Prognostic Factors and Scoring Systems in Chronic Myelomonocytic Leukemia: A Retrospective Analysis of 37 Patients

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ABSTRACT

Main objective of this study was to evaluate hematological, clinical and demographic features of our chronic myelomonocytic leukemia (CMML) patients according to different classification systems and prognostic variables.
Thirty-seven consecutive patients with CMML diagnosed between February 1994 and December 2005 were evaluated retrospectively. Male and female ratio was 29/8. The median age at diagnosis was 72. Median follow-up time for all patients was 12 months (1-119 months). 70.3% of patients were classified as CMML-MP, others were classified as CMML-MD type according to FAB. When they were reclassified according to WHO, 86.5% of them were CMML-I and 13.5% were CMML-II. Karyotyping analysis could be made in only 22 patients.
Median laboratory values were as follows: hemoglobin (Hb) 9 g/dL (range 6.1-14 g/dL), white blood cell (WBC) count 9.7 x 10^9/L (range1.8-157 x 10^9/L), peripheral monocyte count 3.5 x 10^9 /L (range 1.2-50 x 10^9 /L), platelet count 85 x 10^9/L (range 6-992 x 10^9 /L). Splenomegaly was observed in 11 patients (29.7%). 14 patients (37.8%) developed AML after a median time of 11 months (1-90 months) and survived a median of 1.5 months after leukemia transformation. The overall survival (OS) was 12 months (MD: 12 months, MP: 25 months, p= 0.3). International Prognostic Scoring Sytem (IPSS) could be applied to only 13 CMML-MD patients (WBC < 12 x 10^9/L). Patients were also assessed using previously published scoring systems. Significant differencies between risk groups were found in case of OS (Modified Bournemouth score: p= 0.039, Duesseldorf score: p= 0.01, IPSS: p= 0.003). In multivariate analysis, only hemoglobine (< 10 g/dL) and bone marrow blast percentage (≥ 10%) have been found to have a prognostic value (p= 0.03, p= 0.002).
Although use of current prognostic scoring systems is encouraging in CMML more reliable disease spesific prognostic factors are needed for clinical decision making.

Key Words: Chronic myelomonocytic leukemia, Myelodysplastic syndrome, Scoring systems, Prognostic factors

ÖZET

Kronik Myelomonositik Lösemide Prognostik Faktörler ve Skorlama Sistemleri: 37 Hastanın Retrospektif Analizi

Çalışmada kronik myelomonositik lösemili (KMML) olgularımızın farklı sınıflama ve prognostik skorlama sistemlerine göre hematolojik, klinik ve demografik özelliklerini değerlendirmeyi amaçladık.

Şubat 1994 ile Aralık 2005 arası tanı almış 37 KMML hastası retrospektif olarak değerlendirildi. Erkek kadın oranı 29/8, tanı anındaki medyan yaş 72 idi. Hastaların medyan izlem süresi 12 aydı (1-119 ay). Olguların FAB'a göre %70.3'ü KMML-MP, diğerleri KMML-MD olarak sınıflandırıldı. WHO'ya göre, %86.5'i KMML-I, %13.5'i KMML-II olarak yeniden sınıflandırıldı. Karyotipik analiz 22 hastada yapılabildi.

Medyan laboratuar değerlerinden hemoglobin (Hb) 9 g/dL (6.1-14 g/dL), beyaz küre (WBC) 9.7 x 10^9/L (1.8-157 x 10^9 /L), periferal monosit sayısı 3.5 x 10^9/L (1.2-50 x 10^9/L), trombosit 85 x 10^9/L (6-992 x 10^9/L) idi. Splenomegali 11 hastada (%29.7) gözlendi. 14 olguda (%37.8) medyan 11 ay sonra (1-90 ay) AML gelişti ve transformasyon sonrası medyan 11 ay yaşadıkları (1-90 ay) izlendi. OS 12 aydı [MD (miyelodisplastik) tipinde 12 ay, MP (miyeloproliferatif) tipinde 25 ay, p=0.3]. Uluslar arası skorlama sisteminde (IPSS) 13 KMML-MD hastasına uygulanabildi (WBC < 12 x 10^9/L). Hastalar yayınlanmış skorlama sistemlerine göre yeniden değerlendirildi. Risk grupları arasında anlamlı OS farkı mevcuttu (Modifiye Bournemouth skorunda:p= 0.039, Duesseldorf skorunda:p= 0.01, IPSS: p=0.003). Multivaryant analizi yapıldığında Hb (< 10 g/dL) ve kemik iliği blast yüzdesinin (≥ %10) prognostik anlam taşıdığı görüldü (p= 0.03, p= 0.002). Güncel prognostik skorlama sistemlerinin KMML'de kullanımı cesaret verici olsa da klinikte karar vermede daha spesifik prognostik faktörlere ihtiyaç olduğu kanısındayız.

Anahtar Kelimeler: Kronik miyelomonositik lösemi, Miyelodisplastik sendrom, Skorlama sistemleri, Prognostik faktörler

INTRODUCTION

Chronic myelomonocytic leukemia (CMML) is a heterogenous hematologic malignancy characterized by increased monocytes in the bone marrow, peripheral blood and a variable degree of marrow dysplasia (1). Because of clinical discrepencies extending from indolent course to rapidly progressing to acute leukemia, there are still some difficulties in classification of this disorder. Although CMML was incorporated into the French-American-British (FAB) classification of myelodysplastic syndromes due to existance of dysplastic changes (2), presence of organomegaly (splenomegaly and/or hepatomegaly, found in 40-50% of CMML patients) and leukocytosis in some patients caused this disorder to be interpreted as a myeloproliferative disorder as well. In 1994, FAB proposed another classification separating CMML as myeloproliferative type (MP) (leukocytes > 13 x 10^9 /L) and myelodysplastic type (MD) (leukocytes > 13 x 10^9 /L) (3). Finally World Health Organization (WHO) classification described CMML as a mixed myeloproliferative/ myelodysplastic disorder apart from myelodysplastic syndrome and proposed to seperate CMML into CMML I and CMML II depending on the medullary, peripheral blast counts (4,5).

Prognosis is also extremely variable with life expectancy ranging from several months to several years. Different prognostic factors have been evaluated in numerous studies (1,6-14).

In this study, we aimed to evaluate hematological, clinical and demographic features of our CMML patients with prognostic variables.

PATIENTS AND METHODS

Patient Characteristics and Clinical Properties

Thirty-seven consecutive patients with CMML diagnosed between February 1994 and December 2005 were evaluated retrospectively. Blood and bone marrow studies were performed on the date of admission. FAB proposal (2) was used as diagnostic criteria for CMML: blood monocytes above 1 x 10^9/L; bone marrow blasts 20% or less associated with hematopoietic dysplastic features; peripheral blasts below 5%; and absence of auer rods in myeloid cells.

Patients were also assessed using previously published scoring systems; modified Bournemouth score developed spesifically for CMML patients (15), Duesseldorf score (6) and International Prognostic Scoring Sytem (IPSS) (16) developed for MDS patients (Table 1).

Table 1. Definitions of scoring systems for CMML

IPSS (16)	Bournemouth (15)	Dusseldorf (6)
Number of cytopenias (0/1: -0-; 2/3: -0.5-)	Hb < 10 g/dl -1-	Hb < 9 g/dl -1-
Karyotype risk group (Good: -0- ;intermediate: -0.5-; poor: -1-)	Absolute neutrophile count < 2500/μL, >16.000/μL -1-	High LDH -1-
Marrow blast (<5%: -0-; 5-10%: -0.5-; 11-20%: -1.5-; >20%: 2)	Platelets <100.000/μL -1-	Platelets <100.000/μL -1-
	Marrow blasts >5% -1-	Marrow blasts > 5% -1-
Low risk 0	0-1	0
Intermediate risk –I 0.5-1		1-2
Intermediate risk –II 1.5-2		
High risk > 2.5	2-4	3-4

For cytogenetic evaluation, 15-20 metaphases were examined according to standard operating procedures in our cytogenetic laboratory. Cytogenetic evaluation could be made in only 22 patients.

Statistical Analysis

All statistical analysis was performed using the SPSS 10.0 statistical package.

Numerical variables were summarized by their median and range. Categoric variables were described by counts and relative frequencies.

Overall survival (OS) was defined as the time between diagnosis and death (due to any causes) or end of follow-up (censored observations). OS was estimated using the Kaplan-Meier product limit method. Multivariate analysis were performed by means of Cox proportional hazards regression to

Table 2. Hematological and clinical charactheristics according to CMML-MD vs CMML-MP

	CMML-MD	CMML-MP
n (%)	26 (70.3)	11 (29.7)
Age (median, range)	71.5 (42-85)	74 (40-84)
M/F	21/5	8/3
Hb	9 (6.1-12.5)	10 (6.6-14)
WBC	7.05 (1.8-12)	35.7 (18.1-157)
BM blast rate (%)	3 (0-19)	1.7 (0-10)
Hepatomegaly (%)	11.5	36.4
Splenomegaly (%)	7.7	81.8
AML transformation (%)	34.6	45.5
Median OS (months)	12 (1-92)	25 (1-119)

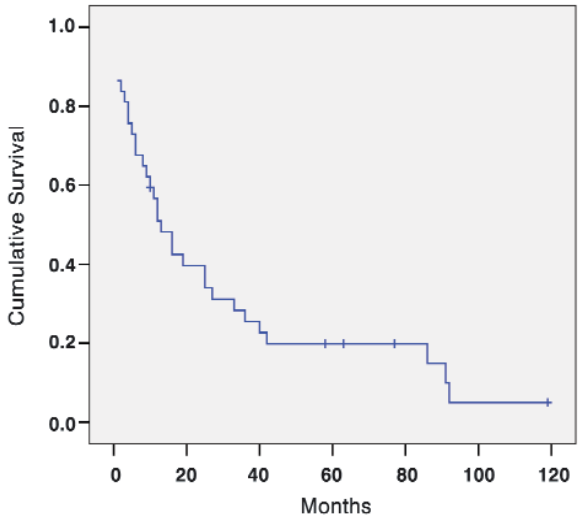

Figure 1. Overall survival of all CMML patients (OS=12 months)

identify the most significant independent prognostic factors affecting survival.

All p-values are two sided. A value of $p< 0.05$ was considered as significant.

RESULTS

Twenty-nine patients were male, eight patients were female (29/8). The median age at diagnosis was 72 (range 40-85). 31 patients were ≥ 60 years of age, 6 patients were < 60 years of age. Median laboratory values were as follows: hemoglobin (Hb) 9 g/dL (range 6.1-14 g/dL), white blood cell (WBC) count 9.7x10^9 /L (range 1.8-157 x 10^9 /L), peripheral monocyte count 3.5 x 10^9 /L (range 1.2-50 x10^9 /L), platelet count 85 x 10^9 /L (range 6-992 x 10^9 /L). Splenomegaly was observed in 11 patients (29.7%).

70.3% of patients were classified as CMML-MP, others were classified as CMML-MD type according to FAB (depending on the WBC >/≤ 13.000 μL) (3). The charactheristics of these subgroups were given in Table 2. When they were reclassified according to WHO, 86.5% of them were CMML-I and 13.5% were CMML-II.

Cytogenetic analysis were evaluated in 22 patients. 68.2% of patients (15/22) had normal karyotype. Karyotype anomalies were seen in 31.8% (7/22) of patients [complex anomaly (at least 3 chromosomal anomalies): 2 patients (9%), -Y: 2 patients (9%), other anomalies (-6, -7, +8): 3 patients (13.8%)].

Median follow-up time for all patients was 12 months (1-119 months). At the time of last follow-up, 32 patients (86%) had died.

Table 3. Hematological parameters and bone marrow blast percentiles of CMML patients and their effect on OS (univariate analysis)

Degree of cytopenia		**n (%)**	**p**
Hemoglobin level	≥ 10 g/dL	15 (40.5%)	
	< 10 g/dL	22 (59.5%)	0.01
Neutrophil count	≥ 1.5 x 10^9/L	26 (70.3%)	
	< 1.5 x 10^9/L	11 (29.7%)	0.2
Lymphocyte count	≥ 2.5 x 10^9/L	16 (43.2%)	
	< 2.5 x 10^9/L	21 (56.8%)	0.9
Platelet count	≥ 100 x 10^9/L	16 (43.2%)	
	< 100 x 10^9/L	21 (56.8%)	0.6
Blast (%)	≥ 10%	5 (13.5%)	
(Bone Marrow)	< 10%	32 (86.5%)	0.001

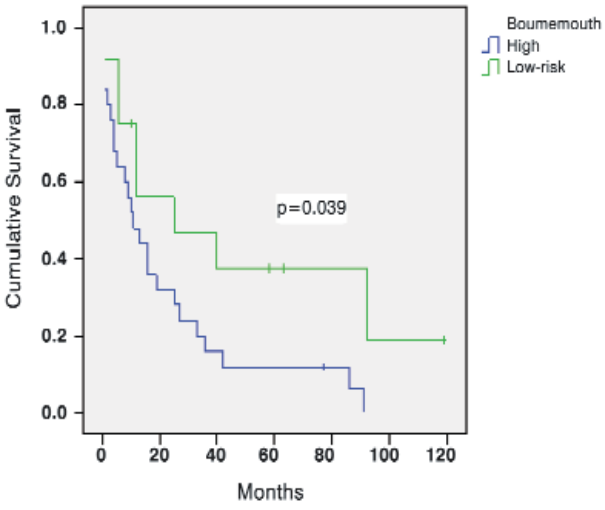

Figure 2. Survival curves of CMML patients according to the Bournemouth modified score

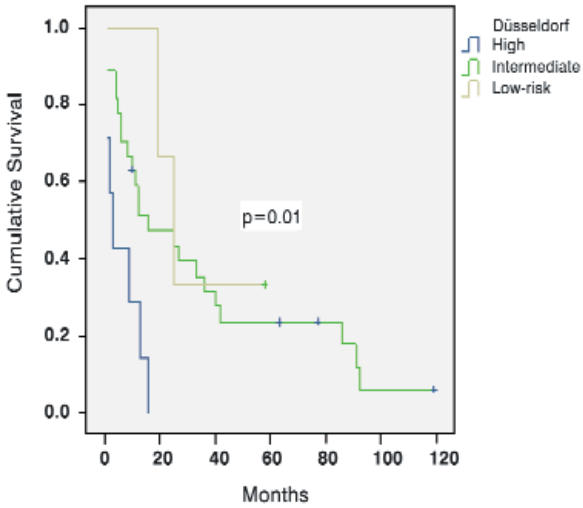

Figure 3. Survival curves of CMML patients according to the Dusseldorf score

14 patients (37.8%) developed AML after a median time of 11 months (1-90 months)[11 months (1-90 months) for CMML-MD, 9.5 months (2-75 months) for CMML-MP patients]. These patients survived a median of 1.5 months (CMML-MD: median 3 months, CMML-MP: median 1 month). Induction treatment (7+3: Ara-C for 7 days and idarubicin for 3 days) was given to 5 patients. The median survival time after AML transformation for those patients who have received induction treatment was 3 months (1-6 months). Due to poor performance status, we could not administer chemotherapy to other 9 patients.

The degree of cytopenia and blast rate in bone marrow and their effects on OS were given at Table 3. In addition to these parameters, WBC count (> 10 x

Table 4. Survival in CMML patients according to different scoring systems

Scoring systems	n (%)	Median survival (month)	p
Bournemouth modified score			
Low-risk	12 (32.4)	25	0.039
High-risk	25 (67.6)	11	
Duesseldorf score			
Low-risk	3 (8.1)	25	0.01
Intermediate-risk	27 (73)	16	
High-risk	7 (18.9)	3	
IPSS (n :13, WBC < 12.000/μL)			
Low-risk	4 (30.8)	77	0.003
Intermediate-risk I	5 (38.5)	19	
Intermediate-risk II	3 (23.1)	13	
High-risk	1 (7.7)	1	

Table 5. The effect of hematological parameters on OS of CMML patients (multivariate analysis, cox-regression analysis)

	P	HR
Hb (< 10 g/dL)	0.03	2.4
Lymphocyte (≥ 2.5x109/L)	0.9	0.9
BM blast count (≥ 10%)	0.002	6.2
platelet (< 100 x 10^9/L)	0.3	1.4

10^9 /L), monocyte count (> 2 x 10^9 /L) also were evaluated and not found as significant (p= 0.8, p=0.1). The median transfusion rate was 4 units.

The causes of exitus are listed as follows: infection (56.3%), bleeding (25%), neutropenic fever (12.5%), cardiovascular events (6.2%).

The OS was found as 12 months (Figure 1). When the patients were classified as MD and MP type CMML, OS was 12 months vs 25 months (p= 0.3). Different scoring systems were also applied to MDS patients. All systems identified patient groups differing significantly in survival (Modified Bournemouth score: p= 0.039, Duesseldorf score: p= 0.01, IPSS: p= 0.003) (Table 4) (Figure 2, 3). IPSS could be applied to only 13 CMML-MD patients (WBC < 12 x 10^9/L) and it was found that IPSS has significant effect on OS (p= 0.003). The prognostic impact of hematological parameters (Hb < 10 g/dL, platelet < 100 x 10^9/L, lymphocyte ≥ 2.5 x 10^9/L), bone marrow blast count (≥ %10) on prognosis were also evaluated (Table 5). In case of multivariate analysis, only hemoglobin and bone marrow blast percentage have been found to have a prognostic value (p= 0.03, p= 0.002).

DISCUSSION

The variances in clinical behaviour of CMML cause difficulties in its classification. Some patients present with mild leukocytosis with monocytosis while others present with significant leukocytosis with extramedullary hematopoiesis (causing development of splenomegaly, skin infiltration and serious pleural and peritoneal effusions) resembling myeloproliferative syndromes (7). Clinical course also varies from slowly progressing disease to rapidly developing acute myeloid leukemia (AML).

In accordance with other CMML and MDS series, median age of our patients was older (72 years) and also showed a predominance of male sex (M/F: 29/8) (1,7-11,17-20). Splenomegaly was observed in 29.7% of our patients. Splenomegaly existancy varied between 11%-54% in other studies (7-12,17-21).

Median survival times of CMML patients vary between 7 and over 60 months (8,13) in the literature. These discrepancies were thought to occur due to selection of the patients influenced by diagnostic criteria in different studies (1). In our study, OS of the patients was found 12 months (range 1-119).

After FAB group distinguished CMML as MP and MD, several groups studied the prognostic significance of this classification (7,11,20,21). Most large single center studies reported shorter OS for MP CMML compared with MD CMML (1,11,14,20, 22,23) Germing et al. (20) reported little prognostic value of this seperation while Breccia et al (14) had stressed that MD and MP groups may identify two distinct categories of patients with different survivals and leukemic transformation rates. OS for MD group and MP groups were 20 months vs 17.4 months (p= 0.007) while disease progression rate was higher for MP type than MD type (29.7% vs 15.2%, p= 0.001) in the study of Breccia et al which included 83 patients. We also seperated our CMML group as MP and MD type. In opposition to the findings of many studies, OS of our MP group was higher than MD group (25 months vs 12 months) although this difference was not statistically significant (p= 0.3). In the series of Onida et al including 213 CMML cases, there was not any difference for

survival experience (median 13 vs 12 months, respectively) and for AML transformation rate (MD: 20%, MP: 18%) (1). We could say that there are still questions for seperating CMML as MD and MP.

Although different scoring systems were used, prognosis assessment in CMML is rather difficult comparing to MDS (1,6,7,15,16). IPSS could not be suitable for evaluating prognosis of CMML, because of existance of patients with leukocyte count above 12.000/μL, low frequency of karyotyping anomalies and rare occurence of multiple cytopenias (24).

In our study, we applied modified Bournemouth score, Duesseldorf score as well as International Prognostic Scoring Sytem (IPSS) to our patients, and all showed predictive power in means of survival similar to the report of Germing et al. Low risk patients in all scoring systems were identified as having good prognosis with survival times ranging from 18 to 93 months in different series (1,6,14,15,24) similar to our findings. Low risk patients according to IPSS seemed to have superior survival rate (77 months) than higher risk groups but by IPSS scoring we could only cover 35% (n= 13) of our CMML patients. It could be concluded that scoring systems could be beneficial to discriminate especially the low risk groups.

In our series, the rate of AML transformation of CMML to AML was higher (37.8%) compared to findings reported before (10,12,22,25) and rate of transformation in dysplastic and proliferative subgroups was relatively identical (Table 1). This might be related with the size of study group.

Several survival-associated prognostic factors for CMML were identified (1,7,11,12,26). In our study, hemoglobin level (< 10 g/dL) and bone marrow blast percentile (> 10%) showed poor prognostic effect on OS by multivariate analysis.

Although current prognostic scorring systems and factors that were defined at present are helpful in clinical decission making of CMML, more objective biological and molecular parameters are needed in order to reveal reliable disease spesific prognostic factors.

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