Most likely those in whom a benefit could be expected, e.g. due to response upon prior alemtuzumab, or because other therapy options were not available, e.g. due to massive pretreatment

(Table 2). For the physicians using alemtuzumab retreatment, another pro-argument might have been good tolerability during first course of alemtuzumab; indeed, in our series the rate of grade IV hematoxicity was definitely low in both first and second course of alemtuzumab, when compared to the literature [6, 9, 10] and to the whole series of our CLL/alemtuzumab registry (with grade IV neutropenia and thrombocytopenia of 33% and 19%, respectively [14]). Similarly, Hui et al. observed low hematological toxicity in the 6 patients who received a second course of alemtuzumab [18].

Thus far, the topic of alemtuzumab retreatment has not been systematically investigated. Egyed et al. presented a patient with CLL with 11q deletion who meanwhile had received five courses of alemtuzumab within a five-year interval and had responded well to each course [17]. Thieblement et al. presented a case series from a total of 17 patients with CLL relapsing after alemtuzumab, seven of whom received alemtuzumab retreatment. The median interval between the two alemtuzumab courses was 10 months. Within the first month of retreatment, normalization of blood lymphocytosis was observed in all cases, and four patients had a response of lymphadenopathies and splenomegaly subsequently. Median time to progression was 5.8 months [19]. Hui et al. documented 6 patients who received alemtuzumab retreatement. Among those, two achieved PR and three SD [18].

For T-PLL, alemtuzumab is considered a standard therapy option for first and following therapy lines. In T-PLL, alemtuzumab retreatment dosing and response have been studied retrospectively [22]. The authors found that 13 of 39 patients with T-PLL treated initially with alemtuzumab received alemtuzumab retreatment, and the median dose of retreatment was 263 mg (range, 40 mg - 1325 mg). Notably, six patients responded (46%) to the second alemtuzumab course, and response to retreatment was seen only in patients who had achieved a complete response upon first alemtuzumab treatment.

In our study, a quite favourable response rate of 47% upon alemtuzumab retreatment was observed. Most important, it was possible to identify factors predicting responsiveness to alemtuzumab retreatment **(Table 3)**. Clinically relevant is the finding that presence of anemia at start of alemtuzumab retreatment is clearly indicating inferior outcome, corresponding to our observation that anemia is an independent risk factor of inferior outcome at first course of alemtuzumab treatment [13, 15]. Obviously, factors predictive of response to alemtuzumab retreatment

correspond closely with favourable PFS and OS after start of alemtuzumab retreatment **(Table 3).** This data compares well with results achieved with retreatment of CLL using purine analogs [23, 24]; of indolent lymphoma using rituximab [25]; of myeloma using bortezomib [26, 27], and of solid tumors such as ovarian [28] and lung cancer [29] using platinum-based chemotherapy. There is strong evidence from retreatments with various agents in different maligancies that the response upon initial treatment and the interval between initial treatment and retreatment were predictive for both clinical benefit and disease outcome [23-29].

In conclusion, our results from this retrospective survey corroborate and expand preliminary data indicating that for carefully selected cases with relapsing or progressive CLL, alemtuzumab retreatment provides a valid therapeutic option. Notably, recent guidelines on the routine use of alemtuzumab in CLL established by an international panel of experts underscore the option of alemtuzumab retreatment [20], based on recently presented, preliminary data from our study [30].

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Table 1. Patient demographics and baseline disease characteristics at alemtuzumab retreatment (n = 30)

Characteristics	N	%
Median age (range) in years	66 (50 to 81)	
Male	22	67
Rai stage		
0-I	4	13
II	9	30
III	1	3
IV	16	53
Response to prior fludarabine		
Refractory	19	63
Sensitive	6	20
Unknown	3	10
No prior fludarabine	2	7
Median number of prior therapies (range)	4 (2 to 12)	
Median leukocyte count (range); G/L, n = 29	49 (3 to 304)	
Median hemoglobin (range), g/dL; n = 28	12.2 (7.9 to 15.7)	
Median thrombocyte count (range), G/L; n = 29	97 (11 to 267)	
Median serum levels of β_2-microglobulin (range), mg/L; n = 14	4.4 (2.4 to 8.1)	
Splenomegaly		
<18 cm	16	53
≥18 cm	11	37
Not reported	3	10
Lymphadenopathy		
None or <5 cm	16	53
≥5 cm	11	37
Not reported	3	10
Cytogenetic categories*, n = 20		
13q deletion (as sole abnormality)	2	10
Normal interphase cytogenetics	7	35
Trisomy 12	3	15
11q deletion	3	15
17p deletion	5	25
Median interval between alemtuzumab courses I and II in months	10.9 (0.9 to 39.6).	

*according to the hierarchical model by Döhner et al. [31].

Table 2. Individual patients' characteristics, alemtuzumab dosing, treatment-free intervals, and responses in CLL patients treated with alemtuzumab (n = 30)

Pat.	Age*/Sex	Year diagn.	No. prior ther.	Kind of prior therapies†	Dose 1st course A (mg)	Resp I	Interval betw. A courses (d)	Dose A re-treatment (mg)	Resp II	Subsequ. Th.	Response subsequent Therapy
S.M.	73/W	1999	2	Clb; F	803	CR	590	180	PR	Alem	PR
S.A.	81/W	1993	5	Clb; F(2x); RCD; CHOP	223	PR	315	173	PR	Alem	PD
G.M.	66/W	2001	1	F	246	PR	863	223	PR	Alem	NE
D.G.	80/M	2004	1	Clb	793	PR	345	NK	PR	RCD	CR
S.R.	63/M	1992	7	Clb; F; CHOP; IMVP16+Dex; PCR; DHAP; Nav+Dex	79	PR	514	343	PR	Alem	PD
K.L.	51/M	2006	1	FCR	316	PR	140	463	PR	R+Dex	PR
W.A.	50/W	1999	3	CHOP; F; HD-C	773	PR	445	600	PR	FCR	PR
K.W.	64/M	2001	3	F; Clb; R-CHOP	303	PR	397	610	PR	R-B	PR
P.F.	62/M	1997	2	COP; F	596	PR	358	723	PR	FCR	PR
D.F.	65/M	2005	1	FC	1033	PR	432	753	PR	none	-
K.F.	64/M	2000	2	F; CHOP	508	PR	675	993	PR	CFAR	CR
P.N.	63/M	2000	2	F; COP	943	PR	697	471	SD	R	SD
F.J.	67/M	2001	2	F(2x)	236	PR	74	283	SD	R-CHOP	NE
B.E.	66/M	1996	4	Clb(3x); F	343	SD	150	133	SD	R-CEOP	NE‡
D.E.	76/W	1994	2	F; COP	123	SD	487	133	PR	Clb	SD
G.J.	67/M	1999	3	COP; F; CHOP	713	SD	309	900	PR	Alem	SD
D.V.	62/M	1990	3	COP; Clb; F	763	SD	264	1000	PR	Alem	PD
R.E.	77/M	2001	2	F(2x)	373	SD	123	270	SD	Alem	SD
A.S.	54/M	2001	1	F	656	SD	518	873	SD	unknown‡	-
R.G.	61/M	1997	3	Clb; COP; F	1093	SD	163	1020	SD	none	-
Z.M.	69/W	1988	4	COP; F; COP; R	386	SD	320	253	PD	FC	PD
T.K.	68/M	1990	7	COP; FMD; FC; CHOP; FCM; Clb; R-COP	959	SD	361	413	PD	none	
K.E.	71/M	1999	3	Clb; F; R-CHOP	233	SD	1209	427	PD	R	PD
K.H.	70/M	2004	1	Clb	533	SD	980	43	NE	none	-
A.J.	71/M	1990	5	F; COP; Clb; C+Pred; F	570	PD	120	NK	PD	R-CEOP	PD
M.A.	79/W	1993	4	COP; F; COP; Clb	793	PD	73	90	PD	none	-
B.R.	71/W	1998	5	Clb; COP; CHOP; RT; FM	393	PD	225	158	PD	none	-
L.H.	75/M	1998	10	CEOP; F; Nav (3x); Clb+P; COPP; M; R; C+R	343	PD	27	240	PD	Alem	PD
H.F.	62/M	1996	11	Clb; COP(4x); F(3x); VAD; HAM; R	433	PD	156	390	PD	none	-
S.F.	62/M	1995	10	Clb; F; CHOP; F(2x); R; FC(2x); IMVP16; 2CDA	813	PD	52	1090	PD	FC	PD

*at the time of alemtuzumab retreatment
†sequence of chemotherapy lines (see abbreviations below); number in parentheses denotes that the indicated regimen was applied repeatedly in a consecutive manner, e.g. F(2x) denotes that fludarabine given as two separate lines.
‡Lost follow-up

Abbreviations: CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease; NE, response not evaluable (due to early death), NK, not known
A, alemtuzumab
C, cyclophosphamide
Clb, Chlorambucil
F, Fludarabine
Dex, dexamethasone
Pred, prednisone
R, rituximab (in patient ZM according to [32])
RCD, rituximab, cyclophosphamide, dexamethasone [33]
IMVP16+Dex, ifosfamide, etoposide, methotrexate, and dexamethasone
PCR, paclitaxel, cyclophosphamide, rituximab [34]
HD-C, high-dose cyclophosphamide (prior to stem cell harvest)
FMD, fludarabine, mitoxantrone, dexamthasone
FCM, fludarabine, cyclophosphamid, mitoxantrone
Nav, Vinorelbine
2CDA, cladribine
HAM, high-dose cytarabine, mitoxantrone
CFAR, cyclophosphamide, fludarabine, alemtuzumab, rituximab
CEOP, cyclophosphamide, etoposide, vincristine, prednisone
R-B, rituximab, bendamustine

Table 3. Univariate analysis for association of baseline characteristics and treatment-related variables with overall response rate, progression-free and overall survival upon alemtuzumab retreatment

Characteristics	No. pat*	ORR n (%)	P value†	PFS, mo. (median)	P value‡	OS, mo. (median)	P value‡
All patients	30	14 (47)	—	6.3 **(Fig. 1)**	—	20.0	—
CLL stage							
Rai 1-2	13	9 (69)	0.030	9.5	0.153	46.0	0.494
Rai 3-4	17	5 (29)		4.6		18.5	
Hemoglobin							
≥11 g/dL	18	14 (78)	<0.001	9.5	<0.001	49.5	0.001
<11 g/dL	10	0 (0)		3.1 **(Fig. 2A)**		9.4	
Leuko							
<50.000 G/L	14	10 (71)	0.040	4.6	0.267	16.7	0.222
>50.000 G/L	15	5 (33)		7.4		46.0	
Lymph nodes							
<5 cm	16	10 (63)	0.023	9.3	0.004	37.7	0.015
≥5 cm	11	2 (18)		3.2		8.4	
Response to initial alemtuzumab therapy							
CR/PR	13	11 (79)	<0.001	11.9	<0.001	57.0	<0.001
Rest	17	3 (21)		3.3		15.5	
Interval between alemtuzumab courses I and II							
<10.9 months	15	11 (27)	0.028	4.1	0.011	11.3	0.002
≥10.9 months	15	10 (67)		9.9 **(Fig. 2B)**		49.9	
Cumulative dose							
<400 mg	14	5 (36)	0.256	3.2	0.013	11.3	0.352
≥400 mg	14	8 (57)		7.5		25.5	
Response to alemtuzumab retreatment							
PR	14		—	9.5	<0.001	49.8	<0.001
SD	6			4.6		17.8	
PD	9			2.7		7.4	
NE	1			0.9		0.9	

Abbreviations: CR, complete response; NCI-WG, National Cancer Institute Working

Group; NE, not evaluable; n.r., not recorded; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

Data for subgroup analyses were not always available for all 30 patients.

†Pearsons qui-square test

‡ Log-rank test.

Figure 1. Kaplan-Meier plots illustrating progression-free survival (PFS) in 30 patients with chemotherapy pretreated CLL who received alemtuzumab monotherapy**.** PFS for the initial alemtuzumab treatment series and alemtuzumab retreatment was 8.9 months and 6.3 months, respectively (P = n.s.).

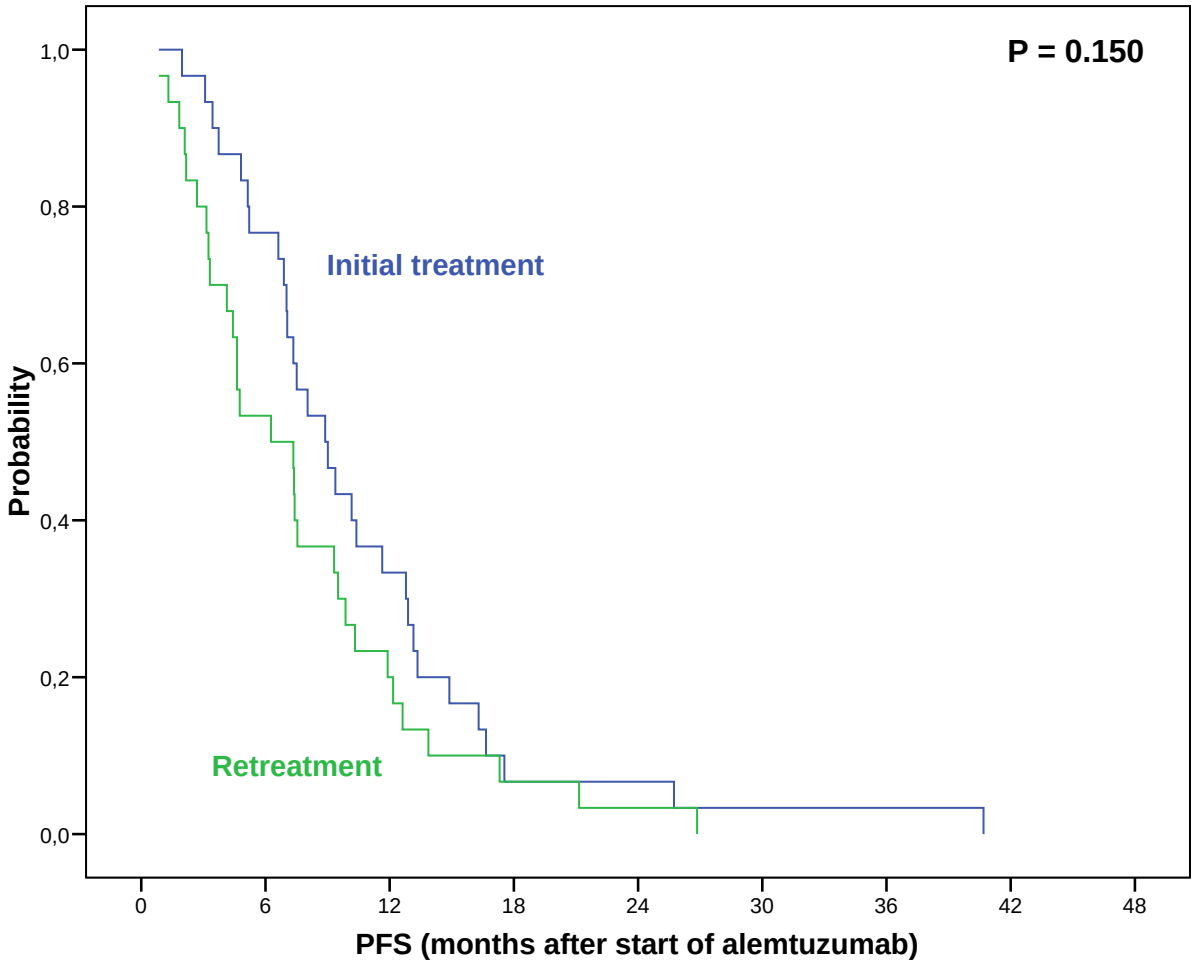


Figure 2. Kaplan-Meier plots illustrating progression-free survival (PFS) in 30 patients with chemotherapy pretreated CLL who received alemtuzumab retreatment. **(A)** According to absence or presence of anemia prior to alemtuzumab retreatment, PFS was 9.5 months and 3.1 months in patients with hemoglobin ≥11 g/dL or less, respectively (P <0.001). **(B)** Plotted according to the length of the treatment-free interval between end of initial alemtuzumab therapy and alemtuzumab retreatment, the median PFS was 9.9 months and 4.1 months in patients with an interval ≥10.9 months or shorter, respectively (P = 0.011).

Fig. 2A

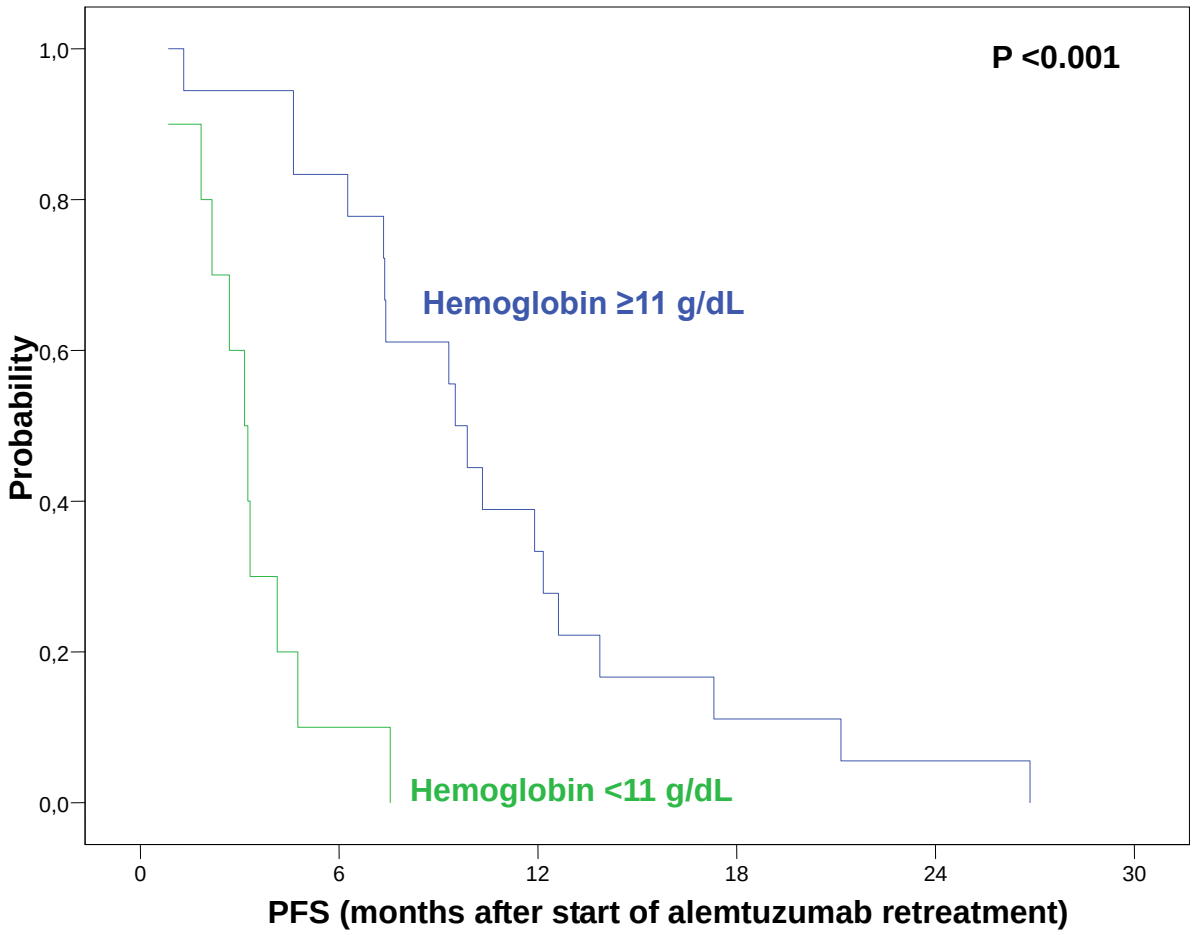
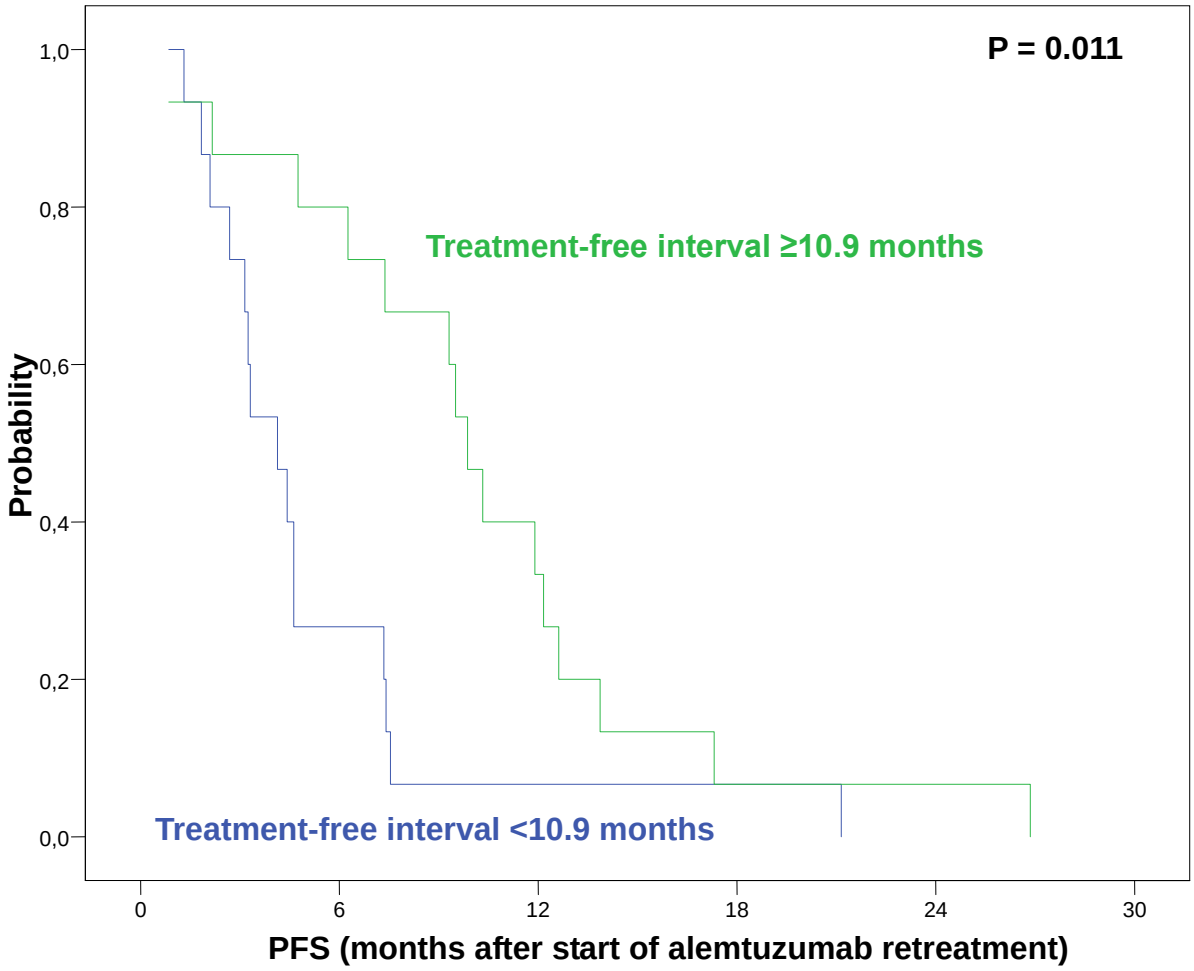


Fig. 2B


P = 0.011
Treatment-free interval ≥10.9 months
Treatment-free interval <10.9 months
Probability
1,0
0,8
0,6
0,4
0,2
0,0
0
6
12
18
24
30
PFS (months after start of alemtuzumab retreatment)