

ORIGINAL ARTICLE

Efficacy and safety of obinutuzumab–chlorambucil combination in the frontline treatment of elderly patients with chronic lymphocytic leukemia and comorbidities

Real-life data from Polish Adult Leukemia Group (PALG) analysis

Monika Długosz-Danecka¹, Wojciech Jurczak¹, Ewa Łątka-Cabała¹, Marta Morawska², Krzysztof Gawroński³, Anna Wiśniewska⁴, Marek Dudziński⁵, Ewa Wąsik-Szczepanek⁶, Ewa Chmielowska⁷, Anna Łabędź⁸, Kamil Wdowiak⁹, Iwona Hus¹⁰

1 Department of Haematology, Jagiellonian University Medical College, Kraków, Poland

2 Experimental Haemato-oncology Department, Medical University of Lublin, Lublin, Poland

3 Department of Haematology, Military Institute of Medicine, Warsaw, Poland

4 Department of Oncology and Chemotherapy, Kopernik Memorial Specialist District Hospital, Koszalin, Poland

5 Department of Haematology, Clinical District Chopin Memorial Hospital, Rzeszów, Poland

6 Department of Haemato-oncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland

7 Department of Clinical Oncology, Oncology Centre, University of Nicolaus Copernicus, Collegium Medicum in Bydgoszcz, Toruń, Poland

8 Department of Haematology, Rydygier Memorial Hospital, Kraków, Poland

9 Department of Internal Medicine and Oncology, Medical University of Silesia, Katowice, Poland

10 Department of Clinical Transplantation, Medical University of Lublin, Lublin, Poland

KEY WORDS

chronic lymphocytic leukemia, comorbidities, Cumulative Illness Rating Scale, obinutuzumab

ABSTRACT

INTRODUCTION Fludarabine- or bendamustine-based upfront immunochemotherapy is the current standard of care in fit patients with chronic lymphocytic leukemia (CLL). These regimens are poorly tolerated by patients with comorbidities, for whom the obinutuzumab–chlorambucil combination became the recommended first-line treatment.

OBJECTIVES We aimed to analyze real-life experience with the obinutuzumab–chlorambucil combination as the frontline treatment in elderly and unfit patients.

PATIENTS AND METHODS The retrospective analysis included 86 elderly patients (median age, 74 years) with CLL and a significant burden of comorbidities, treated with obinutuzumab–chlorambucil as the frontline regimen. All patients had a Cumulative Illness Rating Scale score greater than 6 and/or creatinine clearance of 30 to 69 ml/min.

RESULTS Overall response rate at 2 months after treatment completion was 95.3%, with complete remission (CR) rate of 43% and partial remission (PR) rate of 52.3%. Stable disease rate was 4.7%. Progressive disease was not observed after treatment completion. The median progression-free survival (PFS) was not reached after a median follow-up of 18 months; estimated PFS at 30 months was 62%. We observed 6 relapses (7%), 3 (3.5%) in patients obtaining CR, and 3 (3.5%) in those with PR after immunochemotherapy. The most frequent adverse events were neutropenia and infusion-related reactions (IRRs). Grade-3 neutropenia occurred in 11.6% of patients, and grade-3 IRRs, in 2.3%. There were no adverse events of grade 4 or 5.

CONCLUSIONS Our data confirm that the obinutuzumab–chlorambucil combination is an effective and well-tolerated regimen in untreated CLL patients with comorbidities.

Correspondence to:

Monika Długosz-Danecka, MD, PhD,
Department of Haematology,
Jagiellonian University Medical College,
ul. Kopernika 17, 31-501 Kraków,
Poland, phone: +48 12 424 76 33,
email: monika.danecka@poczta.onet.pl

Received: April 4, 2018.

Revision accepted: June 6, 2018.

Published online: July 11, 2018.

Conflict of interest: none declared.

Pol Arch Intern Med. 2018;

128 (7-8): 421-426

doi:10.20452/pamw.4294

Copyright by Medycyna Praktyczna,

Kraków 2018

INTRODUCTION Chronic lymphocytic leukemia (CLL) is the most common type of leukemia diagnosed in the Western world, with an incidence rate of 4.2/100 000 increasing to >30/100 000/year above the age of 80 years.¹ The median age at diagnosis is 72 years.¹ In older CLL patients, comorbidities compromising the effective treatment are the major problem, and chlorambucil alone remained for years the standard of care in frail patients.^{2,3,4} The introduction of purine analogue-based regimens did not improve the outcome in this population,⁵⁻⁸ and fludarabine-based chemotherapy proved to be too toxic.⁹ This is why, addition of rituximab, an anti-CD20 monoclonal antibody, to fludarabine and cyclophosphamide (FCR), while significantly increasing overall survival in physically fit patients,^{10,11} did not change the outcome for frail and elderly population.¹² In a recent retrospective international multicenter study of CLL patients treated with the bendamustine and rituximab (BR) regimen as frontline therapy, a significant burden of comorbidities (Cumulative Illness Rating Scale [CIRS] score ≥ 7) was independently associated with shorter progression-free survival (PFS).¹³ According to the European Society for Medical Oncology guidelines, intensive immunotherapy regimens like FCR and BR are recommended in treatment-naïve CLL patients without significant comorbidities, defined as creatinine clearance (CrCl) exceeding 70 ml/min and a CIRS score of 6 or less.¹

Obinutuzumab, a second-generation monoclonal antibody, combined with chlorambucil, was a breakthrough for unfit patients with CLL, increasing their overall survival and becoming the current first-line standard of care.¹ Obinutuzumab is a humanized, glycoengineered, type-2 anti-CD20 antibody, with enhanced antibody-dependent cellular cytotoxicity compared with rituximab in a randomized phase-III clinical trial.^{14,15} Additionally, 2 network meta-analyses confirmed the superior efficacy of the obinutuzumab–chlorambucil regimen to other treatment options for unfit CLL patients.^{16,17} The objective of this retrospective analysis was to evaluate the efficacy and safety of the obinutuzumab–chlorambucil regimen in newly diagnosed patients with CLL not eligible for intensive immunochemotherapy in routine clinical practice (real-life experience).

PATIENTS AND METHODS **Patients** In this retrospective analysis, we collected the data of CLL patients who were ineligible for intensive immunochemotherapy due to significant comorbidities and who received obinutuzumab and chlorambucil as the first-line therapy. Diagnosis of CLL, as well as indications for starting the treatment, was based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines.¹⁸ All patients fulfilled the inclusion criteria to start treatment according to the IWCLL guidelines and

to be administered the obinutuzumab–chlorambucil regimen.

The burden of comorbidities was evaluated using the CIRS,^{19,20} and CrCl calculated according to the Cockcroft–Gault formula. The inclusion criteria were based on ESMO recommendations¹: a CIRS score greater than 6 and/or CrCl lower than 70 ml/min.¹⁹⁻²¹

Treatment Obinutuzumab was infused at a dose of 1000 mg intravenously on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 to 6 (28-day cycles), with the first infusion split over 2 days for patients' safety. Chlorambucil was administered orally at a dose of 0.5 mg/kg of body weight on days 1 and 15 of each cycle. Prophylaxis of infusion-related reactions included the use of intravenous premedication with acetaminophen (1000 mg/dose), dexamethasone (20 mg/dose), and clemastine (2 mg/dose). All patients received supportive treatment as required, including adequate fluid intake and allopurinol for tumor lysis syndrome prevention with antibacterial (trimethoprim–sulfamethoxazole) and/or antiviral (acyclovir) prophylaxis. Granulocyte colony-stimulating factor (G-CSF) was not used for primary prophylaxis of neutropenia, but secondary prophylaxis was allowed according to local standards. Drugs used in the treatment of comorbidities were not an interfering factor and did not affect the outcome of obinutuzumab–chlorambucil therapy. Efficacy (response rate and PFS) and safety data were collected. Response to treatment was assessed 2 months after the end of therapy according to the IWCLL guidelines.¹⁸ Due to the short period of follow-up after the end of treatment, the minimal residual disease results were not included in the current analysis and will be provided later. Adverse events (AEs) were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.²²

Ethical considerations This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained from all subjects to participate in the study.

Statistical analysis The impact of categorized parameters on the response to treatment was assessed by the Pearson χ^2 test. PFS, estimated by the Kaplan–Meier method, was defined as the time from treatment initiation to the last date on which the disease activity was assessed, including death for any reason. Follow-up was too short to achieve meaningful overall survival results. A multivariate analysis of factors predicting response to treatment, including cytogenetics and immunoglobulin variable region heavy chain (*IGHV*) gene mutational status, was also performed. Statistical analyses were performed using Statistica, version 10 (StatSoft, Kraków, Poland).

TABLE 1 Patient and disease characteristics at baseline

Parameter	Value
Demographic and clinical data	
Male sex, n (%)	47 (54.6)
Age, y, median (range)	74 (51–86)
Age ≥70 years, n (%)	63 (73.3)
ECOG PS, median (range)	1 (0–1)
CIRS score, median (range)	8 (4–14)
CIRS score ≥7, n (%)	70 (81.4)
CrCl, ml/min, median (range)	64 (35–95)
CrCl <70, ml/min, n (%)	55 (63.9)
Organ or system disorders	
Cardiac, n (%)	62 (72.1)
Vascular, n (%)	59 (68.6)
Hypertension, n (%)	71 (82.6)
Eye, ear, throat or larynx, n (%)	19 (22.1)
Respiratory, n (%)	27 (31.4)
Upper gastrointestinal, n (%)	12 (13.9)
Lower gastrointestinal, n (%)	16 (18.1)
Hepatic or biliary, n (%)	21 (24.4)
Renal, n (%)	19 (22.1)
Genitourinary, n (%)	24 (28.9)
Endocrine or metabolic, n (%)	39 (45.3)
Musculoskeletal, n (%)	15 (17.4)
Neurologic, n (%)	7 (8.1)
Psychiatric, n (%)	6 (7.2)
Number of comorbidities, median (range)	4 (2–7)
Disease characteristics	
Lymphocyte count ≥25 × 10 ⁹ /l, n (%)	74 (86.0)
Lymphocyte count ≥100 × 10 ⁹ /l, n (%)	30 (34.8)
Binet stage A, n (%)	10 (11.6)
Binet stage B, n (%)	50 (58.1)
Binet stage C, n (%)	26 (30.2)
Cytogenetics (n = 69)	
17p deletion, n (%)	7 (10.1)
11q deletion, n (%)	11 (15.9)
Trisomy 12, n (%)	11 (17.4)
13q deletion, n (%)	18 (26.1)
Normal karyotype, n (%)	14 (20.3)
IGHV status (n = 52)	
Unmutated, n (%)	29 (55.8)

Abbreviations: CrCl, creatinine clearance; CIRS, Cumulative Illness Rating Scale; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IGHV, immunoglobulin heavy-chain variable-region gene

RESULTS Between April 2015 and November 2017, 86 consecutive patients with CLL were treated with obinutuzumab and chlorambucil in 10 Polish Adult Leukemia Group (PALG) centers. Patient characteristics and demographic data are presented in **TABLE 1**. The median age at the start of treatment was 74 years (range, 51–86 years) with a male-to-female ratio of 1.15. All patients had a CIRS score greater than 6 and/or CrCl of 30 to 69 ml/min.^{19–21} The median CIRS score

was 8 (range, 4–14) and the median CrCl was 64 ml/min. Most patients (94.2%) presented with 4 or more comorbidities, with ischemic heart disease, arterial hypertension, and endocrine or metabolic disorders being the most frequent. At baseline, the assessment of the following genomic aberrations was performed by fluorescence in situ hybridization (FISH) in 69 patients: deletion of the short arm of chromosome 17, del(17p); deletion of the long arm of chromosome 11, del(11q); deletion of the long arm of chromosome 13; and trisomy of chromosome 12. The analysis of IGHV mutation was performed in 52 patients.^{22,23} Unfavorable risk factors such as del(17p), del(11q), and unmutated IGHV genes were found in 10%, 16%, and 56% of patients, respectively.

The median number of obinutuzumab and chlorambucil cycles was 6; only 1 patient (1.2%) discontinued the therapy after the third cycle due to grade-3 infusion-related reaction (IRR). There were no dose reductions. The overall response rate at 2 months after completion of immunochemotherapy was 95.35%, with a complete remission (CR) rate of 43% and partial remission (PR) rate of 52.3%. Four patients (4.7%) had stable disease and no progression during therapy. The median PFS was not reached after a median follow-up of 18 months; the estimated PFS at 30 months was 62% (**FIGURE 1**). Relapse was observed in 6 patients (7%): 3 patients with CR and the other 3 with PR after chemoimmunotherapy. There were no significant differences in response rates in high-risk groups: del(17p) (42% CR, 57.1% PR), del(11q) (36.4% CR, 54.5% PR), or unmutated IGHV (37.9% CR, 55.2% PR). No deaths were observed during the treatment and follow-up. The relatively small number of patients in the study did not allow for any meaningful subgroup PFS analysis, but it should be noted that 3 of the 7 patients with del(17p) had already made progress during the relatively short follow-up.

In the analyzed group, adverse events (AEs) of grade 2 and higher occurred in 45 patients (52.3%), including grade-2 AEs observed in 34 patients (39.5) and grade-3 AEs in 15 patients (17.4%) (**TABLE 2**). Grade-3 neutropenia resolved completely and did not reappear when G-CSF was used as secondary prophylaxis. There were no episodes of febrile neutropenia. The most frequent AEs were neutropenia and infusion-related reactions. In 82.1% of patients (23/28), IRRs occurred only during the first infusion of monoclonal antibody. Except for 1 patient, who discontinued the treatment after the third cycle, no grade-3 IRRs were observed during subsequent obinutuzumab infusions. The tumor lysis syndrome occurred in 4 patients (4.6%) and resolved after hydration and treatment with rasburicase. Two patients (2.3%) required hospitalization related to AEs (infections). There were no AEs of grade 4 or 5. The details of AEs are summarized in **TABLE 2**.

FIGURE 1 Progression-free survival (PFS) in the study group. Blue circles denote complete observation.

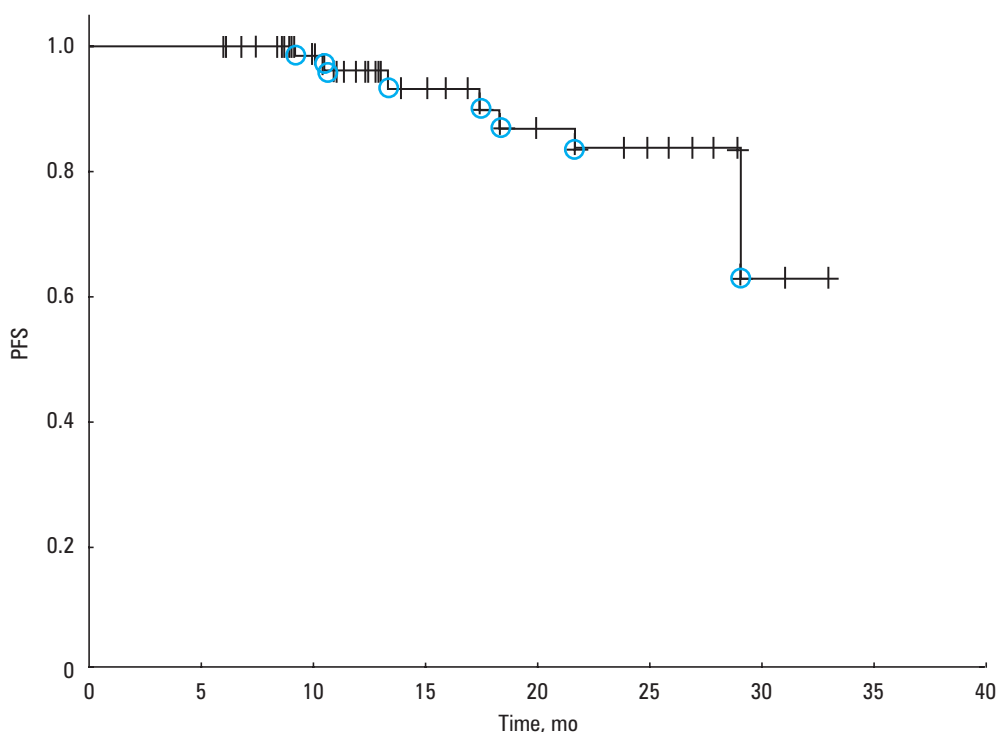


TABLE 2 Safety analysis

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Infusion-related reactions	15 (17.5)	11 (12.8)	2 (2.3)	0
Neutropenia	17 (19.8)	19 (22.1)	8 (9.3)	0
Anemia	4 (4.6)	1 (1.2)	1 (1.2)	0
Thrombocytopenia	3 (3.5)	0	1 (1.2)	0
Tumor lysis syndrome	1 (1.2)	3 (3.5)	1 (1.2)	0
Infection	4 (4.6)	0	2 (2.3)	0

Data are presented as number (percentage) of patients.

DISCUSSION Although the standard of care for physically fit patients with CLL was established nearly a decade ago, after the results of the CLL8 study were published,¹¹ FCR is no longer an optimal treatment for frail and elderly individuals: in patients aged 65 years or older, the CR rate was 20%, as compared with 43% in younger ones.²⁴ There was no overall survival benefit observed in the elderly. In a study by Ferrajoli et al,²⁵ FC and FCR were complicated by severe myelotoxicity and infections in 60% and 22% of patients, respectively, leading to early treatment discontinuation.²⁵ The CLL10 study, comparing the FCR to the BR regimen, also failed to demonstrate better CR rates (36% and 32%, respectively) with a median PFS of 48 months in patients older than 65 years.²⁶ The less favorable outcomes of elderly patients treated with purine analogue-based protocols were due to low adherence caused by the high incidence of AEs. The incidence of severe hematologic toxicities and infections was higher with both regimens in elderly patients. In patients treated with BR, grade-3 and -4 neutropenia and infections were noted in 61% and 26% of patients, respectively,

and treatment-dose reduction was required in 56% of the cases.²⁶ The analysis of 555 elderly patients with CLL enrolled in 2 trials with first-line treatment of fludarabine (with and without cyclophosphamide) or chlorambucil (CLL4 and CLL5) identified comorbidities as an independent predictor of poor prognosis in terms of overall survival.²⁷ On the other hand, CLL was the major cause of death in patients with 2 or more comorbidities, suggesting the need for more efficient treatment but with a better safety profile.

The CLL11 study of the German CLL Study Group was the first clinical trial that was designed for unfit elderly patients with CLL. Obinutuzumab was approved by the European Medicine Agency in 2014 for use in combination with chlorambucil as a first-line therapy for CLL patients with comorbidities that make them unsuitable for full-dose fludarabine-based therapy. In Poland, obinutuzumab has been reimbursed since 2015, so the present report is the first Polish “real-world” analysis of the efficacy and safety of the obinutuzumab–chlorambucil regimen in clinical practice. It addresses the increasingly debated issue of differences between the populations treated in clinical trials and in routine practice.

In the CLL11 study, chlorambucil—regarded a standard of care at that time—was compared with its combination with rituximab and obinutuzumab in treatment-naïve CLL patients with coexistent conditions. The results for the obinutuzumab–chlorambucil regimen were superior to those of rituximab–chlorambucil, with the overall response rate of 58.4% vs 65.1%, including the CR rate of 20.7% vs 7% and almost doubled PFS (median, 29 vs 15 months).^{28,29} In a retrospective analysis of the PALG, patient demographic data were similar to those in the CLL11 registration

trial, with a median age of 74 years (63% of patients >70 years), a median CIRS score at baseline of 8, and similar rates of unfavorable cytogenetic and molecular aberrations. Our results confirmed the high efficacy of obinutuzumab–chlorambucil: we observed similar overall response rates and even an increased proportion of CR (43%) compared with the registration trial.^{28,29} This may be partially due to less stringent methods of response evaluation in clinical practice based on IWCLL criteria.¹⁸ Computed tomography and bone marrow biopsy are recommended for CR confirmation in clinical studies, while ultrasound imaging remains the preferred method in clinical practice.¹⁸ Similar results with higher CR rates as compared with a clinical trial^{30,31} were also reported in an observational study by Laurenti et al,³² who evaluated rituximab–chlorambucil as the first-line regimen in unfit patients with CLL. The other possible explanation is a lower number of patients with obinutuzumab dose reductions and therapy discontinuation in the PALG analysis. In the CLL11 trial, obinutuzumab was discontinued due to IRR in 7% of patients compared with 1.2% in the PALG analysis, while treatment had to be reduced or delayed in 36% and 0% of patients, respectively. This was probably due to enhanced obinutuzumab premedication, based on intravenous dexamethasone, acetaminophen, and clemastine, originally used only in a subgroup of CLL11 trial patients, after protocol amendment.

None of the patients in the PALG analysis progressed during therapy; in the median follow-up of 18 months, only 4 patients (4.7%) required second-line treatment. The good response rate was further confirmed by prolonged estimated PFS (62% at 30 months), also longer than in the CLL11 study (26.7 months). In the CLL8 trial, estimated PFS at 3 years was 68% in patients aged 65 years or older without significant comorbidities and normal renal function. It is surprising that in the PALG analysis the response rates in patients with del(17p) were similar to those observed for the whole group; however, there were only 7 patients with del(17p), and 3 of them had already progressed despite response to treatment.

In our analysis, obinutuzumab–chlorambucil was well tolerated with a lower number of AEs (of any grade) compared with the registration study. This could be due to a smaller percentage of patients with high CIRS scores: in the PALG study, the maximum CIRS score was 14, compared with 20 in the CLL11 trial. We also observed a lower incidence of grade-3 neutropenia or higher, possibly due to efficient secondary prophylaxis with G-CSF. No febrile neutropenia or serious grade-4 AEs were noted during the treatment or follow-up after the therapy. In addition, no deaths were reported. Autoimmune cytopenias are a common complication of CLL; therefore, the higher dose of steroids used in premedication in our study may account for the lower rates of anemia and thrombocytopenia.

The relatively high incidence of reactions related to obinutuzumab infusion is possibly caused by rapid and profound B-cell depletion and cytokine release due to recruitment and activation of immune effector cells.^{14,33} In our analysis, we observed significantly fewer allergic reactions to obinutuzumab infusion: grade-3 IRRs or higher were observed in 2.3% of cases, compared with 21% in the CLL11 trial. Again, this could be attributed to the enhanced premedication protocol.

The PALG study has limitations related to its retrospective design and the limited availability of data on the *IGHV* mutational status and cytogenetic/FISH tests. This reflects clinical practice in Poland, where the *IGHV* mutational status is evaluated only in a few hematology centers, since it does not influence therapeutic decisions. Similarly, cytogenetic/FISH tests for identifying high-risk patients are usually only performed in relapsed or refractory cases, because alternative drugs, including Bruton kinase inhibitors, are not available in Poland for patients on first-line treatment. There is also no historical control group, since CIRS scores have only recently been implemented in Poland, and patients were not stratified according to comorbidities in previous analyses.

In conclusion, the data from this retrospective analysis confirm the high efficacy and safety of obinutuzumab-based therapy in routine clinical practice. Longer follow-up, together with planned minimal residual disease analysis, will provide additional information on the real-life effectiveness and safety of this new standard of first-line treatment in CLL patients who are not eligible for intensive fludarabine-based immunochemotherapy.

CONTRIBUTION STATEMENT MD-D, WJ, and IH designed and performed the study, analyzed the data, and critically revised the manuscript for important intellectual content. MD-D, WJ, IH, and EŁ-C had substantial contribution to the concept and design of the work. MD-D and IH drafted the manuscript. MD-D, WJ, IH, EŁ-C, MM, KG, MD, AW, EW-Sz, AŁ, and KW contributed to the acquisition, analysis, and interpretation of data. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed with the content of the manuscript as written.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons AttributionNonCommercialShareAlike 4.0 International License ([CC BY-NC-SA 4.0](https://creativecommons.org/licenses/by-nc-sa/4.0/)), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for non-commercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.

REFERENCES

- 1 Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015; 26 Suppl 5: v78-84.
- 2 Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. *Blood*. 2009; 114: 3382-3391.
- 3 Woyach JA, Ruppert AS, Rai K, et al. Impact of age on outcomes after initial therapy with chemotherapy and different chemoimmunotherapy regimens in patients with chronic lymphocytic leukemia: results of sequential cancer and leukemia group B studies. *J Clin Oncol*. 2013; 31: 440-447.
- 4 Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2007; 25: 5616-5623.
- 5 Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med*. 2000; 343: 1750-1757.
- 6 Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. *Lancet*. 2007; 370: 230-239.
- 7 Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol*. 2009; 27: 4378-4384.
- 8 Eichhorst BF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood*. 2006; 107: 885-891.
- 9 Shvidel L, Shtalrid M, Bairey O, et al. Conventional dose fludarabine-based regimens are effective but have excessive toxicity in elderly patients with refractory chronic lymphocytic leukemia. *Leuk Lymphoma*. 2003; 44: 1947-1950.
- 10 Byrd JC, Rai K, Peterson BL, et al. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. *Blood*. 2005; 105: 49-53.
- 11 Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010; 376: 1164-1174.
- 12 Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2005; 23: 4079-4088.
- 13 Gentile M, Zirlik K, Ciolli S, et al. 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*. 2016; 60: 154-165.
- 14 Herter S, Herting F, Mundigl O, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. *Mol Cancer Ther*. 2013; 12: 2031-2042.
- 15 Patz M, Isaeva P, Forcob N, et al. Comparison of the in vitro effects of the anti-CD20 antibodies rituximab and GA101 on chronic lymphocytic leukaemia cells. *Br J Haematol*. 2011; 152: 295-306.
- 16 Ladyzynski P, Molik M, Foltynski P. A network meta-analysis of progression free survival and overall survival in first-line treatment of chronic lymphocytic leukemia. *Cancer Treat Rev*. 2015; 41: 77-93.
- 17 Stadler N, Shang A, Bosch F, et al. A Systematic Review and Network Meta-Analysis to Evaluate the Comparative Efficacy of Interventions for Unfit Patients with Chronic Lymphocytic Leukemia. *Adv Ther*. 2016; 33: 1814-1830.
- 18 Hallek M, Cheson BD, Catovsky D, et al. 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*. 2008; 111: 5446-5456.
- 19 Parmelee PA, Thuras PD, Katz IR, et al. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. *J Am Geriatr Soc*. 1995; 43: 130-137.
- 20 Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc*. 2008; 56: 1926-1931.
- 21 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16: 31-41.
- 22 Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med*. 2000; 343: 1910-1916.
- 23 Stilgenbauer S, Sander S, Bullinger L, et al. Clonal evolution in chronic lymphocytic leukemia: acquisition of high-risk genomic aberrations associated with unmutated VH, resistance to therapy, and short survival. *Haematologica*. 2007; 92: 1242-1245.
- 24 Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood*. 2016; 127: 208-215.
- 25 Ferrajoli A, O'Brien S, Wierda W, et al. Treatment of patients with CLL 70 years old and older: a single center experience of 142 patients. *Leuk Lymphoma*. 2005; 46(Suppl1):S86 (abstract P95).
- 26 Eichhorst B, Fink AM, Bahlo J, et al. 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*. 2016; 17: 928-942.
- 27 Goede V, Cramer P, Busch R, et al. Interactions between comorbidity and treatment of chronic lymphocytic leukemia: results of German Chronic Lymphocytic Leukemia Study Group trials. *Haematologica*. 2014; 99: 1095-1100.
- 28 Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014; 370: 1101-1110.
- 29 Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. *Leukemia*. 2015; 29: 1602-1604.
- 30 Foa R, Del Giudice I, Cuneo A, et al. Chlorambucil plus rituximab with or without maintenance rituximab as first-line treatment for elderly chronic lymphocytic leukemia patients. *Am J Hematol*. 2014; 89: 480-486.
- 31 Hillmen P, Gribben JG, Follows GA, et al. Rituximab plus chlorambucil as first-line treatment for chronic lymphocytic leukemia: Final analysis of an open-label phase II study. *J Clin Oncol*. 2014; 32: 1236-1241.
- 32 Laurenti L, Innocenti I, Autore F, et al. Chlorambucil plus rituximab as front-line therapy for elderly and/or unfit chronic lymphocytic leukemia patients: correlation with biologically-based risk stratification. *Haematologica*. 2017; 102: e352-e355.
- 33 Cartron G, de Guibert S, Dilhuyd MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. *Blood*. 2014; 124: 2196-2202. [↗](#)