High Dose Chlorambucil versus Binet's Modified Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Regimen in the Treatment of Patients with Advanced B-Cell Chronic Lymphocytic Leukemia

Results of an International Multicenter Randomized Trial

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BACKGROUND. In recent years, much attention has been paid to the possible efficacy of intensive chemotherapy in the treatment of advanced, progressive B-cell chronic lymphocytic leukemia (CLL) patients. For this reason, the International Society for Chemo-Immunotherapy, Chronic Lymphocytic Leukemia Cooperative Group, has begun a randomized multicenter trial comparing Binet's modified cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen with continuous high dose chlorambucil (HD-CLB).

METHODS. During the period January 1987 to May 1993, 228 previously untreated CLL patients from 7 cooperative institutions were randomized to this trial. Advanced and/or progressive disease was defined by high Total Tumor Mass (TTM) score (>9), and/or short doubling time (DT) (<12 months), and/or bone marrow failure. The response to therapy was defined by reduction of the initial TTM score. The end points of the trial were response rate, survival, and toxicity.

RESULTS. HD-CLB resulted in a higher response rate than CHOP in evaluable cases, with 89.5% overall responses (complete response + partial response) versus 75%, respectively ($P < 0.001$). At the time of an analysis performed in July 1995 (after a median follow-up period of 37 months), overall survival was also longer in the HD-CLB treatment arm (median survival, 68 months) than in the CHOP treatment arm (median survival, 47 months) ($P < 0.005$). Toxicity was acceptable and comparable in the two treatment arms.

CONCLUSIONS. The current study showed that HD-CLB is an effective and well-tolerated therapeutic option for patients with advanced and/or progressive CLL. Therefore, the authors recommend its wider use, possibly in comparison with and/or in combination with new therapeutic agents, such as purine analogues. ***Cancer* 1997;79:2107–14.** © *1997 American Cancer Society.*

KEYWORDS: chronic lymphocytic leukemia, chemotherapy, advanced stages, chlorambucil, CHOP, response, survival, randomized trial.

B-cell chronic lymphocytic leukemia (CLL) is characterized by variable course and prognosis.[1,2] Prognostic classifications devised in the past 20 years have made stratified clinical trials accumulating the evidence for more appropriate differential therapeutic approaches in distinct CLL subsets possible.[3–5] Although immediate conventional treatment is not indicated in early and stable disease,[6–8] it is commonly accepted that treatment with the aim to control disease is warranted in advanced disease.[9]

Although CLL patients with advanced stage disease have a poor prognosis—with a median survival ranging from 19 to 38 months according to the different staging systems[3–5] or to the presence of unfavorable parameters such as a short doubling time (DT)[5,10] and the presence of diffuse pattern of infiltration at bone marrow histology[11]—the older age of the majority of CLL patients has prevented extensive studies aimed at evaluating aggressive therapeutic approaches. As a result of this limitation, the clinical responses obtained by conventional chemotherapy are very rarely paralleled by the eradication of the B-neoplastic clone as evaluated at the phenotypic and molecular levels.[12,13]

The initial results reported by the French Cooperative Group on CLL of a modified cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen in Binet Stage C cases[14] provided greater expectations for the treatment of these poor prognosis patients. These results also encouraged implementation of several randomized studies to test the efficacy of this regimen or, more generally, of the addition of an anthracycline in CLL treatments for which results did not confirm the initial finding.[15–18]

Triggered by those initial promising results, the CLL cooperative group of the International Society for Chemo-Immunotherapy (IGCI, Vienna, Austria) has decided to evaluate, in a randomized trial, the Binet modified CHOP schedule versus high-dose continuous chlorambucil (HD-CLB), which in a previous randomized study was demonstrated to be superior to the Sawitsky schedule of monthly CLB plus prednisone.[19,20]

The present trial design is based on the Total Tumor Mass (TTM) score system[5] for the definitions of advanced phase of the disease, response to therapy, DT, and progression. As previously reported,[8] this system is not only prognostically reliable, but its continuous quantitative character is particularly useful in therapeutic trials. This is because it allows an evaluation of the response to therapy by measuring tumor parameters independently of the hematotoxic effect of chemotherapy itself.[5,21–24]

Because this study is based on the TTM score system, some Binet Stage A and B cases with a large tumor burden or with a short DT and all Stage C cases have been included. To allow comparison of the present study with other studies, the results have been also evaluated by using the Binet classification.

PATIENTS AND METHODS

The IGCI CLL-02 trial started in January 1987 and was closed in May 1993. This is the report of the final analysis performed after 37 months of median follow-up time.

Study Design

The design of the trial is based on the TTM score system[5] is shown in Figure 1. Patients were considered to be in the advanced or progressive phase of the disease according to one or more of the following parameters: TTM score >9, DT <12 months, presence of bone marrow failure as defined by hemoglobin level <10 g/dl and/or platelet count $<100 \times 10^9$/l. In addition, there was an upper age limit of 75 years. Because of the possible use of the anthracycline containing regimen, patients with a previous history of cardiopathy or with abnormal cardiac examinations were not eligible. Patients were also classified according to Rai et al.[3] and Binet et al.[4] systems. Eligible patients were randomized for either HD-CLB or CHOP therapy; all responding patients (complete and partial responses) received maintenance therapy for an additional 18 months in both treatment arms.

Treatment

HD-CLB consisted of CLB at the fixed dose of 15 mg daily up to complete response (CR), or Grade 3 toxicity, or a maximum of 6 months. This induction treatment was followed by maintenance therapy for 18 months with CLB, 5 to 15 mg, according to the hematologic tolerability, twice a week. Prednisone administration was allowed according to the usual indications (i.e., autoimmune hemolytic anemia). Prednisone was added during induction in case of persistent enlarged tumor masses after a reduction of the peripheral lymphocytosis below 5×10^9/l.

The CHOP schedule was identical to the original scheme proposed by the French Cooperative Group on Chronic Lymphocytic Leukemia,[14] with 6 monthly cycles of doxorubicin 25 mg/m^2 on day 1, vincristine 1 mg/m^2 on day 1, cyclophosphamide 300 mg/m^2/day, and prednisone 40 mg/m^2/day on days 1–5. This induction treatment was followed in responding cases by maintenance therapy with six additional CHOP courses administered every 3 months.

Response to Therapy and Toxicity

Response to therapy, evaluated according to the TTM score reduction (which uses criteria for partial remission definition more similar to the National Cancer Institute (NCI) proposal[25,26] then the International Workshop on Chronic Lymphocytic Leukemia guidelines[27]), was defined as follows. CR for a TTM score reduction below 2.3, which represents the diagnostic threshold for CLL; Partial response (PR) for more than 50% reduction of the initial TTM score. No response

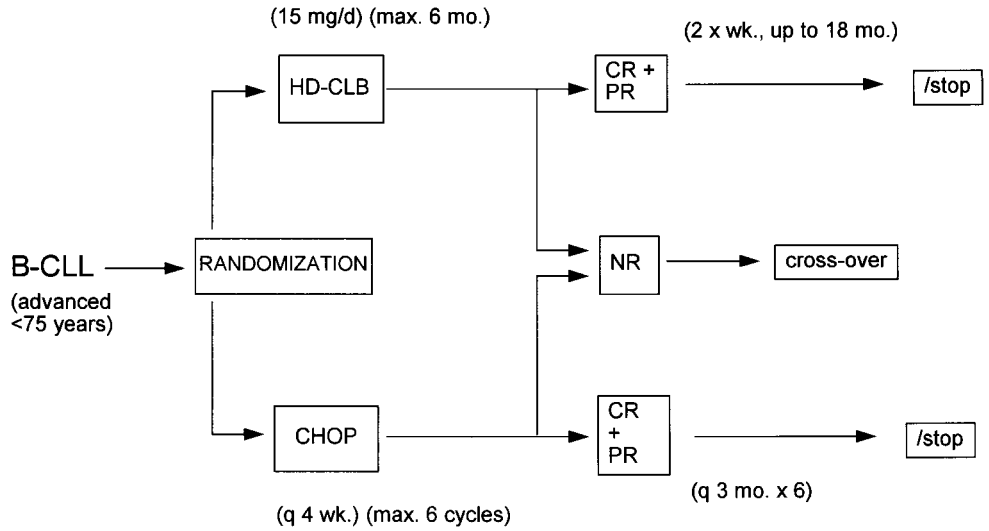

FIGURE 1. Design of the IGCI CLL-02 trial.

(NR) for the failure to achieve CR or PR. Progression (PG) was defined as the increase of TTM score while patient was receiving treatment.

Toxicity was graded according to the World Health Organization criteria.

Patients

From 7 cooperative IGCI institutions, 228 previously untreated patients were considered evaluable. Informed consent was given by the patients according to the rules of the different countries. Of 228 patients, 142 were males. Mean age was 60.4 years. Patients were subdivided according to the following age strata: younger than 51, 51–60, 61–70, and older than 70 years. The main clinical features are reported in Table 1.

Statistical Analysis

The main end point of the study was the comparison of the survival probability of the two treatment arms, considering all causes of death.

The BMDP (Statistical Solutions, Cork, Ireland) package was used for the statistical analyses. Survival was calculated from the date of randomization according to the Kaplan–Meier method, and significance was calculated by the log rank and Wilcoxon tests. The Cox proportional hazards method was used for the multivariate analysis.[28] The case–control study was performed by the comparison of patients matching for the same Binet stage and the same age strata distribution taken randomly from the two groups of treatment at a ratio of 1:1.

TABLE 1
Comparison of Patient Characteristics (Whole Series)

	HD-CLB	CHOP	*P* value
No. (%)	116 (51)	112 (49)	NS
Sex (M/F)	68/48	74/38	NS
Age			
Mean ± SD	60.7 ± 10.2	60.2 ± 8.5	NS
Median	63	61	
TTM			
Mean ± SD	15.2 ± 6.98	15.8 ± 6.14	NS
Median	13	13	
Rai			
0	1 (0.9)	0 (0.0)	0.054
I	24 (21.4)	13 (11.9)	
II	57 (50.9)	48 (44.0)	
III	13 (11.6)	23 (21.1)	
IV	17 (15.2)	25 (22.9)	
Binet			
A	31 (27.7)	15 (13.6)	0.004
B	52 (46.4)	46 (41.8)	
C	29 (25.9)	49 (44.5)	

NS: Not significant.

RESULTS

The clinical features of the patients and the comparison between the two treatment arms are reported in Table 1. Of 228 patients, 116 were randomized for HD-CLB and 112 for CHOP. Seven patients were not evaluable because of protocol violation. The two groups are fully comparable for sex, age, and TTM size, although imbalance was found in Rai stage distribution and there was a significant difference for Binet stage distribution. To overcome this problem, a case–control

TABLE 2
Comparison of Patient Characteristics (Case–Control Series)

	HD-CLB	CHOP	*P* value
No. (%)	90 (50)	90 (50)	NS
Sex (M/F)	53/37	60/30	NS
Age			
Mean ± SD	60.6 ± 10.3	60.0 ± 7.4	NS
Median	62.5	61	
TTM			
Mean ± SD	15.90 ± 7.24	15.11± 5.78	NS
Median	13	13	
Rai			
0	1 (1.1)	0 (0.0)	NS
I	11 (12.2)	13 (14.4)	
II	48 (53.3)	48 (53.3)	
III	13 (14.4)	13 (14.4)	
IV	17 (18.9)	16 (17.7)	
Binet			
A	15 (16.7)	15 (16.7)	NS
B	46 (51.1)	46 (51.1)	
C	29 (32.2)	29 (32.2)	

NS: Not significant.

TABLE 3
Response Rates in Whole Series and Case–Control Study

	HD-CLB	CHOP	*P* value
Whole series			
CR	69 (59.5)	34 (30.4)	0.0012
PR	33 (28.4)	47 (42.0)	
NR	12 (10.3)	26 (23.2)	
NE	2 (1.8)	5 (4.4)	
Total	116 (100)	112 (100)	
Case–control series			
CR	54 (60.0)	30 (33.3)	0.0029
PR	24 (26.7)	35 (38.9)	
NR	10 (11.1)	23 (25.6)	
NE	2 (2.2)	2 (2.2)	
Total	90 (100)	90 (100)	

CR: Complete response; PR: partial response; NR: nonresponsive; NE: nonevaluable.

study has also been performed as described in the Patients and Methods section. Table 2 shows the clinical characteristics of this group of 180 fully comparable cases.

For the whole series of 221 patients evaluable for response, HD-CLB was associated with a significantly higher response rate ($P = 0.0012$). As shown in Table 3, the response rate (CR + PR) of evaluable cases was 89.5% and 75.0% for HD-CLB and CHOP groups, respectively. The mean time to achieve CR was 2.3 months for HD-CLB treatment and 4.8 months for CHOP therapy. The evaluation of the response rate in the case–control study confirmed the results obtained on the whole series.

TABLE 4
Toxicity Graded According to World Health Organization Criteria and Expressed as Percentage of Cases

Toxicity				
Type	**WHO grade**	**HD-CLB**	**CHOP**	***P* value**
Infection	2	2.6	5.6	NS
	3	3.5	0.9	
	4	—	1.9	
Hematologic	2	7.0	0.9	NS
	3	5.3	0.9	
Allergy	2	1.7	—	NS
Hepatic	2	—	1.9	NS
	4	—	0.9	
Cardiac	2	—	0.9	NS
Gastrointestinal (nausea)	2	0.9	1.8	NS
	4	0.9	—	
Alopecia	2	—	25.9	0.000
	3	—	21.3	

NS: Not significant.

Toxicity was very low in both treatment arms (Table 4). Alopecia was present only in the CHOP group, and the remaining toxic events were comparable in the two treatment arms. In particular, Grade 3 hematologic toxicity, which was slightly but not significantly higher in the HD-CLB treatment arm, caused the interruption of the induction and the start of maintenance before the achievement of CR in five patients.

In addition, only 4 of 12 cases not responding to HD-CLB and 15 of 24 not responding to CHOP were crossed to the alternative regimen with the following results. Two of three evaluable cases crossed to CHOP remained NR, and one patient achieved PR. Of 13 evaluable cases crossed to HD-CLB, 9 maintained NR, 1 achieved CR, and 3 achieved PR.

Also in terms of survival, HD-CLB therapy was associated with a better outcome (Fig. 2A). After 37 months of median follow-up, the median survival of the HD-CLB group was significantly longer (68 months) than that of the CHOP treated cases (47 months) ($P = 0.0024$). The median overall survival of the entire series was 59 months. The results of the survival analysis were confirmed in the case–control series, with a significant difference between the two treatment arms ($P = 0.0308$) (Fig. 2B).

The multivariate analysis of factors influencing survival was performed using Cox proportional hazards model, entering as covariates center, sex, age, Rai stage, Binet stage, bone marrow failure, TTM size, TTM distribution, and therapy. The analysis was performed on three levels (Table 5). Analysis without forc-

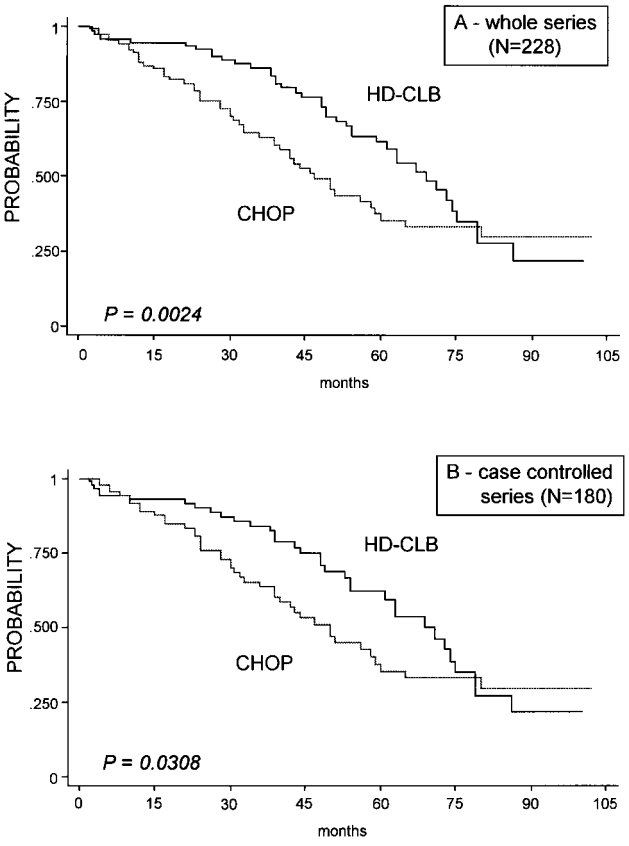

FIGURE 2. Survival analysis of HD-CLB versus CHOP treated cases. (A) Whole series. (B) Case–control study. Solid line: HD-CLB; dotted line: CHOP.

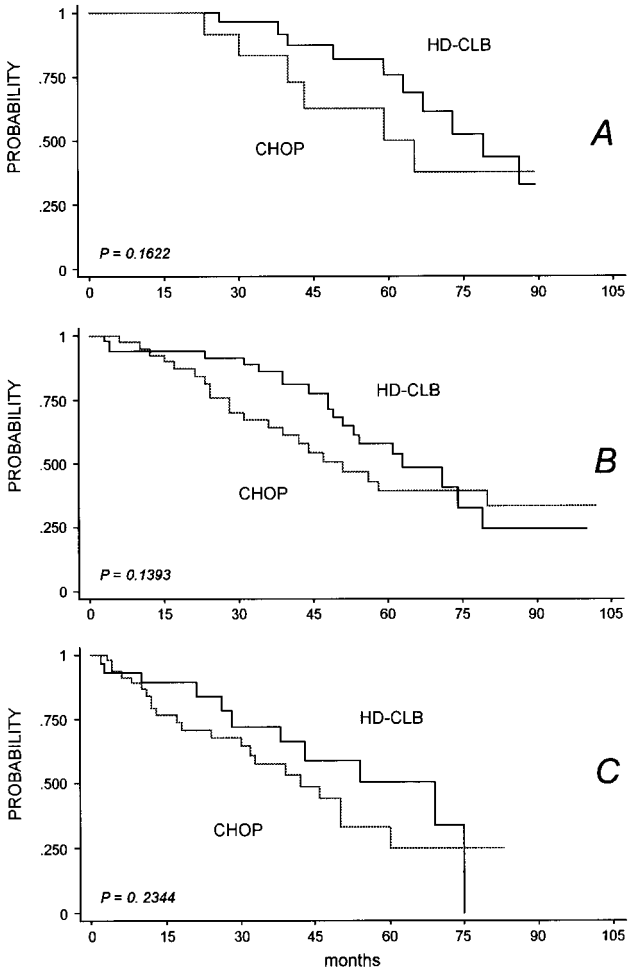

FIGURE 3. Survival analysis of HD-CLB versus CHOP treated cases divided according to Binet stage. (A) Binet Stage A (46 patients). (B) Binet Stage B (98 patients). (C) Binet Stage C (78 patients). Solid line: HD-CLB; dotted line: CHOP.

ing variables into the model performed on total trial time follow-up shows only TTM size and Binet stages to be significant, whereas the influence of therapy is only marginal. After therapy was forced into the model (being in step 0 at a significant level), TTM size and Binet stages were shown to be significant without forcing. However, the analysis performed for the first 60 months of trial time without forcing variables into the model disclosed a marked independent influence on survival by therapy, followed by TTM size, and marginally by sex and age.

When patients were subdivided according to the Binet stage, HD-CLB treated cases had a better survival curve in every stage, although the difference was not significant (Fig. 3).

DISCUSSION

The comparison of the schedule of continuous administration of 15 mg CLB up to complete clinicohematologic response or to toxicity followed by biweekly CLB maintenance resulted in a better outcome of advanced and progressive CLL patients in terms of response rate and survival, compared with cases treated with Binet modified CHOP schedule. In the original report on this treatment[14] and in its subsequent update evaluations,[29,30] this treatment produced significantly superior results in comparison to the CHOP regimen in CLL patients with advanced disease (Binet Stage C). By contrast, no difference has so far been found between the two regimens in Binet Stage B cases at the second interim analysis of the same trial.[18,30]

Several randomized trials have addressed the same topic. The interim results of the trial of the Spanish Cooperative Group PETHEMA comparing the same CHOP schedule to intermittent CLB plus prednisone in Stage C cases,[15] the results of the Swedish Cooperative Group[16] comparing full-dose CHOP versus CLB

TABLE 5
Multivariate Analysis: Summary of Stepwise Results

				Improvement		Global	
Step no.	Variable entered	DF	Log likelihood	χ^2	*P* value	χ^2	*P* value
Level 1 (no forcing of variables, overall trial time)							
0			−408.504				
1	Binet stage	1	−403.442	10.124	0.001	10.047	0.002
2	TTM size	2	−401.022	4.839	0.028	16.282	0.000
3	Sex	3	−399.435	3.174	0.075	18.782	0.000
Level 2 (therapy forced, overall trial time)							
0			−408.504				
1	Therapy	1	−406.305	4.397	0.036	4.447	0.035
2	TTM size	2	−401.766	9.078	0.003	14.805	0.001
3	Binet stage	3	−399.881	3.771	0.052	18.486	0.000
Level 3 (no forcing of variables, first 60 mo of trial time)							
0			−316.968				
1	Therapy	1	−311.599	10.739	0.001	10.863	0.001
2	TTM size	2	−309.563	4.073	0.044	15.402	0.000
3	Sex	3	−308.164	2.798	0.094	18.588	0.000
4	Age	4	−306.803	2.722	0.099	20.620	0.000

Cox proportional hazards model—risk type is loglin.
Covariates: center, sex, age, Rai, Binet, bone marrow failure, TTM size, TTM distribution, and therapy. DF: degrees of freedom.

plus prednisone in active/progressive CLL cases as defined by NCI criteria,[31] and the results of the Danish Cooperative Group trial[17] comparing full-dose CHOP to intermittent CLB plus prednisone in B and C stage cases did not show any difference in terms of survival between the two treatment arms. Further information on the role of the anthracycline in this disease will be provided by the forthcoming results of the ongoing British MRC study.[7]

Our experience differs from the others because of the use of the HD-CLB schedule, which was chosen on the basis of the results of a previous trial by our group.[19,20] According to the results of that study, we concluded that HD-CLB was superior to the monthly CLB plus prednisone schedule. Therefore, it is not surprising that HD-CLB is more active than CHOP, which in many other trials resulted in similar efficacy compared with intermittent CLB plus prednisone.[15–17]

The criteria for the definition of response in the present study were tailored according to the reduction of the initial TTM score. The value of this system, which is more similar to the NCI guidelines for PR definition in CLL,[25,26] is confirmed by the important impact of response to therapy evaluated according to TTM criteria on survival, in agreement with previous reports.[32] The authors believe that this system is very easily calculated in a uniform way in different centers and is not biased by the erythrocyte and/or platelet cytoreduction due to chemotherapy itself. Moreover, because we do not expect to eradicate the disease by any conventional treatment,[12,13] an ''operational'' definition of CR can be useful to differentiate among different levels of clinical response.

Regarding toxicity, HD-CLB is an acceptable schedule for CLL patients who are mainly elderly and frequently have concomitant diseases. The comparison of the two schedules showed a similar toxicity. The hematologic toxicity caused the interruption of the induction phase with HD-CLB therapy in a very limited number of cases; some of these cases achieved CR soon after the start of maintenance therapy (data not shown). Prednisone was added to CLB with the indication of persistent organomegaly with normal peripheral blood lymphocyte count in less than 15% of cases.

The higher response rate after the induction phase in patients treated with HD-CLB is paralleled by a longer survival. Five-year survival was shown to be significantly different (61% for HD-CLB vs. 36% for CHOP) by Kaplan–Meier product limit and was also corroborated by Cox multivariate analysis. An interesting shape of the curves was observed, indicating a potential crossing after approximately 7 years, although this finding is uncertain due to the small number of observations. This may be due to the fact that when, in the late course of the disease, most patients experience a number of different treatments, the front-line therapy at randomization becomes irrelevant. However, it may also have a more profound biologic significance indicating the incurability of the disease

and relatively little contribution by the currently used treatment modalities for eventual positive outcome and survival.[33,34]

Because the randomization was not based on Binet stage, we found at the closure of the study that the two groups of treatment were not comparable according to this parameter. Therefore, we performed a case–control analysis of response rate and survival on a large subset of age-matched patients comparable according to this feature. The results of this analysis confirmed the findings obtained in the whole patient population.

In addition, because the number of nonresponding cases crossed to the alternative regimen was negligible in this study, we can exclude that the survival of each group has been significantly influenced by the effect of the alternative therapy, as occurred in the Danish study.[17]

When the survival analysis was performed after dividing all patients according to the Binet stage distribution, a trend for a better outcome of cases treated with HD-CLB was obtained, although it was not significant. This is possibly due to the smaller number of cases included in each subgroup.

The overall median survival of the entire population of advanced CLL patients in the present study (59 months) was longer than that reported in historical controls, defined as being in advanced phase of the disease according to the same criteria.[5,21] Among the possible explanations for this finding are the presence of an upper age limit and the exclusion of cases with cardiac dysfunction.

Finally, the TTM score system, used as the basis to design this trial, proved to be an independent and very powerful prognostic parameter in multivariate analysis.

In conclusion, this study confirms that the HD-CLB schedule followed by CLB maintenance is effective and well tolerated in CLL patients in advanced phase of the disease, as defined by high TTM score, short DT, and/or presence of bone marrow failure. Therefore, we suggest a wider use of this therapeutic approach as the conventional standard treatment to be compared with promising new agents, such as fludarabine[35,36] and 2-chlorodeoxyadenosine,[37,38] intravenously or orally in prospective randomized trials.

APPENDIX

CLL-02 Cooperative Institutions of the International Society for Chemo-Immunotherapy, Vienna (President, Professor D. Lutz): Internal Medicine Department, University Hospital ''Merkur,'' Zagreb, Croatia (B. Jaksic, A. Planinc-Peraica, R. Kusec); Hematology Department, General Hospital, Reggio Calabria, Italy (M. Brugiatelli, F. Morabito, P. Iacopino); II Internal Clinic, University of Olomouc, Olomouc, Czech Republic (I. Krc); I Clinic of Internal Disease, Silesian Medical Academy, Katowice, Poland (J. Holowiecki); I Department of Internal Medicine, University of Pecs, Pecs, Hungary (H. Losonczy); Hematology Division, University Hospital ''Rebro,'' Zagreb, Croatia (B. Labar); and III Medical Clinic, Semmelweis University, Budapest, Hungary (V. Schranz).

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