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PROGNOSIS OF CHRONIC MYELOMONOCYTIC LEUKEMIA

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ABSTRACT

Background. **Cytopenia caused by ineffective hematopoiesis and monocyte overproduction coexist in CMML, providing grounds for discussion to supporters of a dysplastic versus a proliferative identity for CMML. Follow-up information from a large series of patients may contribute to clarifying the position of this infrequent disease.**

Methods. **We analyzed data from 77 patients followed in five institutions. Thirty-two variables were studied for their influence on survival and on progression to acute leukemia by univariate and multivariate analysis. For some parameters, we performed a quartile analysis to reveal a possible non-monotonic influence on survival.**

Results. **Median survival was 17 months. Evolution to acute leukemia (ANLL) occurred in 11 patients (14%) within a median time of 8 months. Multivariate analysis assigned a poorer prognosis to patients presenting with thrombocytopenia, anemia and leukocytosis. Thrombocytopenia and the presence of circulating blasts were risk factors for transformation to ANLL, while raised serum aspartate transaminase at diagnosis seemed to be associated with a lower probability of blastic evolution. The Bournemouth score for CMML proved to be a valid tool for predicting survival but not acute transformation.**

Conclusions. **CMML is a severe disease. The prognostic independence of cytopenia (anemia, thrombocytopenia) and leukocytosis underlines the coexistence of aspects typical of myelodysplastic and myeloproliferative syndromes.**

Key words: chronic myelomonocytic leukemia, myelodysplastic syndromes, myeloproliferative syndromes

In 1976 the French-American-British Cooperative Group (FAB) introduced the term *dysmyelopoietic syndromes* to delineate conditions of dysregulated hematopoiesis for which immediate chemotherapy might not be indicated. Two broad types were recognized: refractory anemia with excess of blasts (RAEB) and chronic myelomonocytic leukemia (CMML), distinguishable from one other by the presence of a prominent monocytic component in the peripheral blood and bone marrow in the latter.[1] In 1982 the same FAB Group proposed new criteria for the classification of myelodysplastic syndromes (MDS), defining five types: refractory anemia (RA), RA with ringed sideroblasts, also called acquired idiopathic sideroblastic anemia, refractory anemia with excess of blasts (RAEB), RAEB in transformation, and CMML.[2]

CMML is not frequent.[3] Most patients affected by this disease are over 50 years of age. Onset is usually insidious; weakness, infection or bleeding bring patients to medical attention. Hepatomegaly and splenomegaly are usually present at diagnosis; polyclonal hypergammaglobulinemia and increased serum and urine levels of lysozyme are frequent. The disease is defined by circulating monocytes in excess of 1×10^9 per liter. Anemia and thrombocytopenia are common. WBC may be normal, moderately elevated or slightly decreased. The marrow is generally hypercellular as a result of granulo-monocytic hyperplasia, with a variable degree of trilineage

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dysplasia. Bone marrow blasts are usually increased but, by definition, do not exceed 20% of all nucleated bone marrow cells.

In vitro studies have demonstrated various growth patterns in CMML, ranging from reduced CFU-GM colony growth with a raised cluster/colony ratio, typical of dysplastic marrows, to spontaneous colony formation.[4,5]

Molecular studies have revealed peculiarities of CMML that bear some similarity to chronic myeloid leukemia (CML). Ras gene abnormalities have been found both in CMML (more frequently than in other MDS FAB subtypes) and in Ph-negative CML.[6] Ras proteins are involved in the transmission of growth signals from outside the cell to the nucleus; disturbances may be caused by point-mutations of the Ras genes or by altered Ras-activating proteins. In CML, Ras genes constitutively activated via bcr/abl activity have been verified in the absence of RAS mutations.[6] An analysis of a number of hematological and clinical parameters at diagnosis combined with information on follow-up and outcome in a large series of CMML patients may help to clarify the position of this rare disease.

Materials and Methods

We collected data from 77 patients observed in five institutions in Southern Italy between 1982 and 1993. All patients met the FAB criteria for a diagnosis of CMML,[2] except four cases in which the upper level of bone marrow (BM) blast cells was between 20% and 30%; in two of them a spontaneous reduction occurred after recovery from septic episodes. Eighteen continuous and fourteen categorical variables, recorded at time of diagnosis, were available for almost all patients and were therefore included in the analysis (Table 1). Monochemotherapy (low-dose arabinosylcytosine, hydroxyurea, etoposide or α-interferon) was employed in 32 patients. Hormonal treatment (danazol) was administered to 9 patients. Treatment was defined as effective if at least one of the abnormal hematological parameters improved. The Bournemouth score system, modified for CMML,[7] was applied to each case: it attributes a score of 1 each for hemoglobin < 10 g/dL, neutrophils < 2.5×10^9/L or > 16×10^9/L, platelet < 100×10^9/L; a score of 2 or more is associated with shorter survival.

Statistical analysis

All the continuous variables were dichotomized at the median value. No cut-off finding procedure was carried out, since the relatively limited sample size did not allow us to perform a validation test. We investigated the relation with evolution towards ANLL and the influence on survival for each variable. These effects were first screened by univariate analysis; Kaplan-Meier curves for survival and the probability of acute transformation were estimated for each class of the dichotomized variables.[8] The log-rank test was used to test the null hypothesis of equivalence between different groups. A quartile analysis was also carried out for WBC and neutrophil count in order to reveal a possible non-monotonic influence on the survival function. Missing data were excluded from the analysis.

Multivariate analyses were then performed by fitting two proportional hazard Cox models,[9] one for survival and one for the probability of ANLL, using stepwise selection of the covariates. Each continuous variable introduced into the Cox model was recodified as 0 or 1 according to the following rule: 0 for values less than or equal

Table 1. Categorical and continuous variables at diagnosis in 77 cases of CMML.

Male/female	54/23			
Median age (yrs)	71 (r.21-83)			
			median	range
	Y/N	Hb g/dL	8.8	3-14.2
Liver*	59/18	WBC $x10^9$/L	18.5	2.7-23.0
Spleen*	42/35	Plt $x10^9$/L	90	1.0-980
Adenopathy	10/67	neutrophils $x10^9$/L	8.9	0.1-117.3
Skin involvement	1/75	monocytes $x10^9$/L	4.0	1.0-80
Serositis	4/67	promyelocytes $x10^9$/L	0	0-9.8
Fever	10/67	myelocytes $x10^9$/L	0.2	0-27.6
Infection	8/59	metamyelocytes $x10^9$/L	0	0-16.7
Transfusions	51/24	circulating blasts $x10^9$/L	0	0-22.0
Dysmegakaryopoiesis	27/37			
Dyserythropoiesis	32/34	BM erythroid cells %	15	1-45
Dysgranulopoiesis	65/5	BM myeloid cells %	58	3-91
		BM monocytes %	10	0-50
		BM blasts %	5	0-30
		LDH U/L	370	116-3300
		AST U/L	19	5-68
		Creatinine mg/dL	1.1	0.1-2.2
		γ-globulins g/dL	1.8	0.2-5

**liver and spleen enlargement > 2 cm*

to the median value, 1 for larger values. Only patients with complete data for every variable were included in the model. In the final model for survival, the effect of acute transformation was then included as a time-dependent covariate. All the analyses were carried out using the BMDP statistical software package (Los Angeles, CA, USA).

Results

Parameters at diagnosis

The median age of the 54 male and 23 female patients was 71 years (range 21-83). Clinical and hematological features at diagnosis (Table 1) consisted mainly of moderate spleen enlargement, anemia, thrombocytopenia and leukocytosis. At differential count, monocytosis and neutrophilia were predominant. Bone marrow examination commonly showed granulocytic hyperplasia with maturation arrest and dyshematopoiesis, mainly dysgranulopoiesis. Polyclonal hypergammaglobulinemia and moderate elevation of lactate dehydrogenase (LDH) were frequent findings (66% and 47% of the patients, respectively). Red cell transfusion requirement was already present at diagnosis in 68% of the patients. Lymph node and skin involvement were rarely detected.

Effect of treatment

None of the patients receiving pharmacological treatment achieved complete remission. Improvement of at least one hematological parameter was observed in 12 cases.

Table 2. Variables influencing the incidence of blastic transformation.

	univariate	*multivariate*	
	p	*p*	*RR*
Platelets > 90×10^9/L	0.002	0.004	0.11
Circulating blasts	0.001	0.008	5.57
Raised AST	0.008	0.018	0.16
Adenopathy	0.003	n.s.	–
BM monocytes > 10%	0.007	n.s.	–
BM erythroid cells < 15%	0.04	n.s.	–

Acute transformation

Evolution to ANLL occurred in 11 patients (14%). Time to transformation ranged from 1 to 50 months, median 8 months. Median survival after diagnosis of blastic phase was two months. According to the univariate analysis, variables significantly correlated with the risk of acute transformation were thrombocytopenia, the presence of circulating blast cells at diagnosis, adenopathy, high BM monocyte and low BM erythroblast percentage. Surprisingly, raised AST values were associated with a reduced incidence of blastic transformation (relative risk = 0.16). Platelet count, the presence of circulating blasts and raised serum aspartate transaminase (AST) maintained independent predictive power in the multivariate analysis (Table 2).

Survival

The median survival time was 17 months (range 2-108). Seven variables showed a correlation with shorter survival at univariate analysis; some of them might be connected with the consequences of dysplastic hematopoiesis (thrombocytopenia, anemia, circulating blasts), others with aspects of effective myeloproliferation (leukocytosis, adenopathy, neutrophilia). Raised AST values were unexpectedly associated with longer survival. A list of these variables and the corresponding p values are reported in Table 3. Survival curves for platelet count, AST and WBC are shown in Figure 1. Interestingly, WBC and neutrophil counts showed a perfect monotonic relationship with survival at quartile analysis (test for trend: p=0.005 and p=0.01, respectively) (Figure 2). However, multivariate analysis demonstrated that only Hb, WBC, platelets and AST showed an independent prognostic value (Table 3). Finally, when acute transformation was included in the model as a time-dependent variable, all the covariates kept their independent prognostic power except AST.

Discussion

CMML is diagnosed mainly in elderly patients, more often males. In our study the median age at diagnosis was 71 years and the M/F ratio was 2:1. The most frequent presenta-

Table 3. Variables influencing survival.

	univariate	*multivariate*	
	p	*p*	*RR*
Platelets > 90×10^9/L	<0.00001	0.004	0.11
Raised AST	0.005	0.004	0.16
Hb > 8.8 g/dL	0.001	0.01	0.15
Leukocytes > 18.5×10^9/L	0.01	0.01	2.91
Adenopathy	0.02	n.s.	–
Circulating blasts	0.02	n.s.	–
Neutrophils > 8.9×10^9/L	0.01	n.s.	–

tion included absolute monocytosis, anemia, thrombocytopenia, and moderate spleen and liver enlargement. Polyclonal hypergammaglobulinemia was frequent.

Median survival (17 months) and percentage of acute metamorphoses (14%) in our cohort of patients are concordant with those reported by other authors,[7,10-16] who described survival ranging from 8 to 60 months and evolution to ANLL between 0 and 50%. A multivariate analysis of risk factors for transformation to ANLL attributed significance to the presence of circulating blasts and to thrombocytopenia, while elevation of serum AST concentration seemed to be associated with a lower risk. The latter is a new and unexplained finding in CMML. AST increase could be due to liver leukemic infiltration, but such an interpretation hardly explains a reduced incidence of acute transformation. Signs of chronic liver damage have occasionally been associated with a favorable course in other oncohematologic diseases,[17,18] leading to the hypothesis of more effective immunological control of the leukemic proliferation. In the present series, histological, virological and immunological data are fragmentary and do not allow any conclusion about the nature of the liver damage. We can only state that AST levels were marginally elevat-

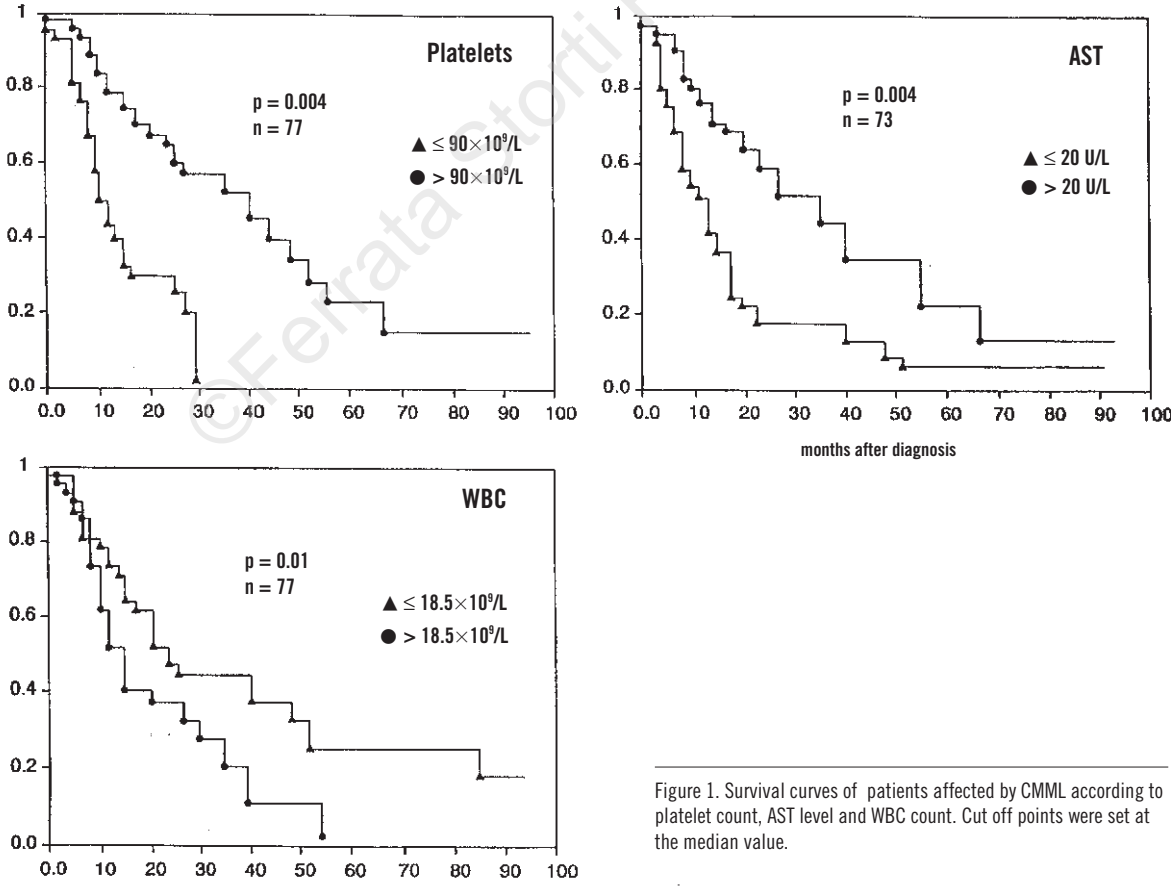

Figure 1. Survival curves of patients affected by CMML according to platelet count, AST level and WBC count. Cut off points were set at the median value.

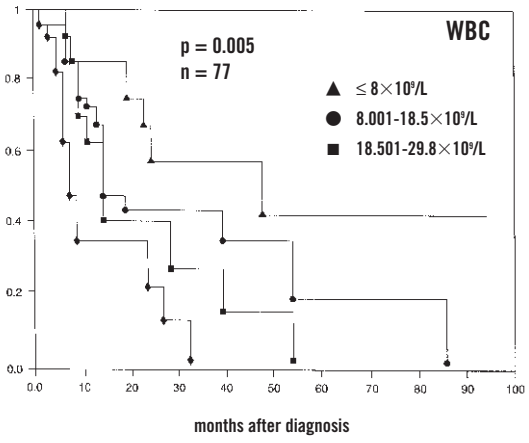

Figure 2. Survival curves of 77 patients affected by CMML according to WBC count quartiles.

ed (upper level 68 U/L) and that the patients belonged to geographical areas with a high prevalence of hepatitis due to B and C viruses. We must add that, at variance with our findings, signs of liver damage were found to be associated with shorter survival in another series.[19]

In our study the statistical weight of circulating blasts and an absence of significance for the number of bone marrow blasts could suggest that the presence of blast cells in the peripheral blood implies more aggressive biological behavior. However, the difficulty in unequivocally identifying leukemic cells in dysplastic marrows showing granulocytic hyperplasia and an excess of myelomonocytic cells may make a reliable blast cell count in the bone marrow difficult in the absence of a centralized revision of marrow cytology. In any case, the prognostic relevance of circulating, but not of bone marrow, blast cells have already been noticed by others.[12]

Our survival analysis attributes prognostic independence to thrombocytopenia, anemia and leukocytosis; the protective effect of raised AST levels is also verified in the survival context, but its significance is lost if we include in the analysis acute evolution as a time-dependent covariate. It is noteworthy that, according to our results, the possibility of predicting survival may be derived from objective parameters such as leukocytes, platelets and hemoglobin levels, which show little variation among different observers. In agreement with other studies,[20] the modified Bournemouth score for CMML[7] proved to be a valid tool for predicting survival (classes 0-1 vs. 2-4: 28 vs 8 months, respectively), but was unable to predict acute transformation. We could not confirm the relevance of neutropenia. Our survival curves, obtained also by quartile analysis of WBC and neutrophil distribution, suggest that a poorer prognosis pertains only to patients with higher WBC and neutrophil counts (Figure 2), as described in most of the analyses published so far. Recently, high levels of serum thymidine kinase have been correlated with a greater risk of evolution to AML.[21]

Our analysis shows that in CMML the consequences of ineffective hematopoiesis (anemia and thrombocytopenia) and of hypertrophic effective myelopoiesis (leukocytosis) influence survival independently. Thus, disagreement about the identity of CMML[22] could be resolved by considering this disease as a *trait d'union* between proliferative and dysplastic syndromes, sharing both aspects of dysregulated hematopoiesis. The efficacy of α-interferon in controlling leukocytosis in a number of CMML patients[5] is further evidence of a hyperproliferative component in CMML.

The FAB Group has recently proposed guidelines for distinguishing CML, atypical chronic myeloid leukemia (aCML) and CMML.[23] Re-evaluation of cases of Ph-negative, bcr/abl-negative MPS has led in some cases to a diagnosis of CMML.[24] The discovery that the molecular genetic alteration underlying the Ph chromosome (the *bcr/abl* hybrid gene) could occur without any morphological evidence of chromosomal abnormality has demonstrated that about 50% of the Ph-negative CML were true cases of CML. The FAB Group has proposed distinguishing aCML (more prominent leukocytosis, the presence of peripheral immature granulocytes and granulocyte dysplasia) from CMML (more prominent monocytosis and bone marrow erythroid hyperplasia).

We cannot exclude that, based on the most recent FAB guidelines, some cases of aCML were included in our series. Cytogenetic analysis was performed in only a portion of our patients, documenting the absence of the Philadelphia

chromosome in 23 cases, trisomy 8 in one case and random hypodiploidy in two cases.

The survival of the majority of CMML patients is short; only one patient in our cohort is alive nine years after diagnosis. Furthermore, the results of any kind of treatment are poor. Our retrospective analysis does not register any survival difference between patients receiving only supportive therapy and those who also received pharmacological treatment. The impact of intensive regimens on the survival of patients in acute transformation, based on drugs that are alternatives to or derivatives of anthracyclines, is still under evaluation.[25] These observations, together with some additional data we have collected but not reported due to the low number of cases analyzed [poorer outcome for patients living far from the hematological center and for patients with the Rh(D) negative blood group], suggest that CMML patients must be given maximum clinical attention and supportive measures, which so far appear to be the only real possibilities for prolonging survival.

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