Chronic Lymphocytic Leukemia and Focusing on Epidemiology and Management in Everyday Hematologic Practice: Recent Data From the Czech Leukemia Study Group for Life (CELL)

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Abstract

Purpose: Currently, pathogenesis, new prognostic factors, or new therapy in chronic lymphocytic leukemia (CLL) are frequently discussed; however, up-to-date data concerning the incidence and the management of CLL in everyday hematologic practice are still missing. The aim of our study was to find out the accurate epidemiologic situation of CLL and the diagnostic and therapeutic preferences of hematologists in the preselect area: the South Moravian Region (1,127,718 inhabitants, white race). **Patients and Methods:** The total number of 540 patients (median age at the time of diagnosis, 65 years; sex, 306 men and 234 women) who had been followed in 2008 were included in the analysis. **Results:** In the years 2006 and 2007, the incidence of CLL was 5.8 and 6.2, respectively, per 100,000; the prevalence was 48 per 100,000. Chronic lymphocytic leukemia treatment was indicated in 194 patients (36%); 93 (17%) of them also underwent the second line of treatment. Of these 194 patients, 64 patients (33%) were given fludarabine-based regimens, and 74 patients (38%) received chlorambucil as a first line of treatment. Thirty patients were treated within clinical trials. Although the treatment was indicated in only one third of patients (36%), new prognostic factors were examined in > 50% of patients. **Conclusion:** The ascertained incidence of CLL in our region is higher than declared incidence in the past. Evidently, CLL became an often misdiagnosed and underreported disease.

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Introduction

Chronic lymphocytic leukemia (CLL) occurs mostly in elderly people and is the most common leukemia in the Western world. Generally, it creates more than 30% of all types of leukemia. However, in Denmark the percentages are even higher, at 35%-40% versus the Chinese and Japanese populations, at only 3%-5%.[1,2] According to data from the US National Cancer Institute, in the United States from 1975 to 2005, a median age at time of diagnosis was 72 years.[3] Incidence rates increase with age and are higher among men than women. In 2009, it was expected that in the United States more than 15,900 newly diagnosed patients and approximately 4396 deaths were the result of CLL.[1] In the US white population, the incidence rate of CLL varies from 3.35 to 3.69 in men to 1.61-1.92 in women; in Europe, from 2.2 to 3.36 in men to 0.9-1.52 in women; and in Oceania, studies report incidence rates of 2.81-2.96 in men and 1.41-1.53 in women.[4,5] In the view of improving the survival of patients with CLL, prevalence of CLL is higher than incidence.[5,6] According to Rawstron et al, even 3.5% of adults and 8% of the population over 70 years of age have an asymptomatic disease or so-called monoclonal B lymphocytosis.[7] As shown in this data, CLL is probably an underdiagnosed disease, and the real incidence of CLL appears to be higher. In addition, questions regarding the number of treated patients with CLL, the types of therapy administered, and the monitoring of these patients still remain unanswered.

Patients and Methods

The aim of our study was to assess the accurate epidemiologic situation of CLL in the South Moravian region. With 1,127,718 inhabitants, this area is one of the largest regions in the Czech

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Table 1 Assessment of New Prognostic Factors in Patients With Chronic Lymphocytic Leukemia Before Treatment

Examination	Percentage of Examined Patients	Percentage of Examined Patients		
Flow Cytometry	97%	*ZAP70* examined in 35% of patients	Positive	40%
			Negative	60%
Mutational Status of *IGVH* Gene	57%	Mutated	51%	
Cytogenetic Abnormalities	54%	Unmutated	44%	
		Polyclonal	5%	
		17p deletion	2%	
		11q deletion	6%	
		Trisomy of 12	10%	
		13q deletion	38%	
		Normal karyotype	32%	
		More than 1 cytogenetic abnormality	12% (in 2 patients, deletion of 17p with another abnormality was found, 0.7%)	

Table 2 First-line Treatment in Patients With Chronic Lymphocytic Leukemia

Regimen	Treated Patients, n	Type of Regimen in Detail	Treated Patients in Detail, n	Complete Response, %
Chlorambucil	74	–	–	16
Fludarabine-Based Regimen	64	FCR	29	62.5
		FC	27	
		F	6	
		FC + ofatumumab	2	
CHOP-Like Regimen	28	CHOP	12	28
		COP	9	
		R-CHOP	6	
		VAD	1	
Corticosteroids	16	Corticosteroids alone	11	6
		Corticosteroids + rituximab	5	
Alemtuzumab	10	–	–	60

Abbreviations: CHOP = cyclophosphamide/doxorubicin/vincristine and prednisone or prednisolone; COP = cyclophosphamide/vincristine and prednisone or prednisolone; F = fludarabine; FC = fludarabine and cyclophosphamide; FCR = fludarabine/cyclophosphamide/rituximab; R-CHOP = rituximab/cyclophosphamide/doxorubicin/vincristine and prednisone or prednisolone; VAD = vincristine/dexamethasone/doxorubicin

Republic.[8] We focused on trends in incidence rates, diagnostic recognition and reporting, and the therapeutic preferences of our hematologists. Overall survival and progression-free survival analyses were not the aim of the study.

Two questionnaires were distributed to all 14 specialized hematologic departments in our region, and we were pleased that all hematologists completed the questionnaires (see online supplement to this article). The data acquired were merged with the database of the Department of Internal Medicine-Hematology/Oncology in Brno.

The survey was a one-shot survey focusing on the incidence and prevalence of CLL in 2006-2008. In the Czech Republic, every patient with hematologic malignancy is diagnosed and followed at a specialized hematology department. Because all hematologists from our region participated in the study, we can confirm that we captured all individuals with CLL in the South Moravian region. The treatment data concern all individuals with CLL who were alive the time of this survey.

Results

On August 1, 2008 (the date the analysis was carried out), a total of 540 patients with a diagnosis of CLL had a permanent residence in the South Moravian region. Of the patients, 306 were men, and 234 were women. The men-to-women ratio was 1.3:1. The median age at time of diagnosis was 65 years (range, 33-92 years). The ascertained prevalence of CLL was 48 per 100,000 in 2007. A slight increase in incidence rates was observed from 5.8 per 100,000 in 2006 (66 newly diagnosed patients) to 6.2 per 100,000 in 2007 (70 new patients with CLL). At the time of diagnosis, 274 patients (51%) had Rai stage 0, 173 patients (32%) had Rai stage I, 36 patients (6.7%) had Rai stage II, 25 patients (4.6%) had Rai stage III, and 25 patients (4.6%) were diagnosed at Rai stage

Table 3 Second-line Treatment in Patients With Chronic Lymphocytic Leukemia

Regimen	Treated Patients, n	Type of Regimen in Detail	Treated Patients in Detail, n	Complete Response, %
Fludarabine-Based Regimen	39	FCR	16	49
		FC	15	
		F	8	
Chlorambucil	19	–	–	5
Corticosteroids	17	Corticosteroids alone	9	0
		Corticosteroids + rituximab	8	
Alemtuzumab	10	–	–	40
CHOP-Like Regimen	8	COP	4	12.5
		CHOP	3	
		R-CHOP	1	

Abbreviations: CHOP = cyclophosphamide/doxorubicin/vincristine and prednisone or prednisolone; COP = cyclophosphamide/vincristine and prednisone or prednisolone; F = fludarabine; FC = fludarabine and cyclophosphamide; FCR = fludarabine/cyclophosphamide/rituximab; R-CHOP = rituximab/cyclophosphamide/doxorubicin/vincristine and prednisone or prednisolone; VAD = vincristine/dexamethasone/doxorubicin

Table 4 First-line Treatment in Patients With Chronic Lymphocytic Leukemia in 2007 and 2008

Regimen	Number of Treated Patients	Type of Regimen in Detail	Number of Treated Patients in Detail
Fludarabine-Based Regimen	23	FCR	12
		FC	7
		F	2
		FC + ofatumumab	2
Chlorambucil	13	–	–
Corticosteroids	8	–	–
CHOP-Like Regimen	5	–	–

Abbreviations: CHOP = cyclophophamide/doxorubicin/vincristine and prednisone of prednisolone; F = fludarabine; FC = fludarabine/cyclophosphamide; FCR = fludarabine/cyclophosphamide/rituximab

IV. In 7 patients (1.3%), the Rai stage was not determined. Flow cytometry was carried out in the remaining 525 patients (97%); the other patients were diagnosed by a histologic examination from either bone marrow or lymph nodes. A typical CLL phenotype was detected in 472 patients (87%). A total of 297 patients (55%) were cytogenetically examined (deletion of 17p [n = 5]; deletion of 11q [n = 18]; trisomy of 12 [n = 29]; deletion of 13q [n = 112]; normal karyotype [n = 94]). Immunoglobulin variable region heavy chain (*IGVH*) gene mutational status was detected in 305 patients (56%; 155 mutated, 134 unmutated, and 16 polyclonal). *ZAP70* was detected in 191 patients (35%; 77 positive and 114 negative). The examination of new prognostic factors at diagnosis is summarized in Table 1.

Treatment for CLL was indicated in 194 patients (36%). Of these, 93 (17%) also underwent the second-line treatment. Out of these 194 patients, 64 patients (33%) were given a fludarabine-based regimen as the first-line treatment, and 40 patients out of the 64 (62.5%) achieved complete remission (CR). Out of the 194 patients indicated for CLL treatment, 74 (38%) received a chlorambucil-based regimen with 12 patients (16% of the 74) achieving CRs. Twenty-eight patients (14% of 194) received a CHOP (doxorubicin/vincristine/prednisone/prednisolone)–like regimen with 8 CRs (29%). Ten patients (5%) received an alemtuzumab regimen with 6 CRs (60%). Eighteen patients (9%) were treated with a combination of rituximab and corticosteroids or corticosteroids alone with 1 CR (6%; Table 2). As mentioned above, 93 patients (17%) also underwent second-line treatment: 39 patients (42%) were given a fludarabine-based regimen with 19 CRs (49%); 19 patients (20%) were given chlorambucil with 1 CR (5%); 8 patients (9%) were given a CHOP-like regimen with 1 CR (12.5%); 10 patients (11%) were given alemtuzumab with 4 CRs (40%); and 17 patients (18%) were given corticoid-based treatment with no CR (Table 3). Thirty patients were treated within clinical trials.

Focusing on the first-line treatment started only in 2007 and 2008, more patients were treated with a fludarabine-based regimen (23 patients) compared with chlorambucil (13 patients), corticosteroids (8 patients), or a CHOP-like regimen (5 patients; Table 4). Most patients receiving fludarabine-based regimens were treated in the academic center. In contrast, patients given chlorambucil were especially managed in the local hematologic departments.

In total, out of 540 patients, 287 patients (53%) were followed at the local hematologic departments and 253 (47%) were treated at 1 main hematologic center. The median follow-up of our patients was 56 months (range, 5-126 months).

Table 5 Epidemiology of Chronic Lymphocytic Leukemia: Summary

Analytic Measure	World Analyses[1-6]					Our Analysis
	United States (2009)	United States, White Race (1999)	Europe, Men (1999)	Oceania, Men (1999)	Southeastern Asia, Men (1999)	
Incidence (per 100,000 Inhabitants)	5.04	3.35-3.69	2.2-3.36	2.81-2.96	0.14-0.58	5.8-6.2
Prevalence (per 100,000 Inhabitants)	–					48
Men:Women Ratio	Switzerland		China			1.3:1
	1.4:1		3.2:1			
Median Age at Diagnosis, Years	72					65

Discussion

Actually, the ascertained incidence of CLL in the South Moravian Region is higher than published data from the analysis carried out in the 1990s (Table 5).[4,6] We confirmed that improved diagnostic methods appeared to strongly affect increasing rates of CLL in the population. Flow cytometry, which is determinative of the diagnostic algorithm of CLL,[9,10] was carried out in 97% of the patients in our region. In contrast, the median age at the time of diagnosis is lower than previously published data (65 years vs. 72 years).[3] It is possible that in the past, patients were diagnosed at an advanced stage of the disease, thus, they were older than patients with the asymptomatic CLL. Currently, these patients are probably diagnosed earlier by flow cytometry testing. The examination of new prognostic factors was affected by many circumstances. In our study, flow cytometry, cytogenetic, and molecular examinations were carried out in > 50% of patients. Most were followed in the main hematologic center and had progressive disease. Consequently, in our analysis 40% of the patients were *ZAP70* positive and 44% of patients had unmutated *IGVH* genes. In contrast, lower incidence rates of unfavorable cytogenetic aberrations, such as deletion 17p or 11q, were observed in these patients.[11] This reinforces the assumption that some of the cytogenetic aberrations appear during the treatment of CLL. The treatment of CLL in our region is based on 2 essential drugs: fludarabine and chlorambucil. Overall, more patients were treated with chlorambucil than fludarabine. However, looking at last 2 years of the analysis (2007 and 2008), the majority of patients have been treated with fludarabine-based therapy. Chlorambucil is still preferred among local hematologists.

Conclusion

The ascertained incidence of CLL in our region is higher than the declared incidence in the past, thus CLL appears to be a misdiagnosed and underreported disease. Currently, the crucial examination for the diagnosis of CLL is flow cytometry. Although the treatment was indicated in only one third of our patients with CLL (36%), the new prognostic factors were examined in > 50% of them. In our opinion, new prognostic factors such as *IGVH* or *ZAP70* are helpful to clinicians at time of diagnosis because they can assess the likely time to progression, whereas others such as 17p deletion should be assessed before treatment to ensure that appropriate therapy is provided.

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Disclosures

The authors have no relevant relationships to disclose.

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