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Prospective observational study in comorbid patients with chronic lymphocytic leukemia receiving first-line bendamustine with rituximab

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ABSTRACT

Chemoimmunotherapy with bendamustine and rituximab is an alternative treatment for elderly patients with CLL. The aim of this observational multicenter study was to prospectively assess efficacy and safety of bendamustine and rituximab in front-line therapy in patients with CLL and significant comorbidities in real hematological practice. Eighty-three consecutive patients with cumulative illness rating scale (CIRS) > 6 who received at least one cycle of BR as first-line treatment were included in the study. The median age was 71 years (range, 53–83), the median CIRS was 8 (range, 7–17), and 60.2% of patients had a creatinine clearance ≤70 mL/min. FISH analysis, available for 78 cases, showed a del(17p) in 11.5% and del(11q) in 20.5% of patients. Overall response rate was 88.0% with a complete response rate of 20.5%. With median follow-up time of 22 months, the estimated median progression free survival was 35.9 months. Progression free survival and overall survival rates at 2 years were 69.9% and 96.2%, respectively. Grade 3 or 4 neutropenia, thrombocytopenia, and anemia were documented in 40 (48.2%), 14 (16.9%), and 8 (9.6%) patients, respectively. Grade 3 or 4 infections occurred in 14.5% of patients. Chemoimmunotherapy with BR is an effective therapeutic option with manageable toxicity for the initial treatment of CLL patients with significant comorbidities. ClinicalTrials.gov Identifier: NCT02381899.

1. Introduction

Chronic lymphocytic leukemia (CLL) is one of the most common lymphoid malignancies characterized by a heterogeneous clinical course. Combined chemoimmunotherapy regimen fludarabine, cyclophosphamide, and rituximab (FCR) have led to improvements in survival in younger patients with CLL and have become the standard front-line therapy in fit patients [1,2]. However, the majority of CLL patients are elderly and/or with significant comorbidities and thus not eligible for aggressive chemoimmunotherapy. The median age at diagnosis of this leukemia is 72 years with only one quarter of the patients being younger than 65 years. In addition, 89% of the patients with a newly diagnosed CLL have one or more comorbidities, and 46% have at least one major comorbidity [3].

An alternative first-line treatment in patients with CLL is the combination of bendamustine and rituximab (BR), which demonstrated promising efficacy and safety in a phase II trial of the German Chronic Lymphocytic Leukemia Study Group (GCLLSG) [4].

More recently, Eichhorst and colleagues published data from a large phase III trial (CLL10) testing BR *versus* FCR for noninferiority in young, fit patients with CLL [5]. BR was inferior to FCR regarding the primary endpoint progression-free survival (PFS) and complete remission (CR) rate. However, no significant difference in PFS was detected in a subset analysis of patients older than 65 years. This result suggests that BR should be considered for elderly fit patients.

Although BR is used in comorbid patients in daily practice, only

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limited data is available regarding BR regimen in comorbid patients with CLL. Therefore, the aim of our prospective, observational, multicenter study was to further evaluate efficacy and safety of BR regimen as first-line therapy in patients with CLL and significant comorbidities.

2. Materials and methods

2.1. Patients and treatment

Previously untreated patients with progressive CLL and a Cumulative Illness Rating Scale (CIRS) > 6, who were assigned to receive BR regimen, were prospectively included in the study. The study was approved by institutional ethics committees and informed consent was obtained from all patients. Patients were treated in five university hospitals. All patients were scheduled to receive bendamustine at the dose of 90 mg/m^2 on days 1 and 2 combined with rituximab 375 mg/m^2 on day 0 of the first course and 500 mg/m^2 on day 1 during subsequent courses every 28 days for a maximum of six cycles. Response to treatment was assessed using National Cancer Institute-sponsored Working Group criteria [6], including bone marrow examination and radiographic confirmation of complete response.

Use of granulocyte colony-stimulating factor (G-CSF) and antimicrobial prophylaxis with sulfamethoxazole-trimethoprim and/or aciclovir was at the discretion of the treating physician.

2.2. Outcomes

The primary objectives were to evaluate the safety and efficacy of BR regimen given as first-line therapy in significantly comorbid (CIRS > 6) patients with CLL. The primary end point of overall response rate (ORR) was calculated on the intent-to-treat (ITT) population defined by all patients who received at least one cycle of BR. Patients with a clinical CR, but without bone marrow biopsy and/or imaging examination, were considered as PR. Safety was assessed by analysis of adverse events monitored throughout the study and graded using NCI common terminology criteria for adverse events (CTCAE) version 4.0. The secondary end points included the progression-free survival (PFS) and the overall survival (OS).

2.3. Statistical analysis

Software MedCalc version 18.6 was used for statistical analysis. OS was defined as the time interval from the start of therapy until death form any cause; PFS was calculated from the start of therapy until disease progression or death. Different clinical and biological characteristics (age, gender, CIRS score, ECOG performance status, Rai stage, bulky lymphadenopathy, chromosomal aberrations, IgVH mutational status, creatinine clearance, and cumulative dose of bendamustine) were evaluated for correlations with response rates and time-to-event outcomes. Statistical comparisons were performed using Chi-square test or Mann-Whitney test. The survival curves were constructed according to Kaplan-Meier method and statistical significance of associations between individual variables and survival parameters were assessed using log-rank test.

3. Results

3.1. Patients' characteristics

Between September 2014 and December 2016, 83 consecutive patients with CLL and CIRS > 6 were prospectively included in the study (Table 1). The median age at treatment initiation was 71 years (range, 53–83), 55 patients (66.3%) were age 70 years or older and 55 patients (66.3%) were at Rai stage III or IV. The median CIRS was 8 (range, 7–17) and 50 patients (60.2%) had a creatinine clearance ≤70 mL/min. Comorbidities by CIRS category are summarized in Table 2. The most frequently affected organ systems or disorders were hypertension (79.5%), endocrine or metabolic (68.7%), vascular (42.2%), and cardiac (41%).

FISH analysis was performed in 78 patients and showed a del(17p) in 9 (11.5%) patients and del(11q) in 16 (20.5%) patients. Data for IgVH mutation status were available in 72 patients with unmutated IgVH detected in 54 cases (75.0%).

Table 1
Patients' clinical and biological features.

Characteristic	Patients (n = 83)
Age, years	
Median (range)	71 (53–83)
≥65	75 (90%)
≥70	55 (66%)
Sex	
Male	51 (61%)
Female	32 (39%)
CIRS score	
Median (range)	8 (7–17)
ECOG performance status	
0	16 (19%)
I	61 (73%)
II	6 (7%)
Rai stage	
0	1 (1%)
I	9 (11%)
II	18 (22%)
III	29 (35%)
IV	26 (31%)
Creatinine clearance, ml/min	
Median (range)	65 (30–139)
≤70	50 (60%)
Bulky lymphadenopathy (> 5 cm)	33 (40%)
IgVH mutational status (n = 72)	
Mutated	18 (25%)
Unmutated	54 (75%)
FISH analysis* (n = 78)	
17p deletion	9 (12%)
11q deletion	16 (21%)
Trisomy 12	16 (21%)
13q deletion	23 (29%)
Normal	14 (18%)
Absolute lymphocyte count, $\times 10^9$/l	
Median (range)	116 (5.2–559)
Hemoglobin, g/l	
Median (range)	102 (60–142)
Platelets, $\times 10^9$/l	
Median (range)	129 (20–435)

Abbreviations: CIRS, cumulative illness rating scale; ECOG, Eastern Cooperative Oncology Group.

* According to Döhner's hierarchical genetic model [17].

Table 2
Comorbidities by CIRS category.

Organ system	N (%)
Cardiac	34 (41%)
Hypertension	66 (79.5%)
Vascular	35 (42.2%)
Respiratory	27 (32.5%)
Eye/Ear/Nose/Throat	30 (36.1%)
Upper Gastrointestinal	22 (26.5%)
Lower Gastrointestinal	20 (24.1%)
Hepatic	17 (20.5%)
Renal	25 (30.1%)
Genitourinary	31 (37.3%)
Musculoskeletal	27 (32.5%)
Neurological	17 (20.5%)
Endocrine/Metabolic	57 (68.7%)
Psychiatric	5 (6%)

Abbreviations: CIRS, cumulative illness rating scale.

3.2. Treatment

The median number of treatment courses administered was 6 (range, 1–6) and the mean number was 5.4 courses. Forty-three patients (51.8%) received the full dose six courses of therapy and 61 (73.5%) received > 80% of the planned dose of bendamustine. Treatment was discontinued early during the first or second course of therapy in 4 patients (4.8%) because of toxicity (death = 1, hematological toxicity = 2, skin rash = 1). Treatment was discontinued before the sixth cycle in 21 pts (25.3%) because of hematological toxicity (n = 9), serious infections (n = 3), stable disease (n = 3), skin rash (n = 2), death (n = 1), injury (n = 1), planned surgery (n = 1), and patient's decision (n = 1).

3.3. Treatment efficacy

In the ITT population, the ORR was 88.0% (n = 73), with a CR rate of 20.5% (n = 17), and a PR rate of 67.5% (n = 56). Stable disease (SD) was observed in 4 patients (4.8%), and 2 patients (2.4%) had progressive disease. In four patients (4.8%), no response assessment was performed because of early death (n = 1) or adverse events (n = 3). Six patients who had a CR were considered as PR because of missing bone marrow biopsy (Table 3).

With median follow-up time of 22.0 months, the estimated median PFS was 35.9 months (95% CI, 26.9-NA). As for OS, the median has not been reached (6 deaths). Two years PFS and OS estimates were 69.9% and 96.2%, respectively (Fig. 1). The presence of del(17p) was the only analyzed variable significantly associated with a lower ORR of 55.6% ($p < 0.001$) and a shorter PFS of 9.0 months ($p < 0.001$). None of the analyzed risk factors significantly influenced OS.

3.4. Safety

Fifty-one patients (61.4%) experienced at least one adverse event grade 3 or 4 (Table 4). The most common adverse events were hematological ones occurring in 46 patients (55.4%). Grade 3 or 4 neutropenia, thrombocytopenia, and anemia were documented in 40 (48.2%), 14 (16.9%), and 8 (9.6%) patients, respectively.

Infection and skin rash were the most common nonhematological toxicities. Grade 3 or 4 infections occurred in 12 (14.5%) patients: 5 patients developed pneumonia, 4 patients had febrile neutropenia, 1 had mycotic esophagitis, 1 had sepsis, and 1 had urinary tract infection. Six (7.2%) patients developed severe skin rash. During treatment, one patient (1.2%) died after the first course of therapy from infection (sepsis).

Granulocyte colony-stimulating factor (G-CSF) as a primary or secondary prophylaxis of neutropenia was administrated to 16 patients (19.3%) and 38 patients (45.8%), respectively. Fifty-five patients (66.3%) received prophylaxis with sulfamethoxazole-trimethoprim and 44 patients (53%) received antiviral prophylaxis (aciclovir).

Of note, patients with creatinine clearance ≤70 mL/min did not require more bendamustine dose reductions (p = 0.59) but did show higher incidence of severe anemia than patients with normal renal function (16% *vs.* 0%, p = 0.019). Age and CIRS failed to predict any severe toxicities or BR dose reduction.

Table 3
Response to treatment.

Assessed for response (ITT population)	83
ORR	73 (88.0%)
CR	17 (20.5%)
PR	56 (67.5%)
SD	4 (4.8%)
PD	2 (2.4%)
Without response assessment	4 (4.8%)

Abbreviations: CR, complete remission; ITT, intent-to-treat; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease.

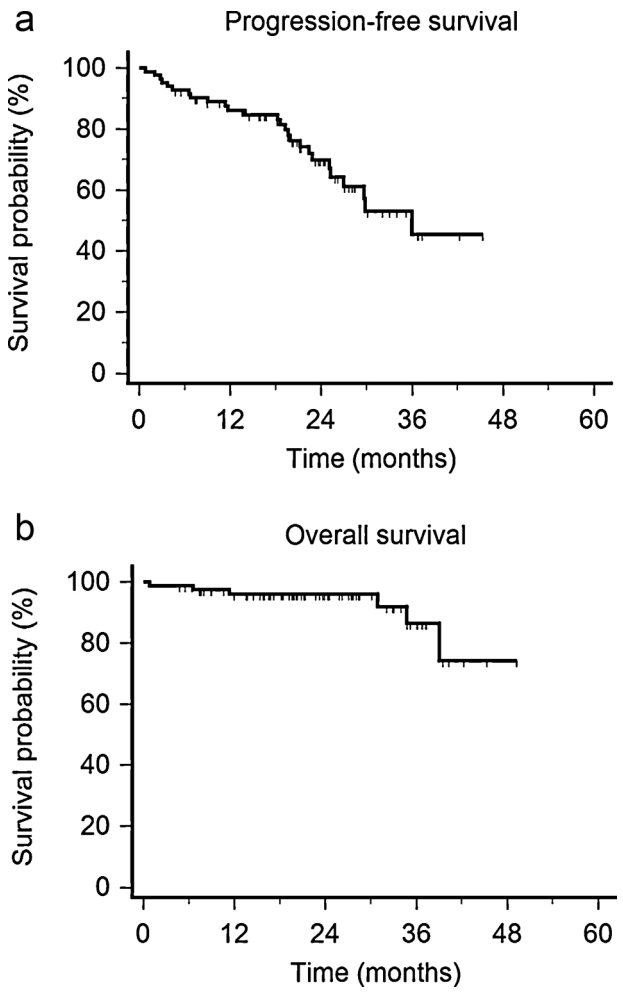

Fig. 1. (A) Progression free survival and (B) overall survival.

Table 4
Incidence of CTCAE grade III/IV adverse events.

Adverse event	Number of pts	%
Hematological toxicity	**46**	**55.4**
Neutropenia	40	48.2
Thrombocytopenia	14	16.9
Anemia	8	9.6
Nonhematological toxicity	**21**	**25.3**
Infection	12	14.5
Skin rash	6	7.2
Allergic reaction	2	2.4
Thromboembolic event	2	2.4
Acute coronary syndrome	1	1.2
Hemolysis	1	1.2
Tumor lysis syndrome	1	1.2

Abbreviations: CTCAE, Common terminology criteria for adverse events.

4. Discussion

Despite the introduction of novel targeted treatments, FCR chemoimmunotherapy still remains the standard front-line therapy for young and fit patients with CLL without del(17p) or *TP53* mutation [7]. However, with a median age of 72 years at diagnosis, most of CLL patients are ineligible to receive fludarabine-based treatments. In the

CLL11 study, the first large randomized phase III trial in patients with previously untreated CLL and significant comorbidities, patients were randomized to receive chlorambucil (Clb), chlorambucil plus obinutuzumab (G-Clb), or chlorambucil plus rituximab (R-Clb) [8]. The patients had a median age of 73 years, creatinine clearance of 62 mL/min, and CIRS score of 8. G-Clb combination achieved higher ORR (78.4% *vs.* 65.1%) and CR rate (20.7% *vs.* 7.0%), significantly prolonged median PFS (26.7 *vs.* 15.2 months), and median time to next treatment compared to R-Clb [9]. There was also a significant OS benefit for both G-Clb and R-Clb arms compared with Clb alone. The final survival analysis also confirmed that G-Clb provides prolongation of OS when compared with R-Clb with two-year survival rate 91% *vs.* 84% [10]. Thus, the findings of the CLL11 study support the use of obinutuzumab plus chlorambucil as preferred first-line treatment for CLL patients with significant comorbidities.

However, one of the most frequently used first-line regimens in routine treatment of patients with CLL is BR combination. Published data from the Tumour Registry Lymphatic Neoplasms showed that BR dominate first-line treatments of CLL (given to 56% of patients) by office-based hematologists in Germany [11].

We herein present the data on the largest cohort of real-world CLL patients with significant comorbidities (CIRS > 6) treated by BR chemoimmunotherapy in a front-line setting (trials investigating first-line BR in CLL patients are summarized in Table 5). Similar to the CLL11 trial, the study population included unfit patients with a median age of 71 years, creatinine clearance of 65 mL/min, and CIRS score of 8. Compared with G-Clb combination our analysis of BR regimen showed comparable CR rate (20.5% *vs.* 20.7%), slightly increased ORR (88% *vs.* 78.4%) and a longer median PFS (35.9 *vs.* 26.7 months). The incidence of grade ≥3 adverse events was also comparable (61.4% *vs.* 70% in G-Clb arm). Although we observed higher incidence of grade 3 or 4 neutropenia (48.2% *vs.* 33% in G-Clb), this did not translate into a higher incidence of severe infections (14.5% *vs.* 12% in G-Clb).

In a phase II GCLLSG trial, Fischer and colleagues demonstrated promising efficacy and safety of BR in previously untreated patients with CLL [4]. Overall response rate was 88.0% with a CR rate of 23.1%; the median PFS was 33.8 months. The median age was 64 years and 35.0% patients had a creatinine clearance ≤70 mL/min; CIRS was not calculated.

Our results are comparable to data published by Fisher at al. despite the fact that our study included older patients (median age, 71 years), with higher proportion of the patients with an impaired creatinine clearance of ≤70 mL/min (60%). Remarkably, the incidence of grade 3 or 4 adverse events observed in our cohort was also comparable (61.4% *versus* 64.1% in Fisher's cohort). The incidence of both severe neutropenia and infection (48.2% and 14.5%, respectively) was higher in our study compared with the reported numbers in Fisher's cohort (19.7% and 7.7%, respectively). However, Eichhorst et al. observed similarly higher rate of severe neutropenia and infection (59% and 25%, respectively) in younger and fit patients (median age, 61 years; median CIRS 2) in a GCLLSG phase III trial [5].

Laurenti and colleagues published a retrospective analysis of the use of BR for elderly patients with previously untreated CLL [12]. They reported data of 70 patients with a median age of 72 years, 8 patients were unfit (CIRS > 6). The ORR was 88.6% and a CR rate 31.4%; median PFS was 35 months. More than 55% of patients required a bendamustine dose reduction due to increased toxicity. Grades 3 and 4 hematological toxicity was recorded in 37.1% of patients and non-hematological toxicity in 25.7% of patients. The most common grade 3 and 4 adverse events were neutropenia (28.5%) and infections (10%). In our prospective study, we obtained similar efficacy in terms of ORR, CR rate and PFS. Interestingly, the incidence of grade 3–4 infections (14.5%) and the proportion of patients with the bendamustine dose reduction (48.2%) were comparable in our cohort, although all included patients were unfit (CIRS > 6).

Our observations are also in the line with recently published results of the phase III MABLE trial, in which efficacy of BR was compared with rituximab and chlorambucil in fludarabine-ineligible patients with CLL [13]. The median age of the study population was 72 years and the median number of comorbidities was three (CIRS was not used). First-line BR patients showed an ORR of 91% including a CR rate of 24%, with a median PFS of 39.6 months. Safety profiles were similar for both arms, although slightly higher incidence of grade ≥3 adverse events was observed with BR. However, comparison of safety data with this trial is difficult, because results were presented for the pooled population only (first and second line patients).

Novel targeted agents have shown promising efficacy in the relapsed/refractory CLL and are now being evaluated in the first-line setting. A phase III trial comparing BR, ibrutinib, and ibrutinib plus rituximab found that treatment with continuous ibrutinib was superior to treatment with BR with regard to PFS (estimated PFS at 2 years 74% with BR *vs.* 87% with ibrutinib alone) [14]. The response rate was lower with BR than with ibrutinib (81% *vs.* 93%) but BR achieved higher CR rate (26% *vs.* 7%). The rate of grade ≥3 hematological adverse events was higher with BR than with ibrutinib (61% *vs.* 41%), whereas the rate of grade ≥3 nonhematological adverse events was lower with BR (63% *vs.* 74%). The median age of patients treated with ibrutinib was 71 years, creatinine clearance of 69 mL/min, and the median number of comorbidities was 2 (CIRS was not used). Compared with ibrutinib arm our analysis of BR regimen in comorbid patients (median CIRS 8) showed comparable ORR (88% *vs.* 93%), higher CR rate (20.5% *vs.* 7%) and a shorter estimated PFS at 2 years (70% *vs.* 87%). The incidence of

Table 5
Studies exploring chemoimmunotherapy with bendamustine and rituximab in treatment-naïve chronic lymphocytic leukemia.

Reference	Treatment	Number of patients treated with BR	Age, median (years)	CIRS, median	CrCl, median (mL/min)	ORR (%)	CR (%)	PFS (months)
Fischer et al. [4]	BR	117	64	NA	79.1	88	23.1	33.8
Laurenti et al. [12]	BR	70	72	NA	NA	88.6	31.4	35
Gentile et al. [18]	BR	279	70	2	68	86.4	28	40
Michallet et al. [13]	BR R-chlorambucil	178	72	NA	NA	91	24	39.6
Eichhorst et al. [5]	BR FCR	279	61	2	86.4	96	31	41.7
Woyach et al. [14]	BR Ibrutinib Ibrutinib + R	183	70	NA	NA	81	26	43
Spacek et al. [present study]	BR	83	71	8	65	88	20.5	35.9

Data of patients treated with BR are shown.
Abbreviations: B, bendamustine; CIRS, cumulative illness rating scale; CR, complete remission; CrCl, creatinine clearance; ORR, overall response rate; PFS, progression-free survival; R, rituximab.

grade ≥3 hematological adverse events was higher in our study compared with the reported numbers in ibrutinib cohort (55% *vs.* 41%). Interestingly, the observed grade ≥3 nonhematological adverse events of the BR regimen compare favorable to the rate in patients receiving ibrutinib (25% *vs.* 74%).

Although ibrutinib may be well tolerated, real-world data suggest that approximately 40% of patients discontinue ibrutinib due to intolerance (with the median time to ibrutinib discontinuation being 7 months) [15]. In addition, recently published retrospective analysis has shown that CIRS has prognostic significance for patients with CLL treated with ibrutinib in both frontline and relapsed setting, regardless of patient age [16]. Furthermore, a high burden of comorbidities (CIRS > 6) was associated with an increased risk of ibrutinib dose reduction and therapy discontinuation. Hence, the optimal treatment of comorbid patients with CLL remains an important clinical question, which should be addressed by prospective studies.

5. Conclusions

In conclusion, this prospective observational study showed that chemoimmunotherapy with BR is an effective therapeutic option with manageable toxicity for the initial treatment of CLL patients with significant comorbidities.

Contribution

MŠp, MT and PO designed the study; MŠp, PO, SH, EC, JK, JM, MŠi, HM, LM, AP, JN, MT, LS and MD collected the data, MŠp, PO, MŠi, MT, LS and MD wrote the manuscript; MŠp, PO and MŠi performed the statistical analyses.

Conflict of interest

MŠp: Honoraria and travel grants from Mundipharma and Roche. LS, MD, MŠi, MT, PO: honoraria and travel grants from Roche. All other authors declare no competing financial interests.

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References

[1] M. Hallek, K. Fischer, G. Fingerle-Rowson, A.M. Fink, R. Busch, J. Mayer, M. Hensel, G. Hopfinger, G. Hess, U. Von Grünhagen, M. Bergmann, J. Catalano, P.L. Zinzani, F. Caligaris-Cappio, J.F. Seymour, A. Berrebi, U. Jäger, B. Cazin, M. Trneny, A. Westermann, C.M. Wendtner, B.F. Eichhorst, P. Staib, A. Bühler, D. Winkler, T. Zenz, S. Böttcher, M. Ritgen, M. Mendila, M. Kneba, H. Döhner, S. Stilgenbauer, Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial, Lancet 376 (2010) 1164–1174, https://doi.org/10.1016/S0140-6736(10)61381-5.

[2] K. Fischer, J. Bahlo, A.M. Fink, V. Goede, C.D. Herling, P. Cramer, P. Langerbeins, J. Von Tresckow, A. Engelke, C. Maurer, G. Kovacs, M. Herling, E. Tausch, K.A. Kreuzer, B. Eichhorst, S. Böttcher, J.F. Seymour, P. Ghia, P. Marlton, M. Kneba, C.M. Wendtner, H. Döhner, S. Stilgenbauer, M. Hallek, Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial, Blood 127 (2016) 208–215, https://doi.org/10.1182/blood-2015-06-651125.

[3] P. Thurmes, T. Call, S. Slager, C. Zent, G. Jenkins, S. Schwager, D. Bowen, N. Kay, T. Shanafelt, Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia, Leuk. Lymphoma 49 (2008) 49–56, https://doi.org/10.1080/10428190701724785.

[4] K. Fischer, P. Cramer, R. Busch, S. Böttcher, J. Bahlo, J. Schubert, K.H. Pflüger, S. Schott, V. Goede, S. Isfort, J. von Tresckow, A.-M. Fink, A. Bühler, D. Winkler, K.-A. Kreuzer, P. Staib, M. Ritgen, M. Kneba, H. Döhner, B.F. Eichhorst, M. Hallek, S. Stilgenbauer, C.-M. Wendtner, Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group, J. Clin. Oncol. 30 (2012) 3209–3216, https://doi.org/10.1200/JCO.2011.39.2688.

[5] B. Eichhorst, A.M. Fink, J. Bahlo, R. Busch, G. Kovacs, C. Maurer, E. Lange, H. Köppler, M. Kiehl, M. Sökler, R. Schlag, U. Vehling-Kaiser, G. Köchling, C. Plöger, M. Gregor, T. Plesner, M. Trneny, K. Fischer, H. Döhner, M. Kneba, C.M. Wendtner, W. Klapper, K.A. Kreuzer, S. Stilgenbauer, S. Böttcher, M. Hallek, First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial, Lancet Oncol. 17 (2016) 928–942, https://doi.org/10.1016/S1470-2045(16)30051-1.

[6] M. Hallek, B.D. Cheson, D. Catovsky, F. Caligaris-cappio, G. Dighiero, H. Do, Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute – Working Group 1996 guidelines, Blood 111 (2008) 5446–5456, https://doi.org/10.1182/blood-2007-06-093906.

[7] B. Eichhorst, T. Robak, E. Montserrat, P. Ghia, P. Hillmen, M. Hallek, C. Buske, ESMO Guidelines Committee, chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 26 (2015) v78–v84, https://doi.org/10.1093/annonc/mdv303.

[8] V. Goede, K. Fischer, R. Busch, A. Engelke, B. Eichhorst, C.M. Wendtner, T. Chagorova, J. de la Serna, M.-S. Dilhuydy, T. Illmer, S. Opat, C.J. Owen, O. Samoylova, K.-A. Kreuzer, S. Stilgenbauer, H. Döhner, A.W. Langerak, M. Ritgen, M. Kneba, E. Asikanius, K. Humphrey, M. Wenger, M. Hallek, Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions, N. Engl. J. Med. 370 (2014) 1101–1110, https://doi.org/10.1056/NEJMoa1313984.

[9] V. Goede, K. Fischer, A. Engelke, R. Schlag, S. Lepretre, L.F.C. Montero, M. Montillo, C. Fegan, E. Asikanius, K. Humphrey, G. Fingerle-Rowson, M. Hallek, Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study, Leukemia 29 (2015) 1602–1604, https://doi.org/10.1038/leu.2015.14.

[10] V. Goede, K. Fischer, M.J.S. Dyer, L. Müller, L. Smolej, M. Bernardo, Chiara Di, A. Knapp, T. Nielsen, M. Hallek, Overall Survival Benefit of Obinutuzumab over Rituximab when Combined with Chlorambucil in Patients with Chronic Lymphocytic Leukemia and Comorbidities: Final Survival Analysis of the cll11 Study, 23rd Congress of the European Hematology Association, Abstract S151, Stockholm, Sweden, 2018 June 14-17.

[11] W. Knauf, W. Abenhardt, S. Dörfel, D. Meyer, R. Grugel, M. Münz, H. Hartmann, N. Marschner, Routine treatment of patients with chronic lymphocytic leukaemia by office-based haematologists in Germany-data from the Prospective Tumour Registry Lymphatic Neoplasms, Hematol. Oncol. 33 (2015) 15–22, https://doi.org/10.1002/hon.2139.

[12] L. Laurenti, I. Innocenti, F. Autore, B. Vannata, D.G. Efremov, S. Ciolli, G. Del Poeta, F.R. Mauro, A. Cortelezzi, P.A. Borza, F. Ghio, P. Mondello, R. Murru, A. Gozzetti, M.R.L. Cariccio, N. Piccirillo, R. Boncompagni, M. Cantonetti, M.I. Del Principe, G. Reda, V. Bongarzoni, G. Cervetti, V. Pitini, R. Foà, S. Sica, G. D'Arena, Bendamustine in combination with rituximab for elderly patients with previously untreated B-cell chronic lymphocytic leukemia: a retrospective analysis of real-life practice in Italian hematology departments, Leuk. Res. 39 (2015) 1066–1070, https://doi.org/10.1016/j.leukres.2015.07.009.

[13] A.S. Michallet, M. Aktan, W. Hiddemann, O. Ilhan, P. Johansson, K. Laribi, B. Meddeb, C. Moreno, J. Raposo, A. Schuh, A. Ünal, T. Widenius, A. Bernhardt, K. Kellershohn, D. Messeri, S. Osborne, V. Leblond, Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study, Haematologica 103 (2018) 698–706, https://doi.org/10.3324/haematol.2017.170480.

[14] J.A. Woyach, A.S. Ruppert, N.A. Heerema, W. Zhao, A.M. Booth, W. Ding, N.L. Bartlett, D.M. Brander, P.M. Barr, K.A. Rogers, S.A. Parikh, S. Coutre, A. Hurria, J.R. Brown, G. Lozanski, J.S. Blachly, H.G. Ozer, B. Major-Elechi, B. Fruth, S. Nattam, R.A. Larson, H. Erba, M. Litzow, C. Owen, C. Kuzma, J.S. Abramson, R.F. Little, S.E. Smith, R.M. Stone, S.J. Mandrekar, J.C. Byrd, Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL, N. Engl. J. Med. 379 (2018) 2517–2528, https://doi.org/10.1056/NEJMoa1812836 NEJMoa1812836.

[15] A.R. Mato, C. Nabhan, M.C. Thompson, N. Lamanna, D.M. Brander, B. Hill, C. Howlett, A. Skarbnik, B.D. Cheson, C. Zent, J. Pu, P. Kiselev, A. Goy, D. Claxton, K. Isaac, K.H. Kennard, C. Timlin, D. Landsburg, A. Winter, S.D. Nasta, S.H. Bachow, S.J. Schuster, C. Dorsey, J. Svoboda, P. Barr, C.S. Ujjani, Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis, Haematologica 103 (2018) 874–879, https://doi.org/10.3324/haematol.2017.182907.

[16] M.J. Gordon, M. Churnetski, H. Alqahtani, X. Rivera, A. Kittai, S.M. Amrock, S. James, S. Hoff, S. Manda, S.E. Spurgeon, M. Choi, J.B. Cohen, D. Persky, A.V. Danilov, Comorbidities predict inferior outcomes in chronic lymphocytic leukemia treated with ibrutinib, Cancer 124 (2018) 3192–3200, https://doi.org/10.1002/cncr.31554.

[17] H. Döhner, S. Stilgenbauer, A. Benner, E. Leupolt, A. Kröber, L. Bullinger, K. Döhner, M. Bentz, P. Lichter, Genomic aberrations and survival in chronic lymphocytic leukemia, N. Engl. J. Med. 343 (2000) 1910–1916, https://doi.org/10.1056/NEJM200012283432602.

[18] M. Gentile, K. Zirlik, S. Ciolli, F.R. Mauro, N. Di Renzo, L. Mastrullo, F. Angrilli, S. Molica, G. Tripepi, A. Giordano, F. Di Raimondo, C. Selleri, M. Coscia, M. Musso, L. Orsucci, D. Mannina, A. Rago, A. Giannotta, F. Ferrara, Y. Herishanu, L. Shvidel, T. Tadmor, I. Scortechini, F. Ilariucci, R. Murru, A. Guarini, G. Musuraca, G. Mineo, I. Vincelli, A. Arcari, G. Tarantini, G. Caparrotti, A. Chiarenza, L. Levato, M.R. Villa, M.R. De Paolis, P.L. Zinzani, A. Polliack, F. Morabito, Combination of bendamustine and rituximab as front-line therapy for patients with chronic lymphocytic leukaemia: multicenter, retrospective clinical practice experience with 279 cases outside of controlled clinical trials, Eur. J. Cancer 60 (2016) 154–165, https://doi.org/10.1016/j.ejca.2016.03.069.