Interactions between comorbidity and treatment of chronic lymphocytic leukemia: results of German Chronic Lymphocytic Leukemia Study Group trials

Valentin Goede,[1,2] Paula Cramer,[1] Raymonde Busch,[3] Manuela Bergmann,[4] Martina Stauch,[5] Georg Hopfinger,[6] Stephan Stilgenbauer,[4] Hartmut Döhner,[4] Anne Westermann,[1] Clemens M. Wendtner,[1,7] Barbara Eichhorst,[1] and Michael Hallek,[1,8] on behalf of the German CLL Study Group

[1]Department I of Internal Medicine, Center of Integrated Oncology Cologne-Bonn, University of Cologne, Germany; [2]Department of Geriatric Medicine and Research, St. Marien Hospital and University of Cologne, Germany; [3]Institute of Medical Statistics and Epidemiology, Technical University of Munich, Germany; [4]Department of Internal Medicine III, University of Ulm, Germany; [5]Private practice, Kronach, Germany; [6]Medical Department III, Paracelsus Medical University Salzburg, Austria; [7]Department of Hematology, Oncology, Immunology, Palliative Care, Infectious Diseases and Tropical Medicine, Schwabing Hospital, Munich, Germany; and [8]Cologne Excellence Cluster on Cellular Stress Responses in Aging Associated Diseases, University of Cologne, Germany

ABSTRACT

This study investigated the impact of comorbidity in 555 patients with chronic lymphocytic leukemia enrolled in two trials of the German Chronic Lymphocytic Leukemia Study Group on first-line treatment with fludarabine plus cyclophosphamide, fludarabine, or chlorambucil. Patients with two or more comorbidities and patients with less than two comorbidities differed in overall survival (71.7 *versus* 90.2 months; $P<0.001$) and progression-free survival (21.0 *versus* 31.5 months; $P<0.01$). After adjustment for other prognostic factors and treatment, comorbidity maintained its independent prognostic value in a multivariate Cox regression analysis. Chronic lymphocytic leukemia was the major cause of death in patients with two or more comorbidities. Disease control in patients with two or more comorbidities was better with fludarabine plus cyclophosphamide than with fludarabine treatment, but not with fludarabine compared to chlorambucil treatment. These results give insight into interactions between comorbidity and therapy of chronic lymphocytic leukemia and suggest that durable control of the hematologic disease is most critical to improve overall outcome of patients with increased comorbidity. The registration numbers of the trials reported are NCT00276848 and NCT00262795.

Introduction

Combined chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab has become the standard of care in previously untreated patients with chronic lymphocytic leukemia (CLL).[1,2] This regimen and comparable treatments have since been explored in different clinical settings in various CLL trials.[3-7] Most participants in these studies were relatively young and not affected by additional health problems. However, many CLL patients in routine practice are elderly and suffer from comorbidities.[8,9]

Recently, comorbidity was identified as an adverse prognostic factor in patients with untreated or treated CLL.[9,10] The underlying causes of the shorter survival of these patients have remained unclear so far, resulting in uncertainty whether treatment approaches in patients with CLL and comorbidity should focus on the prevention of therapy-related morbidity and mortality or whether the potential loss of disease control associated with such a strategy will offset its net benefits by increasing disease-related morbidity and mortality.

To better understand the modes of interaction between comorbidity and CLL therapy, we assessed the comorbidity burden in patients enrolled in the CLL4 and CLL5 trials of the German Chronic Lymphocytic Leukemia Study Group (GCLLSG)[11,12] and investigated its impact on treatment outcome in detail.

Methods

Study population

From June 1999 until July 2003, a total of 581 patients from Germany and Austria were accrued to the CLL4 and CLL5 trials of the GCLLSG: 375 younger patients (up to 65 years) were enrolled in the CLL4 trial and randomized to receive either fludarabine alone or fludarabine plus cyclophosphamide; 206 elderly patients (65 years or older) were enrolled in the CLL5 trial and were treated with either fludarabine or chlorambucil. In both studies, the diagnosis of CLL was confirmed according to the 1996 guidelines of the National Cancer Institute sponsored Working Group (NCI-WG).[13] Only treatment-naïve patients fulfilling the NCI-WG/IWCLL criteria for treatment requirement were included.[13,14] Study treatments were administered as previously reported.[11,12] Treatment response and status of remission during follow-up were assessed according to the NCI-WG guidelines.[13] Treatment toxicity was judged according to the NCI Common Toxicity Criteria (CTC version 2.0).[15] For patients who died the cause of death was determined by the treating physician based on the available clinical information and sometimes autopsy reports. Based on

 doi:10.3324/haematol.2013.096792
The online version of this article has a Supplementary Appendix.
Manuscript received on August 15, 2013. Manuscript accepted on February 26, 2014.
Correspondence: valentin.goede@uk-koeln.de

this on-site documentation, causes of death were grouped into the following categories: therapy-related, CLL-related, CLL-unrelated, or unknown. Both studies were approved by the Institutional Review Board and Ethics Committee of the University of Munich and performed in accordance with the Declaration of Helsinki.

Comorbidity assessment

For both trials, comorbid conditions present at baseline had to be assessed and documented in the patient's case report form by the treating physician. Further quantification of the comorbidity burden by use of specific comorbidity scores was not part of the study protocols. Thus, all comorbid conditions reported within the case report form were captured only in a qualitative manner. Health problems resulting from the CLL itself and CLL as the primary disease were not recorded as comorbidity.

To assess the comorbidity burden for each patient individually in the absence of quantitative data derived from scores, the number of comorbidities was calculated as the sum of all conditions abstracted from the patient's case report form according to the rules described above. Since information on the severity of comorbid conditions was mostly unobtainable, a retrospective scoring of comorbidity by use of a validated comorbidity score was not reliably possible (although an attempt was made to calculate the Charlson comorbidity index from the available data).[16] For a general description of the spectrum of comorbidities in the study population, each of the concomitant diseases was assigned to disease categories abstracted from the Cumulative Illness Rating Scale.[17]

Statistical analysis

The statistical analysis was performed with SPSS 17 software (SPSS Inc., USA) and based on data collected by December 17th 2009 for the CLL4 trial and August 1st 2007 for the CLL5 trial (parts of this analysis were also performed earlier on a 2005 dataset and previously presented in abstract format). Estimates of overall and progression-free survival were calculated using the Kaplan-Meier method. The log-rank test was used to compare survival times between groups. A Cox regression model was applied for univariate and multivariate analyses to estimate hazard ratios. Parameters others than survival were compared using the χ^2 test and the Fisher exact test.

Further details on the methods of this study are available in the *Online Supplementary Appendix*.

Results

Baseline characteristics

Of the 581 patients recruited into the CLL4 and CLL5 trials, 555 were eligible for this analysis. Twenty-six patients were excluded because of inaccurate diagnosis (n=5), no need of therapy (n=2), previous therapy (n=3), consent issues (n=6), or other reasons (n=10). The characteristics of the study population are summarized in Table 1. The median time of follow-up for all patients was 58 months. Patients treated within the CLL4 and CLL5 trials were younger and older, respectively (median: 58 *versus* 70 years).

Comorbidity burden

The patients' comorbidity burden at baseline is presented in Table 2 and *Online Supplementary Table S1*. Fifty-three percent of the patients had at least one concurrent disease. The number of comorbidities ranged from zero to seven (median: 1) and increased continuously with advanced age (P<0.001). Of 139 patients presenting with more than one comorbidity, most had two or three co-existing diseases, while there were only 24 patients with more than three health problems.

Impact of comorbidity on overall prognosis

By univariate analysis, patients with ≥2 comorbidities had a significantly shorter median overall survival than patients with <2 comorbid conditions (71.7 *versus* 90.2 months, P<0.001). Differences in survival between these groups of patients were significant in both younger (CLL4

Table 1. Baseline characteristics of patients (all subjects and by trial).

	Total (n=555)	CLL4 (n=362)	CLL5 (n=193)
Male sex, n. (%)	388 (70)	266 (74)	122 (63)
Age group, n. (%)			
30-39 years	11 (2)	11 (3)	-
40-49 years	53 (9)	53 (15)	-
50-59 years	149 (27)	149 (41)	-
60-69 years	238 (43)	149 (41)	89 (46)
70+ years	104 (19)	-	104 (54)
ECOG performance status, n. (%)			
0	257 (50)	181 (53)	76 (44)
1	237 (46)	150 (44)	87 (50)
2	20 (4)	10 (3)	10 (6)
Binet stage, n. (%)			
A	62 (11)	34 (9)	28 (15)
B	293 (53)	204 (56)	89 (47)
C	196 (36)	124 (34)	72 (38)
Risk factors, n/pts analyzed (%)			
TK > 10 U/L	353/477 (74)	247/329 (75)	106/148 (72)
β2M > 3.5 mg/dL	235/488 (48)	141/339 (42)	94/149 (63)
17p-	26/479 (5)	16/317 (5)	10/162 (6)
11q-	88/476 (19)	66/315 (21)	22/161 (14)
12+	78/469 (17)	42/308 (14)	36/161 (22)
IGHV unmutated	270/418 (65)	215/330 (65)	55/88 (63)
Treatment allocation, n. (%)			
Fludarabine+cyclophosphamide	180 (32)	180 (50)	-
Fludarabine	275 (50)	182 (50)	93 (48)
Chlorambucil	100 (18)	-	100 (52)

ECOG: Eastern Cooperative Oncology Group; pts: patients; TK: thymidine kinase; β2M: β_2-microglobulin; IGHV: *immunoglobulin heavy chain region;*

Table 2. Comorbidity burden of patients (all subjects and by trial).

	Total (n=555)	CLL4 (n=362)	CLL5 (n=193)
Number of comorbidities, n. (%)			
0	260 (47)	192 (53)	68 (35)
1	156 (28)	94 (26)	62 (32)
≥ 2	139 (25)	76 (21)	63 (33)
Disease category, n. (%)			
Cardiac	65 (12)	25 (7)	40 (21)
Vascular	118 (21)	63 (17)	55 (29)
Respiratory	28 (5)	13 (4)	15 (8)
Eyes/ears/nose/throat	9 (2)	7 (2)	2 (1)
Intestinal	20 (4)	10 (3)	10 (5)
Hepatic	13 (2)	7 (2)	6 (3)
Renal	14 (3)	4 (1)	10 (5)
Urogenital	22 (4)	11 (3)	11 (6)
Metabolic/endocrine	145 (26)	89 (25)	56 (29)
Musculoskeletal	26 (5)	15 (4)	11 (6)
Neurological	10 (2)	7 (2)	3 (2)
Psychiatric	8 (1)	6 (2)	2 (1)

trial) and older (CLL5 trial) patients. In a multivariate analysis including additional variables with potential impact on overall survival (gender, age, performance status, disease stage, thymidine kinase and β_2-microglobulin levels, and treatment regimen), comorbidity maintained its independent prognostic value (Figure 1). The Charlson comorbidity index was also prognostic, but less suitable for further endpoint studies because of the limited number of subjects with higher scores (*Online Supplementary Figure S1*). Specific comorbidities predicting overall survival could not be identified.

Higher 1-year and 5-year mortality rates in the group of patients with ≥2 comorbidities were attributable to a combined increase of therapy-related, CLL-related, and CLL-unrelated deaths during and after treatment (Table 3). However, deaths considered CLL-related by the treating physicians contributed most to increased mortality in these patients.

Impact of comorbidity on treatment efficacy

Patients with ≥2 comorbidities had an overall response to treatment of 75% compared to 85% in patients with <2 comorbidities (P<0.05) (Table 4). There were, however, no significant differences in overall response rates between these two groups of patients when adjusting for age or treatment (*Online Supplementary Table S2*), i.e. lower overall response rates in patients with ≥ 2 comorbidities were biased by more frequent use of less intense regimens (fludarabine alone, chlorambucil) in these patients.

By univariate analysis, the median progression-free survival was shorter in patients with ≥2 comorbidities than in patients with <2 comorbidities (21.0 *versus* 31.5 months; P<0.01). Differences in progression-free survival between the groups of patients were minimal when younger (CLL4 trial) and older (CLL5 trial) patients were analyzed separately, but in a multivariate analysis performed in all subjects and including other parameters with potential impact on progression-free survival (gender, age, performance status, disease stage, thymidine kinase and β_2-microglobulin levels, and treatment regimen), comorbidity continued to be an independent determinant of progression-free survival (Figure 2).

The longest progression-free survival in patients with ≥2 comorbidities was seen in those receiving combined purine analog-based chemotherapy. Independently of their comorbidity burden, younger patients treated in the CLL4 trial benefited from the use of this combination treatment while older patients treated in the CLL5 trial had no benefit from the use of a purine analog compared to alkylator-based treatment (Figure 3).

Impact of comorbidity on treatment tolerability

Incidence rates of grade 3-4 adverse events caused by the study treatment were not significantly different in patients with ≥2 *versus* <2 comorbidities (Table 4). Significant differences in toxicity between these two groups were not found when patients were analyzed separately by age or treatment (*Online Supplementary Table S3*), i.e. equal toxicity was not solely due to more frequent use of less intense regimens (fludarabine alone, chlorambucil) in patients with ≥2 comorbidities. There was no association between occurrence of toxicity and specific comorbidities.

Doses of study drugs were more frequently reduced in patients with ≥2 comorbidities than in patients with <2 comorbidities (40% *versus* 31%; P<0.05) and therapy was

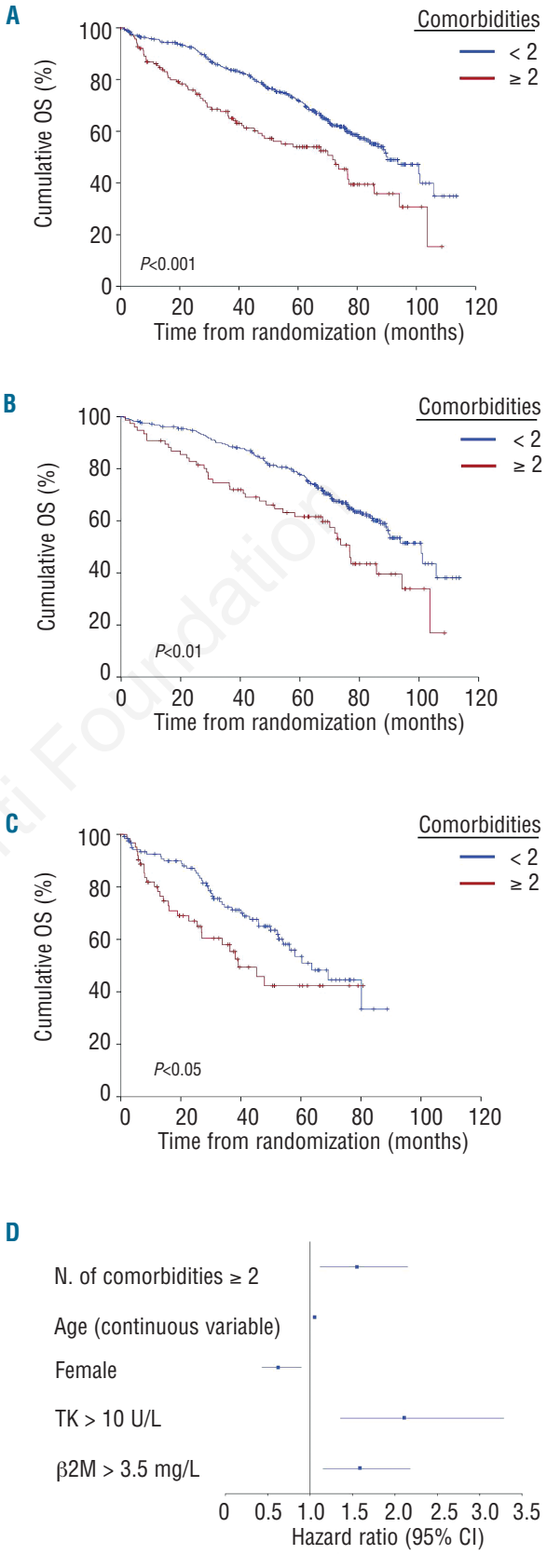

Figure 1. Overall survival (OS) by number of comorbidities. Kaplan-Meier estimates for (A) all subjects, (B) CLL4 subjects, (C) CLL5 subjects. Hazard ratios (D) of prognostic factors identified by multivariate analysis (boxes represent the hazard ratios, lines the 95% confidence intervals). TK: thymidine kinase; β2M: β_2 microglobulin.

discontinued in 45% of patients with ≥ 2 comorbidities compared to 31% of those with < 2 comorbidities (P<0.01).

Discussion

Two retrospective studies recently reported on comorbidity as a prognostic factor in CLL.[9,10] The aim of this study of 555 subjects enrolled in the CLL4 and CLL5 trials of the GCLLSG was to explore the underlying causes of the poorer outcome observed in CLL patients with comorbidity.

In subjects with cancers others than CLL, comorbidity is associated with shortened survival,[18-23] and commonly has the greatest impact in patients with early-stage tumors while losing its relevance in patients with advanced-stage tumors.[24] Our study identifies comorbidity as an independent predictor of poor prognosis specifically in patients with progressive CLL treated with chemotherapy. Rather than becoming less important with more advanced disease, this finding suggests clinically meaningful interactions between comorbidity and CLL when treatment must be given. Understanding the nature of this interaction is crucial to the choice of appropriate treatments for CLL patients with comorbidity, and further dissection of the interaction in our study led to important findings. First, deaths considered CLL-related by the treating physicians were the major contributor to higher mortality in patients with increased comorbidity. Second, disease control was less sufficient in patients with increased comorbidity than in subjects with little or no comorbidity. As shown by multivariate analysis, this finding was not entirely

Table 3. Mortality by number of comorbidities.

	N. of comorbidities		Odds ratio
	0 or 1	≥ 2	
1-year mortality			
All-cause	4 %	14 %	3.5
Therapy-related	1 %	2 %	3.0
CLL-related	3 %	9 %	2.9
CLL-unrelated	0 %	2 %	9.1
Unknown	0 %	1 %	3.0
5-year mortality			
All-cause	25 %	40 %	2.1
Therapy-related	1 %	3 %	4.1
CLL-related	15 %	25 %	1.9
CLL-unrelated	4 %	8 %	2.1
Unknown	5 %	4 %	0.8

Table 4. Treatment response and toxicity by number of comorbidities.

	N. of comorbidities		P
	0 or 1	≥ 2	
Treatment response			
Overall response	85 %	75 %	< 0.05
Complete response	12 %	8 %	0.204
Treatment toxicity			
Hematologic grade 3-4	44 %	45 %	0.917
Infections grade 3-4	8 %	9 %	0.759
Others grade 3-4	16 %	19 %	0.341
Dose reduction	31 %	40 %	< 0.05
Discontinuation	31 %	45 %	< 0.01

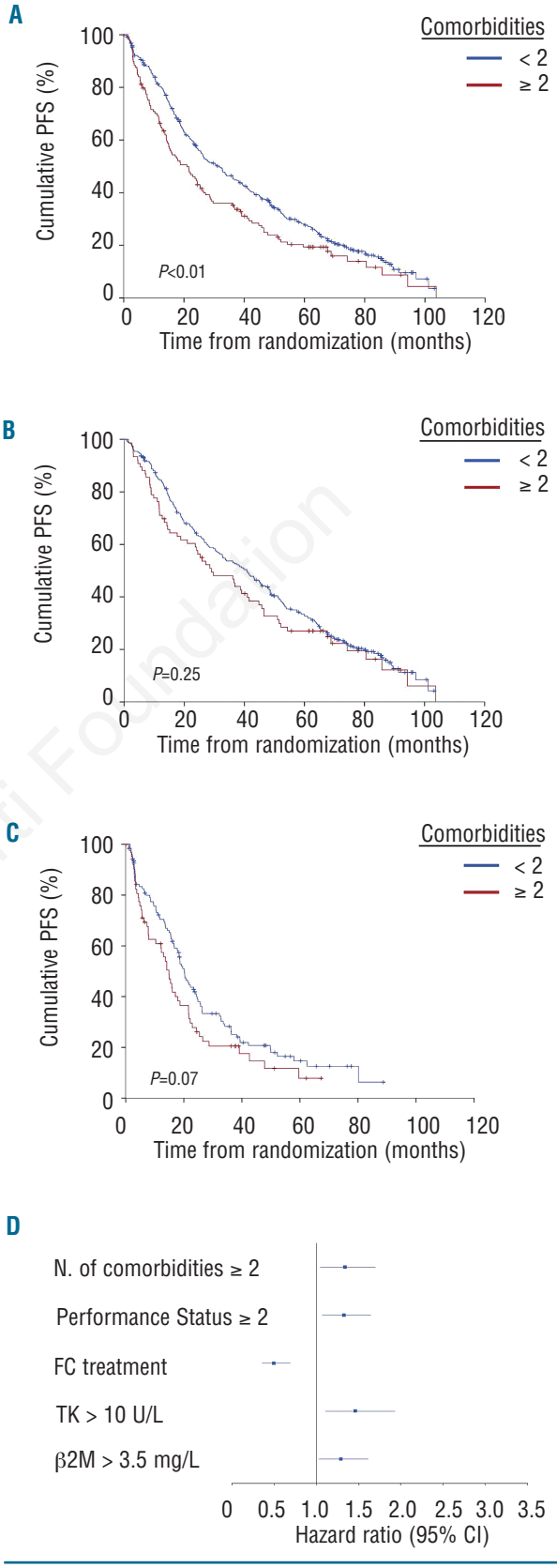

Figure 2. Progression-free survival (PFS) by number of comorbidities. Kaplan-Meier estimates for (A) all subjects, (B) CLL4 subjects, (C) CLL5 subjects. Hazard ratios (D) of predictive factors identified by multivariate analysis (boxes represent the hazard ratios, lines the 95% confidence intervals). FC: fludarabine+cyclophosphamide; TK: thymidine kinase; β2M: β_2 microglobulin.

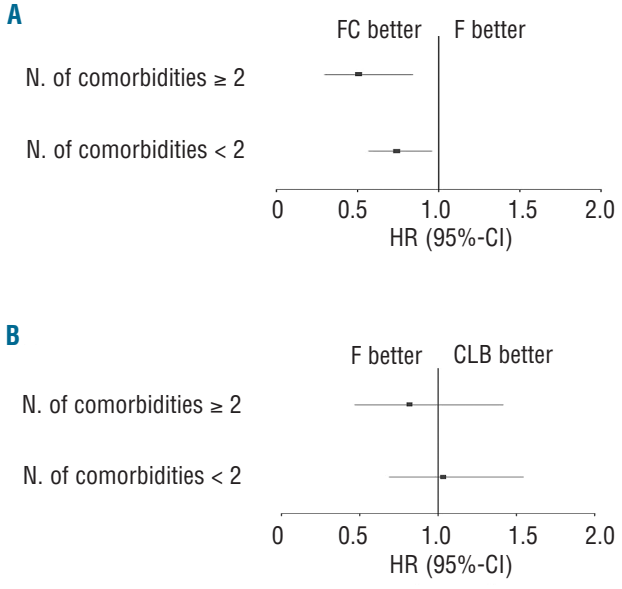

Figure 3. Hazard ratios (HR) for progression-free survival by number of comorbidities and treatment. (A) Fludarabine+cyclophosphamide (FC) *versus* fludarabine (F), (B) F *versus* chlorambucil (CLB).

explained by differences in administered treatment regimens and trial allocation. Likely, the observed loss of disease control in patients with increased comorbidity was also due to more dose reductions and treatment discontinuations in these patients. Despite these dose reductions and treatment discontinuations, toxicity rates in such patients were still equivalent to those in subjects with little or no comorbidity. Together, these observations suggest that CLL patients with increased comorbidity are at greater risk of dose attenuations which will limit therapy-related morbidity, but at the expense of higher CLL-related morbidity and, thereby, mortality.

Treatments able to achieve durable control of CLL rather than only symptom control or undue protection from potential side effects thus appear important for these patients. In our study, disease control in such patients was best obtained through the most intensive therapy (combined chemotherapy). A limitation of this study is, however, that it was restricted to chemotherapy-treated CLL patients prior to the introduction of monoclonal antibodies and other experimental compounds. It does not, therefore, enable a specific therapeutic regimen to be recommended for patients with increased comorbidity. Neither does it allow a definitive conclusion that, over adverse events and intercurrent illness, uncontrolled CLL due to dose attenuations will also be the major threat to these patients in the era of chemoimmunotherapy. Nonetheless, current standard therapy with fludarabine, cyclophosphamide and rituximab in community-based patients was recently associated with limited adherence to the dosing schedule and a significant risk of losing treatment efficacy due to dose attenuations.[25] These findings support our conclusion that in CLL patients with comorbidity, the use of therapies that have sufficient antileukemic activity but that can also be administered without significant loss of dose intensity (i.e. therapies carefully balanced for treatment activity and adherence) is critical.

Both trials considered for this study were conducted prior to the use of specific comorbidity scores in CLL trials (mostly the Cumulative Illness Rating Scale which uses severity and number of concurrent conditions as a surrogate for comorbidity burden).[17] While it was difficult to abstract severity of comorbidities from recorded data, the number of comorbidities could be assessed easily and reflect, in part at least, what is normally captured by comorbidity scores. The limited means to weigh the severity of comorbidities further could, however, explain why our study was unable to identify single conditions associated with poor outcome. This inability was likely compounded by the lower prevalence of comorbidities (53%) in our study compared to that in the general CLL population (90%).[9] Even with this selection bias, dissecting the impact of comorbidity in a clinical trial population has strengths, because it allows for the analysis of endpoints which cannot be well studied in samples of patients derived from other sources. Population-based patients' registries usually do not record outcome measures of treatment efficacy and tolerability in great detail and information on cause-specific in addition to all-cause mortality is rarely available. It is also difficult to retrieve information on cause-specific deaths from standard patients' charts. Determining the cause of death in individual CLL patients requires detailed knowledge of the clinical course and it is sometimes difficult even if an autopsy is performed. However, since clinical data are collected with greatest accuracy in interventional trials, it can be expected that the risk of misclassification is lowest in this setting.

In summary, this study identifies comorbidity as an independent predictor of adverse outcome in CLL. Trials in CLL should, therefore, document comorbidity accurately, ideally through the use of comorbidity scores. Dissection of interactions between comorbidity and CLL treatment indicated that proper control of CLL appears most important for improving the overall prognosis of CLL patients with comorbidity. This knowledge must be taken into account when designing randomized trials in this population of patients and when treating such patients in routine clinical practice.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Gribben JG, O'Brien S. Update on therapy of chronic lymphocytic leukemia. J Clin Oncol. 2011;29(5):544-50.
2. Hallek M, Pflug N. State of the art treatment of chronic lymphocytic leukaemia. Blood Rev. 2011;25(1):1-9.
3. Tam CS, O'Brien S, Wierda W, Kantarjian H, Wen S, Do KA, et al. Long term results of the fludarabine, cyclophosphamide & rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood. 2008;112(4):975-80.
4. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, 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(9747):1164-74.
5. Robak T, Dmoszynska A, Solal-Celigny P, Warzocha K, Loscertales J, Catalano J, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophos-

phamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2010;28(10):1756-65.
6. Kay NE, Geyer SM, Call TG, Shanafelt TD, Zent CS, Jelinek DF, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood. 2007;109(2):405-11.
7. Reynolds C, Di Bella N, Lyons RM, Hyman W, Richards DA, Robbins GJ, et al. A phase III trial of fludarabine, cyclophosphamide, and rituximab vs. pentostatin, cyclophosphamide, and rituximab in B-cell chronic lymphocytic leukemia. Invest New Drugs. 2012;30(3):1232-40.
8. Seer.Cancer.gov [Internet]. Bethesda: NCI Surveillance, Epidemiology and End Results (SEER) Program. SEER Stat Fact Sheets: Chronic Lymphocytic Leukemia [cited 2013 May 7]. Available from http://seer.cancer.gov/.
9. Thurmes P, Call T, Slager S, Zent C, Jenkins G, Schwager S, et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. Leuk Lymphoma. 2008;49(1):49-56.
10. Reyes C, Satram-Hoang S, Hoang K, Momin F, Guduru SR, Skettino S. What is the impact of comorbidity burden on treatment patterns and outcomes in elderly chronic lymphocytic leukemia patients? Blood. 2012;120(21):758.
11. Eichhorst BF, Busch R, Hopfinger G, Pasold R, Hensel M, Steinbrecher C, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood. 2006;107(3):885-91.
12. Eichhorst BF, Busch R, Stilgenbauer S, Stauch M, Bergmann MA, Ritgen M, 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(16):3382-91.
13. Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood. 1996;87(12):4990-7.
14. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, 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(12):5446-56.
15. CTEP.Cancer.gov [Internet]. Bethesda: NCI Cancer Therapy Evaluation Program (CTEP). Retired CTC and CTCAE Versions Archive: CTC v2.0 [cited 2013 May 7]. Available from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ ctc.htm/.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
17. Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. J Am Geriatr Soc. 1995;43(2):130-7.
18. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA. 2004;291(20):2441-7.
19. Janssen-Heijnen ML, van Spronsen DJ, Lemmens VE, Houterman S, Verheij KD, Coebergh JW. A population-based study of severity of comorbidity among patients with non-Hodgkin's lymphoma: prognostic impact independent of International Prognostic Index. Br J Haematol. 2005;129(5):597-606.
20. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912-9.
21. Hines RB, Chatla C, Bumpers HL, Waterbor JW, McGwin G, Jr., Funkhouser E, et al. Predictive capacity of three comorbidity indices in estimating mortality after surgery for colon cancer. J Clin Oncol. 2009;27(26):4339-45.
22. Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol. 2011;29(10):1335-41.
23. Wang S, Wong ML, Hamilton N, Davoren JB, Jahan TM, Walter LC. Impact of age and comorbidity on non-small-cell lung cancer treatment in older veterans. J Clin Oncol. 2012;30(13):1447-55.
24. Read WL, Tierney RM, Page NC, Costas I, Govindan R, Spitznagel EL, et al. Differential prognostic impact of comorbidity. J Clin Oncol. 2004;22(15):3099-103.
25. Bouvet E, Borel C, Oberic L, Compaci G, Cazin B, Michallet AS, et al. Impact of dose intensity on outcome of fludarabine, cyclophosphamide, and rituximab regimen given in the first-line therapy for chronic lymphocytic leukemia. Haematologica. 2013;98(1):65-70.