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Clinical Presentation and Outcome of Thai Patients with Chronic Lymphocytic Leukemia: Retrospective Analysis of 184 Cases

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SUMMARY Chronic lymphocytic leukemia (CLL), which is the most common leukemia in adult population in the Western world, is surprisingly rare in Thailand. The objective of our study was to retrospectively analyze the clinical presentations and outcome of a large cohort of Thai CLL patients diagnosed at a single institution in Bangkok, Thailand, from 1963-1998. One hundred and eighty-four patients were included in the study. The most frequent age group was 60-80 years old with the male to female ratio of 2:1. Only 12% of patients were younger than the age of 50. Most patients were from the central agricultural region of Thailand. Clinical findings at presentation included splenomegaly (64%), lymphadenopathy (60%), anemia (54%), hepatomegaly (49%), fatigue (39%), weight loss (33%), fever (21%), thrombocytopenia (18%), and anorexia (8%). Only 8% of Thai CLL patients were asymptomatic at presentation. The majority of patients were categorized as stages III and IV with the median survival of 20 months and 8 months, respectively. Infection was the most common cause of death, particularly in the elderly patients who had comorbid illnesses. Twenty-two percent of the patients had associated autoimmune disorders. The unfavorable prognostic factors observed were older age (> 70 years), weight loss and hepatosplenomegaly. We concluded that the age and gender of Thai CLL patients were similar to those of the Western countries but our patients came to medical attention at a later and more advanced stage. Prospective studies at a multi-center level in Thailand should be pursued to investigate further the genetic and epidemiologic nature of Thai CLL patients.

Chronic lymphocytic leukemia (CLL) is characterized by extensive proliferation and accumulation of small lymphocytes in the blood, bone marrow and lymphoid organs.[1] It is the most common leukemia seen in the Western countries, particularly in the population aged greater than 50 years.[2] Patients may present with localized or generalized lymphadenopathy, hepatosplenomegaly, anemia, thrombocytopenia or systemic symptoms. A large number of CLL patients are, however, asymptomatic and the diagnosis can only be achieved by the incidental finding of abnormal complete blood counts (CBC).[2-3] At present, no curative therapy exists for CLL patients and eventually the patients will succumb to death either due to lymphoma transformation, associated infections or other unrelated causes.[1-2] The overall survival of CLL patients can vary from less

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than a year to over 10 years depending on their stages and prognostic features.[1-4]

Very limited data exists in Thailand with respect to the clinical presentations and outcome of CLL patients, as the number of newly diagnosed patients each year was very low. The objective of our research was to study the incidence, clinical features, clinical staging, natural history, prognosis, treatment and complications of a group of Thai CLL patients seen at Siriraj Hospital, Bangkok, which is the largest hospital in Thailand from 1963-1998 and compared the results with those reported from the Western countries from the same period of time.

PATIENTS AND METHODS

This was a retrospective review of the approved medical records available at the Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand. One hundred and eighty-four patients with the clinical and laboratory diagnosis of CLL during 1963-1998 were identified. The inclusion criteria were absolute and persistent lymphocytosis in peripheral blood (> 5 x 10^9/l), whereby lymphocytes were mostly mature and > 30% of lymphocytes were demonstrated in the bone marrow.[3] The following features were recorded: age, gender, systemic symptoms (fever, weight loss, anemia, fatigue), lymphadenopathy, hepatomegaly, splenomegaly, total white blood cell count (WBCC), absolute lymphocyte count, hemoglobin (Hb) concentration, and platelet (Plt) count. The results were compared to other large CLL series that were reported in the literature. Patients with complete follow-ups were also analysed for prognostic factors using t-test and one-way ANOVA methods.[5] The standard staging criteria for CLL patients in our study are shown in Table 1.

Table 1 Modified Rai's staging system[4]

Stage	Criteria
0	Lymphocytosis in blood and bone marrow only
I	Lymphocytosis with palpable adenopathy
II	Lymphocytosis with hepatic and/or splenic enlargement
III	Lymphocytosis with anemia (hemoglobin < 11 g/dl)
IV	Lymphocytosis with thrombocytopenia (platelets < 100 X 10^9/l)

Table 2 Geographic regions of Thai CLL patients seen at Siriraj Hospital

Region of Thailand	% of patients
Central	75.16
North-Eastern	6.78
Southern	6.78
Eastern	5.27
Western	3.76
Northern	2.26

RESULTS

The study group consisted of 184 Thai CLL patients. The geographic distribution of CLL patients in our study is shown in Table 2. Seventy-five percent of the CLL patients at Siriraj Hospital came from the central part of Thailand, most of whom were agriculturists. The distribution of patients by gender and age is shown in Table 3 and Fig. 1. There were 122 males and 62 females (male:female = 2:1) with the mean age of 62.8 (range 39-91 years). The highest number of patients was in the age range of 60-80 years. The summary of the relationship between the stage of disease and the age of patients according to Modified Rai's staging system is shown in Table 3. A correlation between age and stage of patients is suggested. Sixty percent of patients whose ages were between 60-69 years were classified as stage III.

The clinical features of Thai CLL patients are shown in Table 4. Clinical findings of Thai CLL patients at presentation included splenomegaly (64%), lymphadenopathy (60%), anemia (54%), hepatomegaly (49%), fatigue (39%), weight loss (33%), fever (21%), thrombocytopenia (18%), and anorexia (8%). Eight percent of our patients were asymptomatic at presentation. Systemic symptoms were present in most patients. Coombs' test proved positive, on one or more occasions in 19 of 68 patients so examined (22%).

Table 3 Distribution of CLL patients according to age and disease stage

Age group	Stage 0	Stage I	Stage II	Stage III	Stage IV	Total
< 50	1	0	4	13	4	22
50-59	2	3	8	24	7	44
60-69	8	6	4	41	9	68
> 70	2	2	5	32	9	50
Total	13	11	21	110	29	184

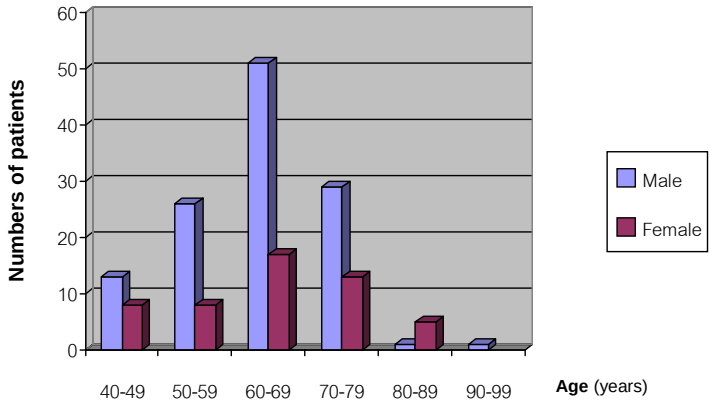

Fig. 1 Age and gender distribution of Thai CLL patients

The median survival time of our CLL patients categorized by Modified Rai's staging criteria was summarized as follows: stage 0, 48 months; stage I, 20 months; stage II, 19 months; stage III, 20 months and stage IV, 8 months (Table 5). The most frequent cause of death of our CLL patients was infection. Cardiovascular disease in the old age group (> 50 years) of our patients also contributed to the mortality in this age group. Other causes of death included chronic obstructive lung disease and upper gastrointestinal hemorrhage. One patient had disease transformation to large cell lymphoma (Richter's syndrome), and two patients had secondary cancer including gastrointestinal and head and neck cancer.

To determine if any prognostic factors exist in Thai CLL patients. Thirty-three patients with complete medical records were analyzed (Tables 6 and 7). A statistically significant difference in survival times was observed for patients having old age (> 70 years; $p < 0.001$) and weight loss ($p < 0.001$) but not for gender, fever and fatigue ($p = 0.954$, 0.896 and 0.447, respectively). Of 33 patients, 51% presented with palpable peripheral lymph node. Thirty-six percent had only a palpable spleen, 15% had only a palpable liver and 13% had both organs palpable. Survival according to the presence or absence of palpable lymph node (cervical, axillary, inguinal) was studied. The median survival time of patients with peripheral lymphadenopathy and without lymphadenopathy was 23 months and 22 months, respectively. The difference was not statistically significant ($p = 0.934$). There was a tendency for a better prognosis if liver < 3 cm, but difference in survival time could not be demonstrated in either group.

In the group of patients with spleen size < 3 cm below left costal margin, the survival times were longer than those with spleen enlarged > 3 cm, although these were not statistically different. The

Table 4 Clinical features at presentation of CLL patients from Thailand and other countries

Clinical features	Thailand (This study)	Japan (1987)[6]	Denmark (1973)[7]	Latvia (1993)[8]	Israel (1987)[9]	France (1980)[10]
Age						
Peak age group	60-69	60-69	60-69	60-70	50-59	60-69
Mean age	63	62	63.3	61.6	66.1	64.4
Male: Female	2	1.17	1.8	1.12	1.25	1.18
Initial symptoms						
Fatigue	38.6%	-	-	-	-	-
Weight loss*	32.6%	-	-	-	-	-
Fever	21.0%	-	-	-	-	-
Anorexia	8.15%	-	-	-	-	-
Asymptomatic	8.15%	-	16%	-	-	-
Organ involvement						
Lymphadenopathy	60%	66%	80%	-	-	-
Splenomegaly	64%	28%	46%	-	-	-
Hepatomegaly	49%	32%	30%	-	-	-
Hematological involvement						
Anemia	54%	-	20%	-	-	-
Thrombocytopenia	18%	-	53%	-	-	-

*Weight loss was defined as > 10% loss of usual body weight.

Table 5 Median survival of CLL patients categorized using Rai's staging criteria from different studies

Rai's stage	Boggs (1966)[23] n = 84	Hansen (1973)[7] n = 152	Rai (1975)[4] n = 125	Binet (1981)[24] n = 99	This study n = 33
0	180	-	> 150	> 120	48
I	60	130	101	100	20
II	47	108	71	> 120	19
III	26	9	19	65	20
IV	20	42	19	20	8

study showed a statistically significant difference in survival times if patients had both organ palpable (under costal margin > 3 cm) as compared to those have neither organ palpable ($p = 0.03$). In this study, hemoglobin concentration was not correlated with survival time but patients with high hemoglobin level (> 12 g/dl) tended to have better survival (median survival of 35 months) as compared to patients with low Hb (< 10 g/dl) (median survival of 23 months). Degree of leukocytosis had no relationship to survival times in our series ($p = 0.7017$) and absolute lymphocyte counts also did not have any prognostic importance ($p = 0.6561$). Patients with thrombocytopenia had shorter survival times than patients with normal platelet levels (median survival times 14.5 and 25 months, respectively), although no statistical significance could be achieved ($p = 0.438$).

DISCUSSION

CLL is the most common form of chronic leukemia in the Western countries but is rarely seen in Thailand and other Asian countries. The reason for this wide disparity in the incidence of CLL in dif-

Table 6 Relationship between clinical features and survival of Thai CLL patients

Clinical features	Category	Number of cases	Mean	S.D.	t-value	*p* value
Sex	Male	16	23.656	31.363	0.06	0.954
	Female	17	23.044	29.660		
Age	< 70 years	22	36.772	28.223	5.23	0.001*
	> 70 years	11	3.700	6.195		
Weight loss	Yes	10	4.031	4.691	-3.81	0.001*
	No	23	30.964	32.966		
Fever	Yes	11	22.318	32.075	-0.13	0.896
	No	22	23.825	29.703		
Fatigue	Yes	18	27.013	31.068	0.77	0.447
	No	15	18.933	29.143		
Lymphadenopathy	Yes	17	23.676	33.089	0.08	0.934
	No	16	22.796	27.608		
Hepatomegaly	< 3 cm	28	40.000	25.603	-1.53	0.174
	> 3 cm	5	20.366	30.170		
Splenomegaly	< 3 cm	22	26.647	32.779	0.99	0.329
	> 3 cm	11	16.750	23.541		
Hepatosplenomegaly	Both	4	5.241	5.462	-3.12	0.03*
	None	21	32.486	35.726		

*Significantly different at the < .050 level, **under costal margin > 3 cm

ferent parts of the world remains unknown. It was consistently found that CLL is the disease of the older age with increasing incidence in the age group of 60-69 years old. The mean age was 63 (Siriraj), 62 (Japan),[6] 63.3 (Copenhagen).[7] and 61.6 (Latvia)[8] (Table 4). Slightly older age was found in Israel (66)[9] and Turin (64.4)[10] but the differences were not statistically significant. Male and female ratio at Siriraj and Copenhagen[7] was 2 and 1.8, respectively, compared with 1.15-1.25 in Japan,[6] Israel,[9] Turin[10] and Latvia.[8] Using Modified Rai's criteria, the relationship between the stage of disease and age of our Thai CLL patients at clinical presentation was similar to other reports. We found that most patients (60%) were at stage III and their age was between 60–69 years. Stage IV patients had the worst prognosis, which is similar to other reports.[8,9,11]

Lymphadenopathy (cervical, axillary, inguinal) was a predominant presentation in approximately 60% of Thai patients. Forty-one percent of Thai patients had both hepatomegaly and splenomegaly. The results were similar to reports from Japan[6] and Copenhagen[7] that lymphadenopathy was the most common clinical feature. Anemia was present in 54% of our patients and thrombocytopenia in 18%. In other series, anemia was present at presentation in only 20% with more patients presented with thrombocytopenia (53%). Anemia at presentation has always been found to be a poor prognostic sign.[7,12,13,14] In our series, the survival pattern of anemic patients were not significantly worse (p = 0.652) than the group of patients with normal hemoglobin level (with the cut off level of 10 g/dl in our series). Reviewed study of Phillip *et al.*[15] found autoimmune hemolytic anemia (AIHA) to be related to prognosis, although not supported by Bernadou *et al.*[16] Our studies did not have any correlation between AIHA and prognosis.

Table 7 Relationship between laboratory features and survival of Thai CLL patients

Laboratory features	Category	No. of cases	Mean	S.D.	f-ratio	*p* value
Hemoglobin (g/l)	< 10	20	23.825	28.190		
	10-12	9	16.785	34.372	0.4339	0.6523
	> 12	4	35.000	41.239		
WBC count (per mm^3)	< 25,000	6	19.541	23.873		
	25,000-50,000	11	30.386	36.853	0.3586	0.7017
	> 50,000	16	21.233	28.245		
Absolute lymphocyte count (per mm^3)	< 20,000	9	31.475	28.314		
	20,000-40,000	15	24.301	33.554	0.4271	0.6561
	> 40,000	9	18.833	24.276		
Platelet count (per mm^3)	< 100,000	6	14.583	23.035	-0.7900	0.438
	> 100,000	27	25.287	31.389		

Our study compared organomegaly with survival times. We found that statistically significant difference in survival time was observed for CLL patients having both organs palpable as contrast to those having neither organ palpable. Difference in the survival of the patients defined by the size of either enlarged organ (i.e., greater or lesser than 3 cm below costal margins) was noted, although these were not different statistically. The report from Bernodau[16] and Hansen *et al*.[7] found that splenomegaly was a significant prognostic factor, but Coeur *et al*.[17] found no difference in survival times between patients with or without hepatomegaly.

There was no relationship between the degree of peripheral blood lymphocytosis and survival time in our study, whether lymphocyte counts were below or above 50 x 10^9/l. Several studies had similar results such as Bethel,[18] Osgood,[19] and Hansen,[7] although other studies[15,16,20-22] showed relationship between survival and lymphocyte counts. Our findings indicated a trend towards shorter survival for patients with low platelet counts, but the difference was not statistically significant.

With regards to treatment and the survival, we could not demonstrate any relationship between survival times and treatment. The reason why the median survival of Thai CLL patients at Siriraj Hospital was shorter than other reports[4,7,23-25] is unknown given the similar age and gender of our patients to those patients in the west. Our patients, however, tended to seek medical attention at a later stage. It is thus possible that those patients who came for regular follow-ups were clinically worse therefore requiring frequent medical attention than the drop-out group. The most frequent treatment regimen used at our hospital was chlorambucil and prednisolone, which had been shown to offer remission but not a cure.[1-2] No effective therapy currently exists to cure CLL patients. Even bone marrow transplantation results in a high relapse rate in most studies.[1-2,25] Most drugs at the present era are thus utilized to induce remission and potentially prolong life. Novel therapy including antibody and gene-targeting therapy are ongoing in the western countries.[26-27]

In conclusion, CLL is not a common disease in Thailand. The age and gender of Thai CLL pa-tients were similar to those reported by the western countries but our patients came to the hospital with more severe symptoms and signs such as anemia and hepatosplenomegaly. Infection was the important cause of death in our patients. The unfavorable prognostic factors observed were older age (> 70 years), weight loss and hepatosplenomegaly. Our study represents the largest study of Thai CLL patients ever reported from a single Asian institution. Prospective studies at a multi-center level in Thailand should be pursued to investigate further the genetic and epidemiologic

nature of Thai CLL patients. It is hoped that better understanding of the clinicobiological characteristics of CLL would result in the discovery of novel treatment modalities that not only prolong life but also lead to cure for these patients.

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