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Analysis of Prognostic Factors Affecting Response to Treatment and Survival in Chronic Myeloid Leukemia Patients

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Objective: To evaluate the prognostic significance of the disease features at presentation in chronic myeloid leukemia (CML) patients.

Design: This is a retrospective study of sixty patients of CML and their follow up over 20 years. Ten clinical and laboratory features of the disease were evaluated for their prognostic significance. All patients received cytoreductive therapy.

Setting: All patients were seen at King Abdul Aziz University Hospital and the National Guard Hospital in Jeddah, Saudi Arabia.

Method: The prognostic value of sex, age, white cell, basophils, promyelocytes and platelet counts, splenomegaly, bone marrow (BM) blast count, BM fibrosis and the presence of the Philadelphia chromosome, was assessed using log-rank tests. All variables significantly associated with survival univariately were included in a Cox regression. The time to either death or transformation from date of diagnosis was analyzed using a Kaplan-Meier survival curve.

Results: Splenomegaly greater than or equal to 13 cm and a bone marrow blast count of greater than 10% at diagnosis, were both found to be significantly associated with a high-risk of transformation or death in this population. Other presenting features studied, did not have a statistically-significant prognostic impact.

Conclusion: The median duration of the chronic phase in the studied group of patients was 120 months. Splenomegaly and a high BM blast count were both associated with a risk of transformation or death in this population.

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Chronic Myeloid Leukemia (CML) is a rare disease, which constitutes 14% of all Leukemias, in the United States and 15.3% of all diagnosed Leukemia cases in Saudi Arabia[1,2].

CML incidence increases exponentially with age, the median age of incidence being 67 years[3]. There is a slight male predominance of 1.4:1. Typically, the course of the disease is divided into three phases; a chronic phase which lasts an average of 3-4 years, an accelerated phase lasting 6-18 months and a blastic transformation which is rapidly fatal within 3-6 months[4]. Blast crisis can either be myeloid or lymphoid. Myeloid blast crisis is more common and less likely than lymphoid crisis to respond to intensive chemotherapy (response rate 20- 30% vs 40- 60%, respectively)[2].

Several prognostic systems were devised to stratify risk groups in patients with CML. These include the Sokal system, Kantarjian, Tura and Cervantis models[5-8]. The main variables studied were age, platelet count, peripheral blast count and spleen size at diagnosis.

The best known scoring system is the Sokal system. Entering the main prognostic factors into an equation allowed the separation of patients into high, intermediate and low-risk groups.

In an attempt to study the biology of this disease in the western region of Saudi Arabia, we performed a retrospective study of CML cases, diagnosed over a period of 17 years. We studied the features of the disease that are peculiar to the patients in this population. The aim of this study is to identify prognostic factors, if any and to determine the median survival and the duration of the chronic phase.

METHOD

Patient Population: the data in this study was obtained from reviewing patient notes at two medical institutes, King Abdulaziz University Hospital and King Abdulaziz Medical City.

The patients included in this analysis were diagnosed in the period from January 1980 up to May 2001. Sixty patients diagnosed with CML were reviewed. Most patients received some form of cytoreductive therapy. Patients who received Imatinib Mesylate were excluded. The diagnosis of CML was based on the history, physical examination and studies of bone marrow aspirate or biopsies, peripheral blood smears and chromosomal analysis.

Samples from patients found to be Philadelphia-chromosome-negative by conventional chromosomal studies were further assessed by rt-PCR (reverse transcriptase polymerase chain reaction). All patients included in the study satisfied the diagnostic criteria for Chronic Myeloid Leukemia (CML). One patient was found to be Philadelphia chromosome- negative and bcr-abl negative by rt-PCR (reverse transcriptase, polymerase chain reaction).

Ten clinical and laboratory features, present at the time of diagnosis were evaluated for their prognostic significance. These factors are age, sex, white blood cells (WBC) counts, basophil count, promyelocyte percentage, bone marrow blasts, platelets count, bone marrow fibrosis, splenomegaly and the presence of Philadelphia chromosome.

The univariate effect of covariates (sex, age, WBC, basophils, promyelocytes and platelet count, splenomegaly, count of BM blasts, BM fibrosis and presence of Philadelphia chromosome) on survival was assessed using log-rank tests. All variables significantly associated with survival univariately were included in a Cox regression. The time to either death or transformation from date of diagnosis was analyzed using a Kaplan-Meier survival curve.

All, but one patient, were positive for Philadelphia Chromosome (Ph') either by cytogenetic analysis or by rt-PCR (reverse transcriptase Polymerase Chain Reaction). The definition of blastic transformation used was (a) blasts 20% or more in the peripheral blood, (b) blasts plus promyelocytes 30% in blood or marrow, (c) presence of leukemic tumor masses or tissue infiltration with immature leukemic cells (extramedullary blastic transformation).

RESULT

There were equal numbers of males and females. Most patients presented at an age of above 40 years (37, 61.7%). A high white cell count of 100,000 was found to be more common at the time of presentation than a lower count (55.2% vs 44.8% respectively). Other findings at presentation are listed in table 1. Two variables, splenomegaly and blast count in bone marrow were significantly associated with survival.

Table 1 – The association of different presenting features with survival in 60 CML cases*

Variable	Median survival in months (SE)	P (log rank)	Variable	Median survival in months (SE)	P (log rank)
Sex			**Platelets**		
Male	120 (38)	0.57	≤ 400 000	192 (74)	0.73
Female	144 (44)		> 400 000	120 (26)	
Age (yrs)			**Splenomegaly**		
≤40	144 (33)	0.39	≤ 15 cm and no spleen	144 (34)	**0.05**
> 40	120 (28)		> 15 cm spleen	48 (38)	
WBC			**BM blasts**		
≤100	92 (27)	0.59	< 10	120 (20)	**0.04**
> 100	144 (23)		10 – 20	15 (-)	
Basophils			**BM fibrosis**		
≤ 5%	144 (32)	0.74	Grade I & II	168 (36)	0.93
> 5%	120 (-)		Grade III & IV	120 (-)	
Promyelocytes					
≤ 5%	92 (-)	0.34			
> 5%	192 (90)				

* Incomplete data in some cases; to calculate percentage, denominator = number for which information was available.

We looked at ten characteristics of the disease at diagnosis (age, sex….etc). Since only one patient was Philadelphia chromosome negative, this feature was not taken into consideration. (Table 2)

Table 2 – Laboratory and clinical findings at diagnosis of CML

Variable	Number (%)	Variable	Number (%)
Sex		**Platelets**	
Male	27 (45)	≤ 400 000	25 (44.6)
Female	33 (55)	> 400 000	31 (55.4)
Age (yrs)		**Splenomegaly**	
≤40	23 (38.3)	≤ 15 cm and no spleen	45 (75.0)
> 40	37 (61.7)	> 15 cm spleen	15 (25.0)
WBC		**BM blasts**	
≤100	26 (44.8)	< 10	52 (86.7)
> 100	32 (55.2)	10 – 20	8 (13.3)
Basophils		**BM fibrosis**	
≤ 5%	47 (87.0)	Grade I & II	49 (81.7)
> 5%	7 (13.0)	Grade III & IV	11 (18.3)
Promyelocytes			
≤ 5%	21 (61.8)		
> 5%	13 (38.2)		

* Incomplete data in some cases; to calculate percentage, denominator = number for which information was available.

Cox regression on splenomegaly alone yielded a relative risk of 2.3 (95% CI 1.05-5.7) of death or transformation for patients having splenomegaly greater than or equal to 15 cm. Bone marrow blasts (BM blasts) ≥10 was also associated with significantly higher risk of mortality with a relative risk of 7.4 (95% CI 1.5-37.0). Splenomegaly as a semi-continuous variable (1 = no splenomegaly, 2 = 1-5 cm, 3 = 6-10 cm, 4 = 11-15 cm, 5>15 cm) yielded a relative risk (RR) of 1.3 per unit increase in splenomegaly (e.g. from 1-5 cm to 5-0 cm), but this was not statistically significant ($p > 0.05$). However, Cox regression of the effect of splenomegaly as covariate jointly with BM blast count showed that both were highly significant, with RR of 1.5 (95% CI: 1.0-2.3, $p = 0.03$) for splenomegaly and 9.9 (95% CI: 1.9-51.9, $p = 0.007$) for BM. (Table 1).

As part of the study, we determined the median duration of the chronic phase in this population (120 months) (Fig 1). Fourteen patients remained in chronic phase for more than 100 months, and six patients for more than 150 months (Table 3).

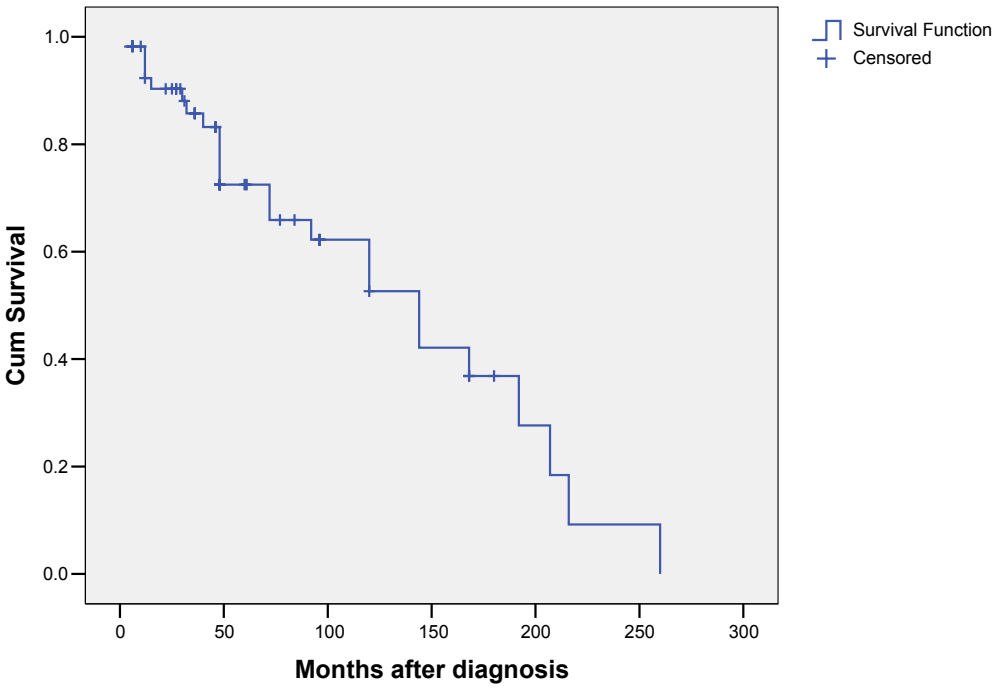

Figure 1 – Survival of CML patients, time to death or transformation

Table 3 – Duration of chronic phase in a subset of patients

Subject Number	Sex	Duration of chronic phase (months)	Ethnic origin
1	Male	96	Non-Saudi
2	Male	96	Saudi
14	Male	120	Saudi
16	Female	192	Saudi
18	Male	120	Non-Saudi
19	Female	216	Saudi
21	Female	120	Non-Saudi
22	Female	144	Saudi
25	Male	168	Non-Saudi
30	Female	144	Saudi
32	Male	180	Saudi
33	Female	168	Saudi
44	Female	96	Saudi
45	Female	124	Saudi
46	Female	101	Saudi
58	Female	168	Saudi

DISCUSSION

Chronic phase CML has been described as a benign premalignant state in which 100% transformation is expected[9]. The first 2 years after diagnosis hold the lowest risk of disease transformation to blast crisis (5-10%). After 2 years, the annual progression rate increases to 20-25%[1]. CML patients have an extremely variable disease course which is thought predominantly to be due to numerous host and disease-related characteristics[5, 7, 10]

Numerous risk stratification approaches have been adopted[7-15]. We analyzed 10 clinical and laboratory features of the disease in a population of 60 patients, all of whom were in chronic phase at the time of presentation. Our results were similar to those found by other

investigators with regards to the prognostic significance of splenomegaly and the bone marrow blast percentage[5,11]. The lack of evidence that other laboratory and clinical variables affects survival in this population may be due to a difference in the biology of the disease or due to the number of patients studied. Validation of a reliable prognostic system, based on larger studies, could result in a more meaningful stratification of our CML patients into various risk groups. Accordingly, individualized management plans could be adopted for such patients based on the risk- benefit ratio.

CONCLUSION

This study showed that splenomegaly greater than or equal to 13 cm and a bone marrow blast count of greater than 10% of nucleated non-erythroid cells, were both associated significantly with a high risk of death or transformation. We could not demonstrate such an association with the rest of the pre-treatment patients or disease-related characteristics. Most patients were on cytoreductive therapy. There was no statistical impact for the type of treatment on the outcome of the disease.

The study also helped to identify features of CML in a population of patients in western Saudi Arabia. Further studies are required to identify epidemiological factors that may influence the biology of the disease in this region.

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