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## Phase III Randomized Study of Bendamustine Compared With Chlorambucil in Previously Untreated Patients With Chronic Lymphocytic Leukemia

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### ABSTRACT

#### Purpose

This randomized, open-label, parallel-group, multicenter study was designed to compare the efficacy and safety of bendamustine and chlorambucil in previously untreated patients with advanced (Binet stage B or C) chronic lymphocytic leukemia (CLL).

#### Patients and Methods

Patients ( $\leq 75$  years of age) were randomly assigned to receive bendamustine 100 mg/m<sup>2</sup>/d intravenously on days 1 to 2, or chlorambucil 0.8 mg/kg (Broca's normal weight) orally on days 1 and 15; treatment cycles were repeated every 4 weeks for a maximum of six cycles. The response to treatment was assessed according to National Cancer Institute Working Group criteria, and the final determination of response was made by a blinded independent review committee.

#### Results

A total of 319 patients were randomly assigned (162 bendamustine, 157 chlorambucil). Complete or partial responses were achieved in 110 (68%) of 162 bendamustine-treated and 48 (31%) of 157 chlorambucil-treated patients ( $P < .0001$ ). More patients showed complete responses with bendamustine than with chlorambucil (31% v 2%). Median progression-free survival was 21.6 months with bendamustine and 8.3 months with chlorambucil ( $P < .0001$ ). Bendamustine was also associated with an improvement in duration of remission, compared with chlorambucil (median, 21.8 v 8.0 months). Hematologic National Cancer Institute Common Toxicity Criteria grade 3 to 4 adverse events were more common with bendamustine than with chlorambucil (occurring in 40% v 19% of patients). Severe infections (grade 3 to 4) occurred in 8% of bendamustine-treated patients and 3% of chlorambucil-treated patients.

#### Conclusion

Bendamustine offers significantly greater efficacy than chlorambucil, and a manageable toxicity profile, when used as first-line therapy in patients with advanced CLL.

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### INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia in the Western world.<sup>1</sup> Although patients with early-stage disease have a life expectancy of longer than 10 years, those who progress or have advanced disease (Binet stage B or C or Rai stage II to IV) have a median survival of approximately 2 to 7 years.<sup>2,3</sup> First-line treatment is frequently conducted with chlorambucil, fludarabine, or fludarabine plus cyclophosphamide, either alone or in combination with rituximab. Fludarabine has been reported to produce higher response rates, a longer duration of remission, and longer progression-free survival than chlorambucil in previously untreated younger patients with CLL, but

without affecting overall survival.<sup>4,5</sup> However, there remains a need for new treatment options in patients with advanced CLL.

Bendamustine is a novel agent, synthesized with the intent of combining the alkylating properties of mechlorethamine and the purine antimetabolite properties of benzimidazole.<sup>6,7</sup> This agent, alone or in combination with other chemotherapeutic agents, has been shown to produce good clinical efficacy and acceptable tolerability in patients with non-Hodgkin's lymphoma<sup>8,9</sup> and multiple myeloma.<sup>10</sup> In phase I/II trials in patients with advanced relapsed or refractory CLL, bendamustine has been shown to produce overall response rates (ORR) similar to or higher than those achieved with chlorambucil.<sup>11-14</sup> Therefore, a phase III trial was

undertaken to compare the efficacy and tolerability of bendamustine with that of chlorambucil in previously untreated patients with CLL.

## PATIENTS AND METHODS

The study was a randomized, open-label, parallel-group, phase III trial conducted at 45 centers in Austria, Bulgaria, France, Germany, Italy, Spain, Sweden, and the United Kingdom. The protocol was approved by local ethics committees at all participating centers, and the study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

### Patients

Previously untreated patients up to 75 years of age with Binet stage B (ie,  $\geq 3$  lymph node regions involved including hepatomegaly and splenomegaly) or Binet stage C (ie, anemia and/or thrombocytopenia regardless of the number of lymph node regions) CLL confirmed by demonstration of coexpression of CD5, CD23, and either CD19, CD20, or both, and in need for treatment<sup>15,16</sup> were included. All patients were required to have a WHO performance status of 0 to 2 and a life expectancy of at least 3 months. Women of childbearing potential were required to use adequate contraception for at least 6 months after treatment. Patients with a second malignancy other than cured basal cell carcinoma or cured cervical cancer were excluded, as were patients with manifest immune hemolysis or thrombocytopenia that could be treated with corticosteroids alone, and patients with Richter's syndrome or transformation to prolymphocytic leukemia. Other exclusion criteria were hepatic dysfunction (bilirubin  $> 2.0$  mg/dL, transaminases  $> 3 \times$  upper limit of normal, or both), renal dysfunction (calculated creatinine clearance  $< 30$  mL/min), significant medical or mental disorders, known HIV infection, pregnancy or lactation, hypersensitivity to study drugs, major surgery within 30 days before the start of the trial, and participation in another clinical trial within 4 weeks before the study. Written informed consent was obtained from all patients before inclusion in the study.

Recruitment started in November 2002 and was stopped in November 2006.

### Study Design and Treatment

Patients were randomly assigned in a 1:1 ratio to receive bendamustine or chlorambucil, and stratified by center and Binet stage. Bendamustine (Ribosepharm, Munich, Germany) was administered by intravenous infusion over 30 minutes at a dose of 100 mg/m<sup>2</sup>/d on days 1 to 2 every 4 weeks. Chlorambucil (GlaxoSmithKline, Uxbridge, United Kingdom) was given orally at a dose of 0.8 mg/kg (Broca's normal weight in kg; the body weight for the dose being the height of the patient in cm minus 100) on days 1 and 15 (or as divided doses on days 1 to 2 and 15 to 16 for patient comfort in some individual cases) every 4 weeks. Treatment was to be suspended if platelet counts decreased to below  $20 \times 10^9/L$ , hemoglobin decreased to below 7 g/dL, or the absolute neutrophil count decreased to lower than  $0.5 \times 10^9/L$ . Doses were to be modified according to the National Cancer Institute Working Group guidelines<sup>15</sup> if hematologic toxicities developed. For Common Toxicity Criteria grade 3 nonhematologic toxicities other than nausea and vomiting or alopecia, the dose was to be reduced by 50% or the patient withdrawn from the study, depending on the investigator's judgment; if any grade 4 toxicity developed, the patient was to be withdrawn. Patients for whom dose reduction was necessary could have the dose restored to the original level if they had tolerated the reduced dose. Prophylactic hyperuricemic treatment was recommended to prevent uric acid-induced nephropathy. Nonprotocol antineoplastic drugs were not allowed. The study protocol did not provide recommendations for the prophylactic use of antibiotics or antiemetics. The use of hematopoietic growth factors was discouraged.

Patients were assessed for response after three cycles of treatment. Two additional cycles were recommended for patients with complete response (CR) or partial response (PR), up to a maximum limit of six cycles in total. The response criteria according to the National Cancer Institute Sponsored Working Group guidelines for CLL<sup>15</sup> had to be met for at least 8 weeks. Patients with no change were allowed to receive additional cycles at the discretion of the

investigator to the same maximum of six cycles. Patients with progressive disease were withdrawn. After the last treatment cycle, patients were monitored for response and survival at 3-month intervals. Final assessment of best response was performed in a blinded fashion by an Independent Committee for Response Assessment (ICRA) and classified as CR, PR, PR with nodular involvement, stable disease, or progressive disease based on the National Cancer Institute Working Group criteria.<sup>15</sup>

Primary end points were the overall response rate and progression-free survival. Secondary end points included time to progression, duration of remission, and overall survival. Safety end points were infection rates and adverse events.

### Statistical Methods and Sample Size Calculation

The statistical analysis was performed on the intention-to-treat (ITT) patient population. The safety population consisted of all patients who received at least one dose of study medication.

Statistical analysis of the primary end points was performed by means of an a priori–sequenced hypothesis testing and an adaptive group sequential test procedure. Overall remission rate was analyzed by means of Fisher's exact test, stratified by Binet stage; progression-free survival was analyzed by log-rank test, stratified by Binet stage. All tests were two tailed with a multiple significance level of  $\alpha = 5\%$ .

A five-stage adaptive group sequential procedure with Pocock cut-offs of  $\alpha_i = .016$  was used, with a maximum of four planned interim analyses, of which three were performed (first analysis after treated 85 patients with a follow-up of at least 5 months; second analysis after 158 patients; third analysis after 264 patients). In each interim analysis, ORR was tested first, while progression-free survival was tested only if the first was significant, thus controlling for multiple testing.<sup>17</sup> The *P* values of the individual sequences were combined using the  $\varphi^{-1}$  method<sup>17</sup>; since patients included in each interim

**Table 1.** Demographic Characteristics of the Intention-to Treat Population

Characteristic	BEN		CLB	
	No.	%	No.	%
No. of patients	162		157	
Sex				
Female	60	37.0	62	39.5
Male	102	63	95	60.5
WHO performance status				
Missing	3	1.9	5	3.2
0	113	69.8	102	65.0
1	43	26.5	45	28.7
2	3	1.9	5	3.2
Age, years				
Mean	63.0		63.6	
SD	7.5		8.8	
Min-Max	45.0-77.0		35.0-78.0	
Median	63.0		66.0	
Q1-Q3	58.0-70.0		59.0-70.0	
Binet stage				
B	116	71.6	111	70.7
C	46	28.4	46	29.3
B symptoms				
Yes	80	49.4	79	50.3
No	81	50.0	74	47.1
Unknown	1	0.6	4	2.5
LDH				
Normal	84	51.9	80	51.0
Out of normal ranges	73	45.1	66	42.0
Not done	5	3.1	6	3.8

Abbreviations: BEN, bendamustine; CLB, chlorambucil; SD, standard deviation; LDH, lactate dehydrogenase.

**Table 2.** Quality of Response According to Independent Committee for Response Assessment: Intention-to-Treat Population

Variable	Binet Stage											
	B				C				B + C			
	BEN		CLB		BEN		CLB		BEN		CLB	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients overall	116		111		46		46		162		157	
Complete response	41	35	3	3	9	20	0	0	50	31	3	2
Nodular partial response	14	12	4	4	3	7	0	0	17	11	4	3
Partial response	27	23	31	28	16	35	10	22	43	27	41	26
Overall response rate	82	71	38	34	28	61	10	22	110	68	48	31

Abbreviations: BEN, bendamustine; CLB, chlorambucil.

analysis were still under observation, these values were not definitive, and were used only to determine whether to continue the study with the new sample size or to terminate the study. After each interim analysis the safety and efficacy data were reviewed by an independent data monitoring committee who decided about study continuation. After the third interim analysis, the independent data monitoring committee recommended the termination of the recruitment and the final analysis to be performed with the available data. Thus, the enrollment of patients stopped in November 2006.

Sample size calculations were based on data from a study comparing fludarabine and chlorambucil in previously untreated CLL patients,<sup>4</sup> which suggesting a 30% difference in overall remission rate between treatments, and a 6-month difference in median progression-free survival. From this, it was calculated that approximately 42 patients per group would be required to achieve 80% power to show a significant difference in overall response rate, assuming a two-sided level of statistical significance of  $\alpha = .05$ . For the second primary end point— progression-free survival—it was calculated that a total of 326 patients would be required if no interim analyses were to be performed. Since it was uncertain whether the assumptions based on the data from the previous study<sup>4</sup> would apply to this study, the adaptive group sequential procedure described above was used. Using this approach, the final sample size was estimated to be approximately 350 patients.

## RESULTS

Between November 2002 and November 2006, 319 patients were randomly assigned, 162 to bendamustine and 157 to chlorambucil. Six patients randomly assigned to chlorambucil and one to bendamustine were not treated. The ITT population includes all 319 randomly assigned patients and the safety population includes 312 treated patients.

Demographic characteristics of the ITT population are summarized in Table 1. Overall, patient characteristics were well balanced between the groups. One hundred sixteen (72%) in the bendamustine group and 111 (71%) in the chlorambucil group had Binet stage B disease, while 46 (28%) and 46 (29%), respectively, had stage C disease. The mean time from initial diagnosis to registration in the trial was 18.8 months (standard deviation [SD], 32.3) in the bendamustine group and 24.6 months (SD, 33.9) in the chlorambucil group ( $P = .12$ ).

### Efficacy

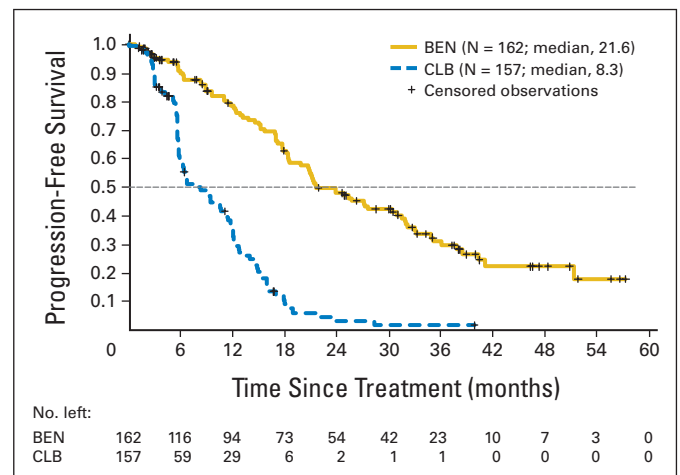
The median number of treatment cycles per patient was six in both arms. The mean number of treatment cycles per patient was 4.9 (SD, 1.7) with bendamustine and 4.9 (SD, 1.7) with chlorambucil. Overall, 54 patients (34%) in the bendamustine group and 46 (31%)

in the chlorambucil group required at least one dose reduction. The principal reasons for dose reduction in both groups were neutropenia and thrombocytopenia.

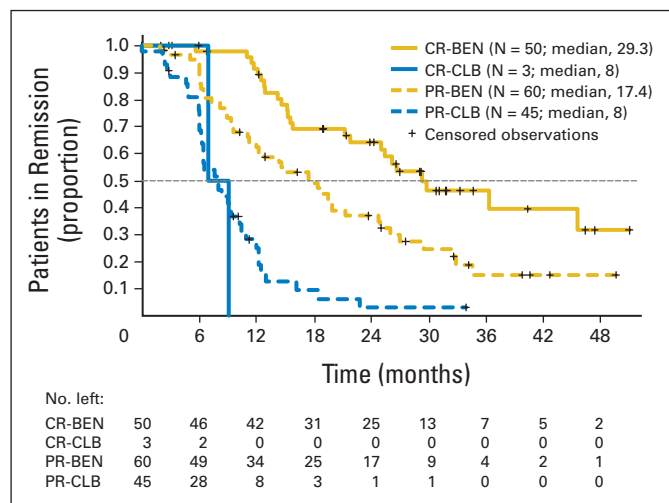
Overall, 110 bendamustine-treated patients (68%), and 48 (31%) chlorambucil-treated patients achieved a CR or PR as determined by the ICRA ( $P < .0001$ ). The proportion of patients with CR or PR is summarized in Table 2. The proportion of patients with a CR was higher with bendamustine than with chlorambucil (31% v 2%), as was the proportion with nodular PR (11% v 3%). Patients with stage C disease showed a higher likelihood of CR with bendamustine: nine patients (20%) with bendamustine showed a CR, whereas no chlorambucil-treated patient did so.

The median observation time was 35 months (range, 1 to 68) at the time of the analysis presented here. The median progression-free survival was 21.6 months in the bendamustine group and 8.3 months in the chlorambucil group ( $P < .0001$ ; Fig 1). This difference was evident in patients with Binet stage B disease (bendamustine: median 21.4 months; chlorambucil: median 9.0 months) as well as in stage C disease (bendamustine: median 25.4 months; chlorambucil: median 6.3 months).

The median duration of response in the bendamustine and chlorambucil groups was 21.8 months and 8.0 months, respectively.



**Fig 1.** Progression-free survival based on the assessment of Independent Committee for Response Assessment: intention-to-treat population. BEN, bendamustine; CLB, chlorambucil.



**Fig 2.** Duration of responses according to Independent Committee for Response Assessment: intention-to-treat population. BEN, bendamustine; CLB, chlorambucil; CR, complete response; PR, partial response.

The median duration of CR (Fig 2) in bendamustine-treated patients was 29.3 months. The median duration of PR was 17.4 months with bendamustine and 8.0 months with chlorambucil.

Further follow-up is required to comment on survival. Overall, 72 patients (31 in the bendamustine group, 41 in the chlorambucil group) died during follow-up. Death due to CLL was reported for 13 patients in the bendamustine group and 21 patients in the chlorambucil group. So far, no significant differences in overall survival have become evident.

### Safety

A total of 23 patients—18 from the bendamustine and five from the chlorambucil group—were withdrawn from the study due to unacceptable toxicity or the risk/benefit assessment was no longer acceptable. The most frequent adverse events (AEs) leading to termination of the study were hypersensitivity reactions including skin and subcutaneous tissue (nine patients treated with bendamustine, two treated with chlorambucil). Two patients in the bendamustine arm but none in the chlorambucil arm experienced grade 3 hypersensitivity reactions. Grade 4 hypersensitivity was not observed at all (Table 3). AEs were reported in 143 (89%) of 161 patients in the bendamustine group and 122 (81%) of 151 in the chlorambucil group. Most frequently occurring AEs were hematologic with the number of events being higher in the bendamustine arm (neutropenia in 27%, thrombocytopenia in 25%, and anemia in 22% of patients) than in the chlorambucil arm (neutropenia in 14%, thrombocytopenia in 21%, and anemia in 14% of patients). GI events (nausea, vomiting, and diarrhea) were also more frequent under bendamustine than under chlorambucil (Table 3). Neutropenia of National Cancer Institute Working Group grade 3 or 4 occurred in 37 bendamustine-treated patients (23%) and 16 chlorambucil-treated patients (11%), granulocyte colony-stimulating factors were used on the discretion of the investigators in 23 (3%) of 783 cycles in the bendamustine and in two (0.3%) of 733 cycles in the chlorambucil arm. Erythropoietin was used in 0.5% and 0.3% of all cycles in the bendamustine and chlorambucil arms, respectively.

The adherence to the dosing schedule was high in both treatment arms. In total, 90% of the planned bendamustine dose and 95% of the planned chlorambucil dose were administered.

Severe infections of grade 3 or 4 occurred in 8% and 3% of treated patients in the bendamustine and chlorambucil arm, respectively, with one singular grade 4 infection in the chlorambucil arm.

Fifty-eight patients (36%) in the bendamustine group and six patients (4%) in the chlorambucil group received antiemetic therapy. Antiemetics were given as preventive therapy in 46 of the 58 patients in the bendamustine group and in two of six patients in the chlorambucil group.

There was a single report of a new malignancy during follow-up; a bronchial carcinoma in a patient who had received bendamustine was detected 12 months after the patient has finished treatment with bendamustine.

There were two reports on tumor lysis syndrome, both in patients who had received their first cycle of bendamustine. However, these events were not fatal and the two patients continued treatment.

## DISCUSSION

This study has shown that bendamustine induces significantly higher response rates and longer progression-free survival than chlorambucil in first-line therapy in patients with CLL. Chlorambucil was chosen as the comparator because it was approved for first-line use in CLL in all participating countries when the trial was planned in 2001. Furthermore, chlorambucil exhibits a favorable toxicity profile that makes this agent suitable in the elderly CLL patients.<sup>4,18</sup>

The cumulative dose of chlorambucil was carefully considered and was at the higher end compared to doses used in other randomized trials (Table 4). The cumulative dose of chlorambucil in this study was similar to that used in a recently completed trial.<sup>19</sup>

The response rate achieved with chlorambucil is comparable with that achieved in another trial<sup>4</sup> with this agent, in which the total dose per cycle was below 100 mg/cycle. A higher response rate of 59% was reported by Eichhorst et al<sup>18</sup> in an elderly study population, however, without external monitoring and without independent response assessment. In our trial, ORR achieved with chlorambucil assessed by the treating physician was 40%, while with the rigorous ICRA assessment, ORR was 31%.

The overall response rate achieved with bendamustine was comparable with that obtained with fludarabine<sup>4,20-22</sup> or cladribine.<sup>23</sup> The 31% CR rate achieved with bendamustine is higher than those recently reported for fludarabine alone.<sup>18,24,25</sup> However, other studies with fludarabine monotherapy have reported CR rates up to 40%.<sup>4,20</sup> Similar or higher CR rates have been reported with combinations of fludarabine with cyclophosphamide<sup>22,24,25</sup> or rituximab<sup>26</sup> or with both.<sup>27-29</sup> Nevertheless, the high CR rate with bendamustine is an important finding because there is evidence that the CR is associated with longer progression-free survival.<sup>28-31</sup>

Progression-free survival was significantly longer with bendamustine than with chlorambucil, and similar to that reported with fludarabine,<sup>22,25</sup> and alemtuzumab.<sup>19</sup> This represents a valuable clinical benefit since prolonged progression-free survival is assumed to be associated with improved quality of life. The median progression-free survival in chlorambucil-treated patients was lower than in other trials.<sup>4,18,19,24</sup> In addition to methodologic

**Table 3.** Summary of Adverse Events Occurring in At Least 5% of Patients by System Organ Class and Preferred Terms

System Organ Class Preferred Term by Disorder	BEN (n = 161)				CLB (n = 151)			
	All Grades		Grade 3/4		All Grades		Grade 3/4	
	No.	%	No.	%	No.	%	No.	%
<b>Blood and lymphatic system</b>								
Neutropenia/granulocytopenia	44	27.3	37	23.0	21	13.9	16	10.6
Thrombocytopenia	40	24.8	19	11.8	31	20.5	12	7.9
Anemia	35	21.7	4	2.5	21	13.9	0	0.0
Leukopenia	28	17.4	23	14.3	5	3.3	2	1.3
Lymphopenia	10	6.2	10	6.2	1	0.7	0	0.0
<b>GI</b>								
Nausea	31	19.3	1	0.6	21	13.9	1	0.7
Vomiting	25	15.5	2	1.2	10	6.6	0	0.0
Diarrhea	16	9.9	2	1.2	6	4.0	0	0.0
<b>General disorders and administration site conditions</b>								
Pyrexia	40	24.8	3	1.9	8	5.3	2	1.3
Asthenia	14	8.7	0	0.0	7	4.6	0	0.0
Fatigue	14	8.7	2	1.2	7	4.6	0	0.0
Chills	9	5.6	0	0.0	2	1.3	0	0.0
<b>Immune system</b>								
Hypersensitivity	8	5.0	2	1.2	3	2.0	0	0.0
<b>Infection and infestation</b>								
Nasopharyngitis	11	6.8	0	0.0	11	7.3	0	0.0
Infection	10	6.2	3	1.9	2	1.3	0	0.0
<b>Investigation</b>								
Weight decreased	9	5.6	0	0.0	5	3.3	1	0.7
<b>Metabolism and nutrition disorders</b>								
Hyperuricemia	12	7.5	3	1.9	2	1.3	0	0.0
<b>Respiratory, thoracic, and mediastinal</b>								
Cough	10	6.2	1	0.6	7	4.6	1	0.7
<b>Skin and subcutaneous tissue</b>								
Rash	15	9.3	4	2.5	7	4.6	3	2.0
Pruritus	8	5.0	0	0.0	4	2.6	0	0.0

Abbreviations: BEN, bendamustine; CLB, chlorambucil.

differences (ie, external monitoring, blinded assessment) this may be due to differences in the patient population. These other studies have included patients with Binet stage A (ie, < 3 lymph node regions involved, corresponding in part to Rai stages 0 to 1) disease who have a better prognosis.<sup>3</sup>

Toxicity of bendamustine was manageable and of short duration. Severe infections are of particular interest since they are a major cause of morbidity and mortality in CLL patients.<sup>32</sup> Common Toxicity Criteria grade 3 to 4 infections occurred in 8% of patients with bendamustine and 3% with chlorambucil. Notably,

grade 3 to 4 infection rates of 11% and 15% have been recently reported for fludarabine<sup>22</sup> and fludarabine with cyclophosphamide<sup>28</sup> in similar populations. The difference may be explained by different etiologies. Infections occurring during bendamustine treatment may be related to transient neutropenia, whereas fludarabine is associated with prolonged T-cell depletion.<sup>33</sup>

There are anecdotal reports on transient hemolysis in two patients treated with bendamustine and one treated with chlorambucil. All of these patients had positive DAT at study entry. At the end of therapy active hemolysis was apparent in none of these patients.

**Table 4.** Comparison of Total Doses Chlorambucil in Different Trials Based on an Average Patient (70 kg/1.75 m/1.85 m<sup>2</sup>)

Study	Regimen	Dose (mg)		
		Total per Cycle	Per m <sup>2</sup> per Cycle	Median Cumulative
Knauf/02CLLIII	0.8 mg/kg d1 + 15	112	60	522
Eichhorst <sup>18</sup>	0.4-0.8 (ø 0.5) mg/kg days 1 and 15	56-112 (ø 70)	30-60 (ø 38)	455
Hillmen <sup>19</sup>	40 mg/m <sup>2</sup> every day 28	74	40	515
Rai <sup>4</sup>	40 mg/m <sup>2</sup> every day 28	74	40	NA
Catovsky <sup>24</sup>	10 mg/m <sup>2</sup> days 1-7	130	70	NA

Abbreviation: NA, not available.

The two reports on tumor lysis syndrome during the first cycle of treatment with bendamustine merit particular attention. Tumor lysis syndrome is reported as a rare but potentially fatal event in fludarabine treatment of CLL and to occur predominantly in high-risk patients presenting with high lymphocyte counts and hepatosplenomegaly.<sup>34</sup> Both affected patients in our trial presented with a high tumor burden. At least in such cases it is urgently recommended to administer prophylactic therapy against hyperuricemia and to provide the patients with adequate fluid intake during the initial phase of treatment.

Meanwhile, the combination of bendamustine with rituximab was reported to be feasible.<sup>35</sup> This combination may offer an additional option for treatment of patients with CLL.

In conclusion, this study has shown that bendamustine offers significantly greater efficacy than chlorambucil, and a manageable toxicity profile, when used as first-line therapy in patients with advanced CLL. In March 2008, the US Food and Drug Administration approved bendamustine for the treatment of CLL with regard to data of this trial.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

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