Chronic Myeloid Leukemia

Identification of risk factors in atypical chronic myeloid leukemia

In the WHO classification atypical chronic myeloid leukemia (CML) has been considered as a new distinct clinical entity included in the category of *mixed myeloproliferative/myelodysplastic disorders*. Little is known about this uncommon disease, whose incidence is about one-two cases every 100 cases of Ph-positive CML. We analyzed our series of 55 patients diagnosed as having aCML, with the aim of identifying clinical factors of possible prognostic value on survival and acute transformation.

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A wide spectrum of presenting features has been observed among the so far reported cases of atypical CML,[1-5] with some patients meeting all the WHO criteria, and others showing some discrepancies.

All our patients included in present study fulfilled the WHO criteria for the diagnosis of atypical CML: persistent leukocytosis, lack of the *BCR/ABL* fusion gene, evidence of marked multilineage dysplasia, monocytosis <1×10^9/L, basophils <2%, immature circulating precursors >10%, bone marrow blast count <20%.[5,6] We considered peripheral blood and bone marrow cellularity, blast percentage, granulocytic hyperplasia and/or erythroid hypoplasia, as well as the presence and degree of fibrosis and of dysplastic features. Chromosome analyses were carried out in all patients with standard procedures; at least 20 metaphases were analyzed and the chromosomes described according to ISCN (1985) nomenclature.[7] In all patients multiplex polymerase chain reaction[8] or fluorescent *in situ* hybridization analysis for the BCR/ABL fusion transcript was performed, to exclude the diagnosis of typical CML. Furthermore we applied the score proposed by Onida *et al.*[9] for hypergranular Ph- and/or BCR/ABL-negative CML, which stratifies patients into low and high risk categories based on age (< or >65 years), hemoglobin level (< or > 10 gr/dl) and leukocyte count (< or >50×10^9/L). Univariate analysis for prognostic value of each variable on survival and disease evolution was estimated according to the Kaplan-Meier method. The terminal event was considered death attributable to the hematologic disease or to non-cancer related causes. The statistical significance of differences in survival among the prognostic groups was evaluated by the log-rank test; p values <0.05 were considered statistically significant. The Cox proportional hazards model was applied to the multivariate analysis, using SPSS software version 6.0. Table 1 summarizes the clinical and hematologic features at diagnosis of our 55 patients with atypical CML. Thus median age was 62 years, with 15 patients being under 50 years old; as the median age of cases reported in the literature ranges between 60 and 76 years,[10] the disease appears to affect predominantly the elderly, with sporadic cases occurring in middle age. Differently from previous reports 10 we found a preponderance of females (57% vs 43% males). The median leukocyte values (ranging from 24 to 761×10^9/L) were, however, similar to those of other series[1-15] although lower than that of about 100×10^9/L reported by the FAB group.[2] Applying WHO criteria atypical CML can be differentiated from classic CML, chronic myelomonocytic leukemia, chronic neutrophilic leukemia, and other form of myeloproliferative disorders mainly on morphological basis. We found signs of megakaryocytic dysplasia in 27 patients, although this was not significant in univariate analysis. Other morphological parameters, such as basophils or eosinophils, were also not statistically significant when tested in univariate analysis.

Table 1. Presenting features and clinical outcome of the 55 patients with atypical CML.

*Characteristic**	*Value**
Age (years)	62 (46-81)
Sex (M/F)	24/31
Hemoglobin (g/dL)	11 (4-18)
White cell count (×10^9/L)	23.7 (14-150)
Platelet count (×10^9/L)	319 (44-2.675)
Monocytes (%)	2 (3-8)
Basophils (%)	1 (0-2)
Immature circulating precursors (%)	13 (10-20)
Bone marrow blasts (%)	2 (0-20)
Peripheral blood blasts (%)	1
Erythroid dysplasia (yes/no)	29/26 (53%)
Severe granulocytic dysplasia (yes/no)	18/37 (32%)
Megakaryocytic dysplasia (yes/no)	27/28 (49%)
Hypoplastic erythroid series (yes/no)	25/30 (45%)
Traces of reticular fibrosis (yes/no)	10/45 (22%)
Splenomegaly (yes/no)	30/25 (54%)
Hepatomegaly (yes/no)	27/28 (49%)
Karyotype (no. of pts)	
Normal	44 (80%)
Abnormal	11 (20%)
Infections (yes/no)	17/38 (30%)
Hemorrhages (yes/no)	21/34 (38%)
Transfusional requirement (yes/no)	36/18 (65%)
Onida score	
Low risk	46 (84%)
High risk	9 (16%)
AML evolution	22 (40%)
Time to AML evolution (months)	18
Therapy	
Hydroxyurea	48
Low-dose ARA-C	4
Interferon	3

**continuous variables median (range).*

The most common karyotypic changes reported in atypical CML include abnormalities of chromosomes 8, 13, 14, 17, 19 and 21;[5,10] in our series the most consistent changes were chromosome 20q deletion (seven patients) and trisomy 8 (four patients) but, given the low number of abnormal cases, we could not identify specific correlations with disease features, although leukemic progression occurred in all patients with karyotypic changes (*data not shown*).

At the time of this writing, 31 patients have died and 24 are still alive, the overall median survival being 25 months, which is longer than that of 11-18 months previously reported,[1-5] but is similar to the 24 months observed by Onida *et al.*[9] in a series of cases defined as having Ph- and BCR/ABL-negative CML but without dysplastic features.

We found that the percentage of acute transformation (22 patients, 40%) was higher than that in previous reports (median time from diagnosis 18 months).[1-5,10] This might be related to the fact that the majority of our patients received

Table 2. Results of univariate and multivariate analyses of significant features with regard to survival and leukemic transformation.

	No. of patients	Univariate analysis Median survival	p	Relative risk	Multivariate analysis 95% CI	p
Prognostic features for survival						
Age <65	23	31		0.869		
Age >65	32	18	0.04	1	0.698-1.260	0.047
Sex						
male	24	25		0.715		
female	31	14	0.002	1	1.063-1.991	0.0001
Hb <10 g/dL	12	18		0.718		
> 10 g/dL	42	32	0.03	1	1.058-2.276	0.618
WBC <50×10^9/L	46	26		0.737		
> 50×10^9/L	8	19	0.01	1	1.073-2.014	0.001
Monocytes						
<3%	45	24		0.890		
>3-<8%	10	13	0.005	1	1.064-1.988	0.07
Immature circulating precursors						
yes	18	14		1		
no	31	26	0.03	0.634	1.069-1.986	0.05
Dyserythropoiesis						
yes	29	19		0.890		
no	26	30	0.04	1	1.239-1.618	0.176
Transf. requirement						
yes	36	16		1		
no	18	26	0.05	0.789	1.486-2.291	0.05
Prognostic features for risk of leukemic transformation						
Hepatomegaly						
yes	27	24		0.705		
no	28	32	0.0001	1	1.238-2.095	0.07
Splenomegaly						
yes	30	23		1		
no	25	31	0.0001	0.600	1.158-1.992	0.03
Hb						
< 10 g/dL	12	20		0.890		
> 10 g/dL	42	31	0.01	1	1.143-2.333	0.194
Monocytes						
<3%	45	26		0.870		
>3-<8%	10	15	0.008	1	1.180-2.081	0.03
BM blasts						
<5%	41	31		0.6310		
>5%	14	18	0.0001	1	1.145-1.970	0.007
Dyserythropoiesis						
yes	29	29		1		
no	26	31	0.03	0.450	1.419-1.796	0.004
Onida score						
low risk	45	29		0.789		
high risk	9	15	0.0001	1	1.088-1.979	0.135
Transf. requirement						
yes	36	16		1		
no	18	28	0.003	0.650	0.085-0.638	0.01
Infections						
yes	17	20		1		
no	38	32	0.04	0.890	1.103-1.456	0.210

only conservative therapy, while patients in other series were mostly treated with AML-like intensive treatments at diagnosis or during a phase of stable disease.

Table 2 shows the results of univariate and multivariate analyses for significant features predicting survival and acute transformation. In multivariate analysis a shorter survival was associated with older age (>65 years, p=0.04), female sex (p=0.0001), leukocyte counts >50×10^9/L (p=0.001), and the presence of immature circulating precursors (p=0.05), whereas hemoglobin level and dyserythropoiesis lost their importance in the Cox regression analysis. Factors predictive for the risk of leukemic evolution were palpable hepato- or splenomegaly (p=0.03), monocytosis (>3<8% with monocytes < 1×10^9/L, p=0.03) , bone marrow blastosis >5% (p=0.007), marked dyserythropoiesis (p=0.004), and transfusional requirement (p=0.01). The score by Onida *et al.*,[9] which did not appear to be of relevance to survival, identified patients at a higher risk of disease transformation (p=0.0001). Given the heterogeneity of clinical and haematologic findings and lack of genomic

markers, the diagnosis of atypical Ph- and BCR/ABL-CML is still based on cytological features of peripheral blood and bone marrow.

The identification of factors able to predict distinct clinical outcomes would, therefore, be of practical use and should be perspectively considered for validation in larger series of patients with atypical CML for whom it is hoped that molecular data will also be available soon.

Massimo Breccia, Francesca Biondo, Roberto Latagliata, Ida Carmosino, Franco Mandelli, Giuliana Alimena

Department of Cellular Biotechnology and Hematology, University La Sapienza, Rome, Italy

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Correspondence: Massimo Breccia, MD,Dept. of Human Biotechnology and Hematology, Via Benevento 6, 00161 Rome. Phone: international +39.06.857951. Fax: international + 39.06.44241984. E-mail: breccia@bce.uniroma1.it

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