Asian Pacific Journal of Allergy and Immunology (1996) 25-30

Multivariate Analysis of Prognostic Factors in Philadelphia Chromosome Positive Chronic Myeloid Leukemia: An Update of the First Series in Thailand

Saengsuree Jootar, Artit Ungkanont, Suporn Chuncharunee and Vichai Atichartakarn

SUMMARY **The prognostic importance of pretreatment clinical and laboratory features was investigated in a group of 243 patients with Philadelphia chromosome positive chronic phase chronic myeloid leukemia from 1977-1995. Chemotherapy consisted of busulfan before 1993 or hydroxyurea after 1993. The overall median survival from dignosis was 28 months. The mean age of the patients was 38 years, about 10 years below that of Western populations. Univariate analysis identified 4 poor prognostic features:- thrombocytopenia, more than 5% peripheral blasts, more than 5% erythroid precursors and less than 7 g/dl of hemoglobin. The median survival times of patients with these 4 risk factors were 5, 11, 11 and 12 months respectively. Multivariate analysis only identified 2 significant prognostic features:- thrombocytopenia and more than 5% peripheral blasts. Splenomegaly of more than 10 cm, basophilia and leukocytosis were associated with a shorter median survival but was not statistically significant. A risk scoring system was developed and used to classify patients into low, intermediate and high risk groups at 30.9%, 30.2% and 38.8% respectively. The median survival time according to the low, intermediate and high risk group was observed at 60, 27 and 14 months respectively. Prognostic factors for Thai patients with chronic myeloid leukemia have both similarities and differences with previously observed factors but the median patient survival time is shorter.**

Reported survival time for chronic myeloid leukemia (CML) vary because of inhomogeneity in the patient composition of individual series and widely varying initial proportions of poor-risk patients.[1] About 15% to 20% of the patients die within 2 years in most series and a similar proportion survive beyond five years.[2,3] The only study of untreated patients reported a median survival of 29 months from the onset of symptoms and 19 months from diagnosis.[4] Therapy has been believed to influence outcome, but median survival has ranged from 6 to 55 months.[5-11] Interest has been focused on the study of prognostic factors in CML to distinguish between patients likely to have long term disease control and those who develop early blast crisis. Several clinical and hematological parameter with initial prognostic value have been identified:- hepatomegaly, splenomegaly, anemia, basophilia, thrombocytopenia, thrombocytosis, presence of erythroid precursors in the peripheral blood, and a high proportion of blasts in the peripheral blood or bone marrow.[11,17] In Thailand the median age of CML patients is about ten years younger than that of western patients.[18] We reported the first series of prognostic factors in Philadelphia chromosome positive CML in Thailand in 1990[18] and found that male sex was the only poor prognostic factor from multivariate analysis. A later series from Siriraj Hospital in which cytogenetic studies were not done reported 5 poor prognostic factors; spontaneous bleeding, hepatomegaly, Wbc over $200 \times 10^3/\mu l$, blast + promyelocytes > 10% and basophil $30 \times 10^3/\mu l$.[19] We now update the information presented in our previous report and use mul-

From the Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Correspondence : Saengsuree Jootar, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

tivariate analysis to identify prognostic factors.

MATERIALS AND METHODS

Patients

From January 1977 through December 1995, a total of 308 patients with CML were seen at Ramathibodi Hospital, Faculty of Medicine. The diagnosis of CML was based on history, physical examination, studies of bone marrow aspirates and biopsy samples, peripheral blood smears, leukocyte alkaline phosphatase and chromosome analysis. Giemsa banding techniques have been used since 1983. Patients who were Philadelphia chromosome positive and in the chronic phase of disease were included in the analysis. Most patients were treated with busulfan until November 1993 when thirty three patients received hydroxyurea as the initial treatment. Intensive chemotherapy with doxorubicin and cytosine arabinoside was used when patients went into the accelerated or blastic phase.

Prognostic factors analysis and statistical methods

Clinical and laboratory characteristics recorded at the time of diagnosis were evaluated for prognostic value : age, sex, spleen and liver size, hemoglobin (Hb) concentration, white blood cell (Wbc) and platelet counts, percentage of peripheral blood eosinophils, basophils, erythroid precursors, myeloblasts and leukocyte alkaline phosphatase (LAP) levels. Survival time was calculated from the time of diagnosis at our institution. Tests of difference in survival distributions were based on the Kaplan Meier method.[20] The multivariate regression method was applied to assess the relative prognostic value of patient characteristics using Cox's proportional-hazard model.[21] Variables were entered in the model using a forward stepwise selection procedure, after initial screening by univariate analysis.

RESULTS

The records of 308 patients were available for review, including 275 patients with cytogenetic studies. Among these 275 patients, 15 were Philadelphia chromosome negative and 17 Philadelphia chromosome positive but were in blastic transformation. The remaining 243 patients were included in our report. The median survival from the date of diagnosis was 28 months (Fig. 1). At the time of analysis, 188 of 243 patients had died, 72 percent died in blastic crisis and 28 percent died of other causes including sepsis, intracranial bleeding and thrombosis.

Univariate analysis of prognostic factors (Table 2)

Clinical characteristics:

The median age of the 243 patients was 38 years with a peak incidence between 20–40 years (range 13–83) and 56 percent of the patients were male. There was no difference in survival by sex, age groups between < 45 years and > 45 years of age and degree of hepatomegaly or splenomegaly. There was a non significant trend towards shorter survival in patients with splenomegaly more than 10 cm, compared to lesser degrees of splenomegaly (27 months vs. 43 and 30 months respectively).

Hematological and biochemical studies:

Univariate analysis of hematological and biochemical data demonstrated 4 poor prognostic parameters: Hb lower than 7 g/dl ($p = 0.002$, Fig. 2a), platelet less than $100 \times 10^3/\mu l$ ($p = 0.001$, Fig. 2b), peripheral blood myeloblasts over 5% ($p = 0.001$, Fig. 2c), and erythroid precursors over 5% ($p = 0.001$, Fig. 2d). There was no statistically significant difference in survival by degree of leukocytosis, eosinophilia, basophilia and leukocyte alkaline phosphatase scores (Table 1). There was a nonsignificant trend towards

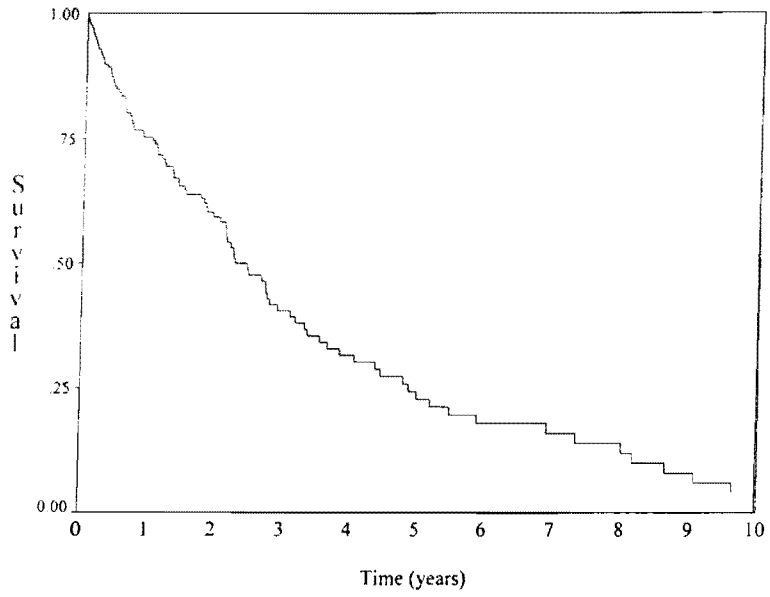

Fig. 1 Survival of Philadelphia chromosome positive CML patients.

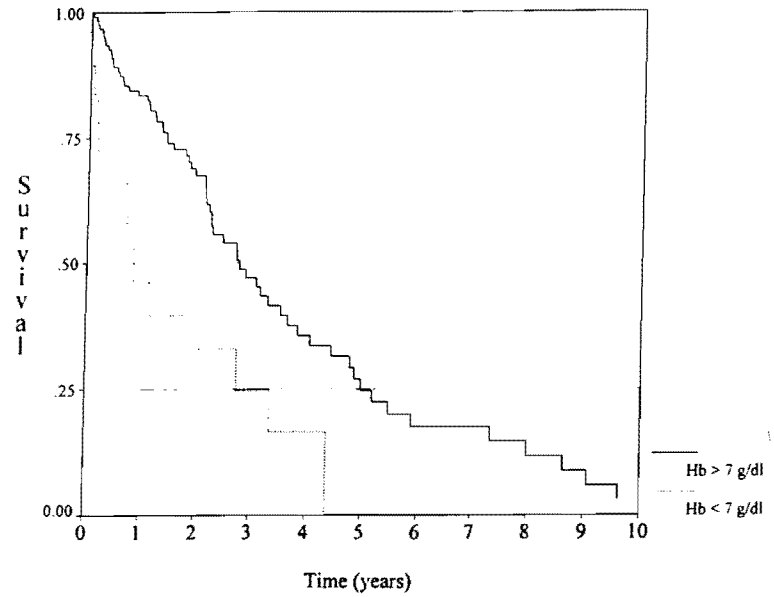

Fig. 2a Survival of patients with hemoglobin (Hb) <7 g/dl and >7 g/dl.

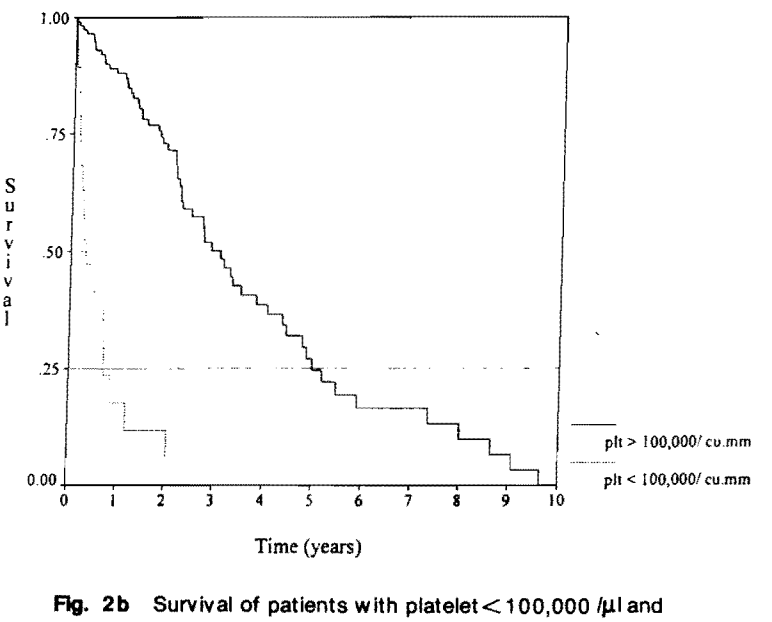

Fig. 2b Survival of patients with platelet < 100,000 /μl and >100,000/μl.

shorter median survival in patients with marked leukocytosis and basophilia.

Multivariate analysis of prognostic factors

Twelve admission characteristics were considered for potential inclusion in a regression model. The regression model selected a combination of 2 features that had additive primary independent prognostic importance. These were percentage of peripheral blood myeloblasts and platelet count below $100 \times 10^3/\mu l$ (Table 2).

Risk score

A scoring system was developed by assigning a weighted score to each admission characteristic and then calculating the sum of the scores. The admission characteristics which had independent prognostic importance from the multivariate analysis were given 3 scores, those which had prognostic significance from the univariate analysis were given 2 scores, and those that had tendency to be of prognostic significance but did not reach the statistic significance were given 1 score. Using this system, we classified patients into low, intermediate and high risk groups (Table 3). There were significant differences ($p = 0.0001$, Fig. 3), in median survival between these groups, with low, intermediate and high risk patients surviving 60, 27 and 14 months, respectively.

DISCUSSION

Patients with CML have a heterogeneous clinical course related to both host and tumor attributes. Knowledge of prognostic factors would facilitate the interpretation of therapeutic trials, application of risk-directed therapy and prediction of individual outcome. A report from Barcelona[14] demonstrated four poor prognostic factors: palpable splenomegaly and hepatomegaly, presence of erythroid precursors in the blood, and marrow blasts over 5%. Later on, several European and American centers formed the International CGL Prognostic Study Group. The first study from this group showed that the initial features associated with unfavorable prognosis in "good-risk" CML were higher age, greater spleen size, platelet count above $700 \times 10^3/\mu l$ and higher blood blast cell percentages.[11] A second study from this group restricted to patients

Table 1. Univariate analysis of CML patient characteristic influencing survival.

Characteristics	Category	No. of patients	Median survival (months)	Significance
Clinical features				
Age (yr)	< 45	168	30	0.59
	> 45	75	26	
Sex	male	135	28	0.79
	female	108	30	
Spleen (cm)	0	21	NR	0.56
	1-4	33	30	
	5-9	82	43	
	>10	107	27	
Hepatomegaly (cm)	< 5	206	30	0.12
	> 5	37	37.6	
Hematological features				
Hemoglobin (g/dl)	< 7	30	12	0.002
	> 7	197	34	
Wbc ($x10^3/\mu l$)	< 200	138	35	0.98
	> 200	100	28	
Platelet count ($x10^3/\mu l$)	< 100	28	5	0.001
	> 100	188	38.0	
Percentage of blast	< 5	169	38.5	0.001
	> 5	48	11	
Percentage of eosihophil	< 10	201	34	0.6
	> 10	15	41	
Percentage of basophil	< 10	165	38.5	0.23
	> 10	49	27	
Percentage of erythroid	< 5	196	33.5	0.01
precursor	> 5	19	11	
LAP	>20	26	54	
	<20	82	33	0.49

NR = not reach

Table 2. Summary of regression model relating survival to CML patient characteristics.

Characteristic	Category	Significance level at entry	Hazard ratio for individual characteristics (95%CI)
Platelet ($x10^3\mu l$)	1≧100, 2<100	0.001	1.82 (1.32-2.54)
Peripheral blood myeloblast (%)	1≦5, 2>5	0.005	1.65 (1.28-2.21)

Regression moded : $\frac{\ln \lambda 1(t)}{\lambda 0(t)}$ = 0.6 (low platelet) + 0.5 (blast>5%)

under 45 years indicated that male sex, greater spleen size, lower hematocrit, higher platelet count (above $700 \times 10^3/\mu l$) and higher blood blast percentage were the main unfavourable prognostic indicators, whereas age lost its significance.[16] Here, we confirm our previous finding[18] and those from another Thai study[19] that Thai CML patients are about 10 years younger than their Western counterparts. However, with a larger number of patients, our findings differ from those of our previous report in two ways: first, sex lost its significance and second, four poor prognostic parameters were identified:- Hb less than 7 g/dl, platelets less than $100 \times 10^3/\mu l$, peripheral blood myeloblast over 5% and peripheral blood erythroid precursors over 5%. Some of our findings agree with those observed by others:-[11,16,17] severity of anemia, higher blood myeloblasts and presentation of erythroid precursors in blood. However, some differ:- degree of splenomegaly, age and sex. These differences may be due to various factors including racial differences. Multivariate analysis identified only two poor prognostic factors in combination, thrombocytopenia below 100,000 and an increased blood myeloblasts to more than 5%. These two prognostic features were also found to be of prognostic significance in other series.[11,14] The median survival time of patients with these two unfavorable prognostic factors was very short (5 months with thrombocytopenia and 11 months with blasts more than 5%). Median survival in patients with severe anemia and peripheral blood erythroid precursors was only 12 and 11 months respectively.

The overall median survival of our patients was only 28 months as was found in another Thai study.[19] This survival time is shorter than those reported in Caucasians.[11,15] This difference is probably explained by differences in risk factors. Most

Table 3. Number and survival of patients according to their risk group.

Risk group	Score*	Number of cases (%)	Median survival (months)
Low	0-1	74 (30.9)	60
Intermediate	2-4	73 (30.2)	27
High	≧5	96 (38.8)	14

*Score are derived by designating each selected admission characteristic a weighing score and calculating the summation of them. These weighing score are shown below:

Admission characteristics	Weighing score
Blast in peripheral blood > 5%	3
Platelet count < 100,000/μl	3
Hb ≦ 7 g/dl	2
Erythroid precursor in peripheral blood > 5%	2
Peripheral blood basophil ≧ 10%	1
Spleen size ≧ 10 cm	1
White blood cell in peripheral blood > 200,000/μl	1

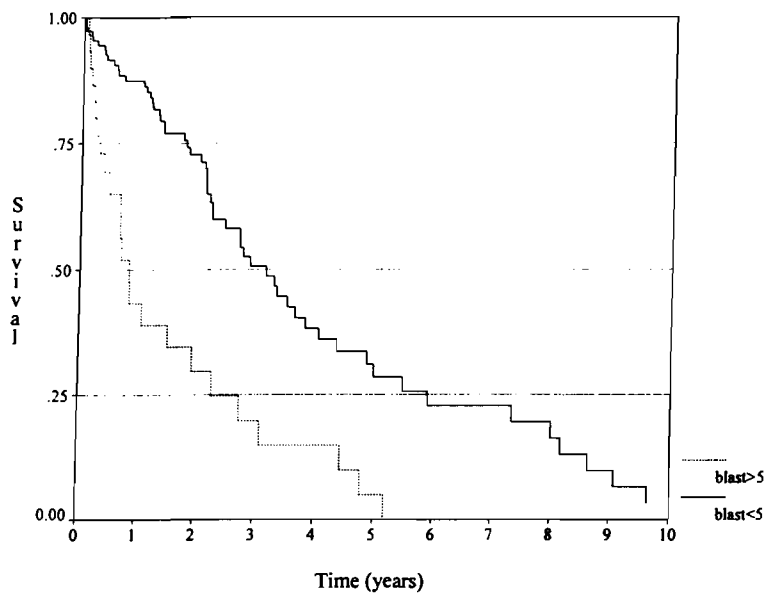

Fig. 2c Survival of patients with blast < 5% and > 5%.

of our patients were high risk, whereas the majority of patients in the 2 studies of Caucasian patients were low risk.[11,15] Different treatments and race may also be factors. Further studies in a large number of Thai CML patients, including the influence of therapy, should help to clarify this problem.

ACKNOWLEDGEMENTS

We express our gratitude to the staff of the medical record division for their kind assistance in retrieving all the medical records. We also acknowledge Miss Duantem Suwannakeree for her secretarial work.

References

1. Sokal JE. Evaluation of survival data for chronic myelocytic leukemia. Am J Hematol 1976; 1 : 493.
2. Canellos GP. Chronic granulocytic leukemia. Med Clin North Am 1976; 60 : 1001.
3. Whang T, Frei III, Tjio JH, Carbone PP, Brechner G. The distribution of the Philadelphia chromosome in patients with chronic myelogenous leukemia. Blood 1973; 22 : 664.
4. Minot GR, Beeckman TE, Isaacs R. Chronic myelogenous leukemia : Age, incidence, duration and benefit derived from irradiation. JAMA 1924; 82 : 1489.
5. Goldman J, Lei DP. New approaches in chronic granulocytic leukemia-origin, prognosis and treatment. Semin Hematol 1982; 19 : 241-56.
6. Conrad FG. Survival in chronic granulocytic leukemia. Splenic irradiation vs busulfan. Arch Intern Med 1973; 131 : 684-5.
7. The Working Party for Theurapeutic Trials in leukemia : Chronic granulocytic leukemia-comparison of radiotherapy and busulfan. Br Med J 1968; 1 : 201-8.
8. Monfardini S, Gee T, Fried J, Clarkson B. Survival in chronic myelogenous leukemia : Influence of treatment and extent of disease at diagnosis. Cancer 1973; 31 : 492-501.
9. Kardinal CG, Bateman JR, Weiner J. Chronic granulocytic leukemia. Review of 536 cases. Arch Intern Med 1975; 136 : 305-13.

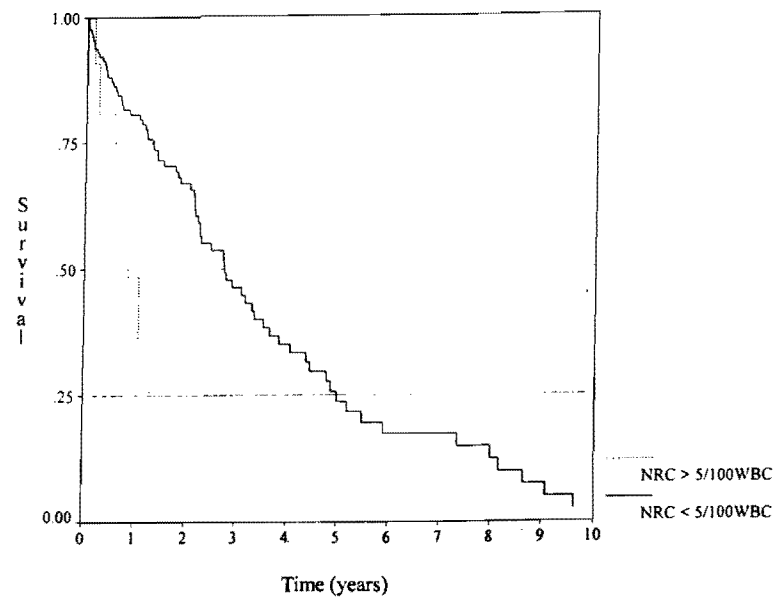

Fig. 2d Survival of patients with NRC<5/100 WBC and >5/100 WBC.

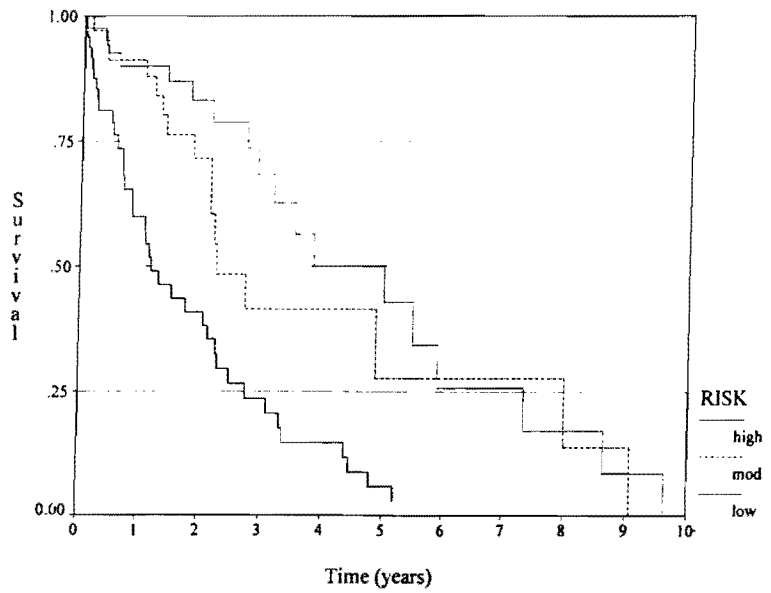

Fig. 3 Survival of CML patients according to their risk.

10. Borin RW, Robinson WA, Sutherland J, Hamman R. Busulfan vs hydroxyurea in long term therapy of chronic myelogenous leukemia. Cancer 1982; 50 : 1683-6.
11. Sokal JE, Cox EB, Baccarani M, *et al.* Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984; 63 : 789-99.
12. Tura S, Baccarani M, Corbelli G and the Italian Co-operative Study Group on Chronic Myeloid Leukemia. Staging of chronic myeloid leukemia. Br J Haematol 1981; 47 : 105-19.
13. Gomez GA, Sokal JE, Walsh D. Prognostic features at diagnosis of chronic myeloid leukemia. Cancer 1981; 47 : 2470-1.
14. Cervantes F, Rozman C. A multivariate analysis of prognostic factors in chronic myeloid leukemia. Blood 1982; 60 : 1298-304.
15. Kantarjian HM, Smith TL, MCCredie KB, *et al.* Chronic myelogenous leukemia: A multivariate analysis of patient characteristics and therapy with survival. Blood 1985; 66 : 1326-35.
16. Sokal JE, Baccarani R, Tura S, *et al.* Prognosic discrimination among younger patients with chronic granulocytic leukemia: Relevance to bone marrow transplantation. Blood 1986; 66 : 1352-7.
17. Sokal JE, Gomez GA, Baccarani M, *et al.* Prognostic significance of addition cytogenetic abnormalities at diagnosis of Philadelphia chromosome-positive chronic granulocytic leukemia. Blood 1988; 72 : 294-8.
18. Jootar S, Chuncharunee S, Ongphiphaphadhanakul B, Atichartakarn V. Multivariate analysis of prognostic factors in chronic myelogenous leukemia. J Med Assoc Thai; 1990; 73 : 662-9.
19. Piankitjagum A, Kummalue T, Visudhiphan S, *et al.* Multivariate analysis of prognostic factors in CML patients. Presented in the Annual Meeting of the Society of Hematology of Thailand, 1992.
20. Kaplan ES, Meier P. Non-parametric estimations from incomplete observations. Am Stat Assoc J. 1958; 53 : 457.
21. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B 1972; 34 : 187.