Chronic myelomonocytic leukemia in the light of the WHO proposals

Ulrich Germing, Corinna Strupp, Sabine Knipp, Andrea Kuendgen, Aristoteles Giagounidis, Barbara Hildebrandt, Carlo Aul, Rainer Haas, Norbert Gattermann, John M. Bennett

From the Department of Hematology, Oncology and Clinical Immunology, Heinrich-Heine-University, Düsseldorf, Germany (UG, CS, SK, AK, RH, NG); Department of Human Genetics, Heinrich-Heine-University, Düsseldorf, Germany (BH); Department of Hematology, Oncology and Clinical Immunology, St. Johannes Hospital, Duisburg, Germany (CA); University of Rochester Medical Center, USA (JMB).

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Correspondence:
Ulrich Germing, Department of Hematology, Oncology and Clinical Immunology, Heinrich-Heine-University Moorenstr. 5, 40225 Düsseldorf, Germany.
E-mail: germing@med.uni-duesseldorf.de

ABSTRACT

The WHO classification moved CMML to myeloproliferative/myelodysplastic disorders, and defined CMML I and CMML II according to medullary and peripheral blast count. To confirm these proposals, we analyzed 266 patients with CMML I and 73 patients with CMML II. Median survival time was 20 months for CMML I, and 15 months for CMML II (p<0.005). The cumulative risk of AML evolution differed between patient groups (p=0.001). No conclusive differences in clinical, morphologic, hematologic or cytogenetic parameters were found. These data support the WHO proposals for the classifi-cation of CMML.

Key words: myelodysplastic syndromes, myeloproliferative syndromes, CMML, prognosis, WHO classification

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The French-American-British (FAB)[1] classification identified chronic myelomonocytic leukemia (CMML) as a medullary blast count of <20% and a peripheral blast count of <5%, and peripheral monocytes of >1000/μL. The authors felt that CMML is closer to MDS than to proliferative disorders. Later it became clear that some CMML patients' presentation is more similar to myeloproliferative disorder, showing organomegaly and hyperleukocytosis. In 1994, the FAB group proposed dividing CMML into a more myeloproliferative type (CMML-MPS) and a more myelodysplastic type (CMML-MDS) using a cutpoint of WBC of 13,000/μL.[2] A previous analysis demonstrated that this division can distinguish two clinical entities but does not provide prognostic information.[3] Nevertheless, the IPSS group[4] excluded CMML with a WBC of more than 12,000/μL from its calculations. In a previous study, dysplastic CMML patients have been distributed to the RAEB I and II groups.[5] The WHO now added cytogenetic and/or molecular examinations to exclude bcr-abl positive CML[6] and proposed to separate two CMML subsets according peripheral and medullary blast counts. CMML is subdivided into CMML I with <10% medullary and ≤5% peripheral blasts, and CMML II with 10-19% medullary and/or 5-19% peripheral blasts. The MDS Düsseldorf Registry now includes 339 patients with CMML. We compared the CMML groups in terms of hematologic, clinical, chromosomal, morphologic, and prognostic features and evaluated whether the WHO proposals are appropriate.

Design and Methods

Between 1975 and 2005, 339 patients with CMML were diagnosed at our hospital and included in our MDS Registry. All bone marrow smears were examined by the same investigator(s) (*CA* and/or *UG*). Cases were selected at random and an additional morphologic review was provided by one of the co-authors (*JMB*) who had not been informed of the initial recording of CMML-I or II. There was agreement on 17/18 specimens, (κ=88.3, p<0.0005). Morphologic diagnosis was made according to the FAB

and WHO classifications.[1,2] A differential white blood count was performed on 100 cells in the peripheral blood to determine the monocyte and peripheral blast count. A differential count was performed on 500 nucleated cells in the marrow to determine the proportion of medullary blasts. In addition, we performed an α-Naphtyl-Esterase-staining to describe monocytes. Patients were followed for survival and leukemic progression through October 31st 2005. Twenty patients were excluded from survival statistics because they received intensive chemotherapy. Cytogenetic analysis was carried out in 104 patients.

Results and Discussion

Two-hundred and sixty-four patients fulfilled the criteria for CMML I, and 73 for CMML II. With the exception of WBC, lymphocytes and monocytes, there were no differences in blood cell counts. There was no difference in clinical signs and morphology between the two groups (Table 1). Medullary blasts were higher in CMML II and the proportion of monocytes was greater in CMML I. Medullary blasts correlated only weakly with WBC, monocytes and LDH. However, LDH was strongly correlated with leukocyte and monocyte count ($p<0.01$) in the entire group. Cytogenetic analyses were available for 104 patients, 35 of whom (33%) had chromosomal aberrations. According to the IPSS cytogenetic risk categories, most belonged to the low-risk group. We then correlated the WHO classification (CMML I vs. II) with the revised FAB proposals to separate a myeloproliferative CMML type (WBC ≥13,000) from a myelodysplastic type (WBC <13,000).[2] The distribution of CMML I and II to the proliferative and dysplastic types was very similar, each with about 50% CMML I and II in both groups.

Elevated LDH, male gender and a hemoglobin value of less than 10 g/dL, lymphocyte count >2,500/μL and CMML type II indicated a poor prognosis as calculated in a multivariate analysis, whereas high WBC was not entered into the regression model. The only parameter that showed independent impact on predicting AML evolution was a medullary blast count of 10% or greater. After 2 years, 14% of patients with CMML I had developed AML, compared to 24% of patients with CMML II. After 5 years, the corresponding numbers were 18% and 63% (p=0.001). Figure 1 shows the cumulative risk of AML transformation in CMML I and CMML II and the survival curves. Median survival was 20 months for CMML I, and 15 months for CMML II (p=0.005). The IPSS was only assessed in patients with less than 12,000 leukocytes and failed to separate different risk groups according to survival and AML evolution. Within the CMML II patients the modified Bournemouth Score,[7] the Spanish CMML score,[8] the MDAPS Score[9] and the Düsseldorf Score[10] identified a

Table 1. Clinical symptoms and laboratory findings in CMML I and CMML II.

	CMML I n=266	*CMML II n=73*	*p*
Age (median and range)	72 (31-95)	71 (32-87)	n.s.
Gender (male/female)	172/94 (1.8:1)	44/29 (1.5:1)	n.s.
Anemia (%)	51	61	n.s.
Infections (%)	34	37	n.s.
Fever (%)	14	22	n.s.
Bleeding (%)	10	30	n.s.
Lymphoma (%)	14	12	n.s.
Hepatomegaly (%)	32	30	n.s.
Splenomegaly (%)	44	36	n.s.
Hemoglobin g/dL	10.7 (2.5-16.3)	10.1 (3.9-15.7)	n.s.
Leukocytes /μL	11900 (1,100-147,000)	19,800 (1,100-145,000)	0.01
Leukocytes /μL >13000	47.7	56.1	n.s.
Granulocytes/μL	5600 (220-91,630)	7100 (200-71,500)	n.s.
lymphocytes/μL	2,100 (100-14,000)	3,600 (700-31,000)	0.001
Monocytes/μL	2,100 (1,000-44,300)	3,100 (1,000-88,400)	0.03
Platelets /μL	112 (1-1,069)	84 (2-907)	n.s.
LDH U/L	211 (75-1,435)	237 (95-1350)	n.s.
Presence of peripheral blasts (%)	20%	35%	0.005
Basophils >2% (%)	7%	6%	n.s.
Peripheral Pseudo-Pelger cells (%)	12%	13%	n.s.
Nucleated red cell precursors (%)	19%	25%	n.s.
Hypogranulated neutrophils (%)	10%	13%	n.s.
Hypocellular bone marrow (%)	5	11	n.s.
Normocellular bone marrow (%)	30	20	n.s.
Hypercellular bone marrow (%)	65	69	n.s.
Percentage of erythroblasts	14 (1-55)	14 (1-52)	n.s.
Megaloblastoid changes (%)	30	45	n.s.
Nuclear fragmentation (%)	26	42	n.s.
Cytoplasmic anomalies (%)	5	5	n.s.
Ring sideroblasts >10% (% pts.)	5	7	n.s.
Medullary blast count (%)	5 (0-9)	15 (10-19)	0.0005
Hypogranulated myelocytes (%)	40	49	n.s.
Hypersegmented neutrophils (%)	51	44	n.s.
MPO-negativity of neutrophils (%)	19	27	n.s.
Pseudo-Pelger cells (%)	32	41	n.s.
Micromegakaryocytes (%)	17	17	n.s.
Non-lobulated mononuclear megakaryocytes (%)	19	30	n.s.
Megakaryocytes with multiple separated nuclei (%)	28	36	n.s.
Proportion of monocytes (%)	16 (4-50)	20 (3-60)	0.008
Esterase positivity (%)	85	82	n.s.
IPSS			
low	55 (68%)	17 (74%)	n.s
intermediate	19 (23%)	4 (17%)	
high	7 (9%)	2 (9%)	

n.s.: not significant, median and range.

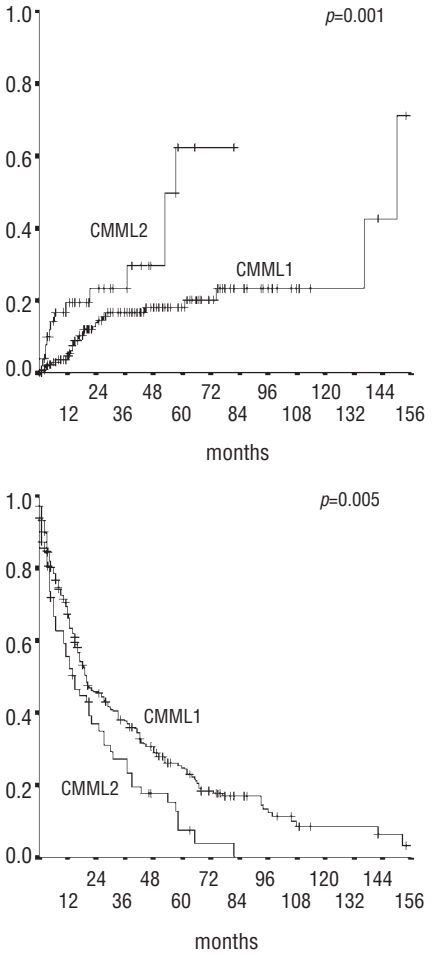

Figure 1. Cumulative risk of AML evolution (p=0.001) and cumulative survival (CMML I *vs.* CMML II) (p=0.005)

Table 2. Relationship between classification systems and prognosis.

CMML-MDS (n=161)	29	p=0.01
CMML-MPD (n=158)	15	
CMML (<5% medullary blasts)		
WBC >13,000	48	p=0.04
WBC ≤13,000	16	
CMML I		
WBC >13,000	33	p=0.0012
WBC ≤13,000	16	
CMML II		
WBC >13,000	22	n.s.
WBC ≤13,000	10	
CMML MDS (WBC ≤13,000)		
CMML I	33	p=0.02
CMML II	22	
CMML MPD (WBC >13,000)		
CMML I	16	p=0.04
CMML II	10	

WBC: white blood cell count.

relatively large number of patients as high risk. However, only the Spanish CMML score was able to identify some patients with a better prognosis. In the CMML I group, many patients were distributed to low- and intermediate risk groups. All scores were able to separate risk groups within the CMML I group. We then split CMML I into two groups, one with a limited medullary blast count <5% (30% of CMML I patients) and the other with a medullary blast count of 5-9% (70% of CMML I patients). The median survival of those with <5% blasts was 25 months compared to 19 months in the other groups (p=0.03). There was no difference in risk of AML evolution. Table 2 shows that the prognostic impact of WBC >13,000/μL was restricted to CMML patients with a medullary blast count of less than 10%. On the other hand, increased medullary blasts influenced survival in patients with and without leukocytosis. Finally, we compared the CMML I and CMML II groups presenting with a WBC <13,000/μL with RCMD (n=370), RAEB I (n=272) and RAEB II (n=310) patients in our MDS registry. There was no significant difference in survival between RCMD and CMML I with <5% medullary blasts. However, both CMML I with >5% medullary blasts and CMML II had better median survival times compared with RAEB I and RAEB II.

Based on the data of 339 patients with CMML, we show that the prognosis of the two CMML subtypes as proposed by the WHO classification for MDS is different in terms of both survival and AML evolution. On the descriptive level of clinical signs, symptoms or laboratory parameters, we found no significant differences between the patients with CMML I and CMML II. The value of the new classification system became obvious when we assessed its prognostic power. According to the Kaplan-Meier estimates, the median survival of patients with CMML I was 20 months, compared with 15 months for patients with CMML II. The risk of developing overt AML was significantly greater for patients with CMML II compared with patients with CMML I. This shows that the medullary blast count is one of the most important prognostic parameters for patients with CMML. This is reflected by the fact that CMML II patients were assigned to higher risk groups in different scoring systems. The prognostic impact of other parameters, such as LDH and cell counts, has been demonstrated in several studies. Our study also confirms the prognostic relevance of elevated lymphocytes in peripheral blood, perhaps reflecting a reactive process rather than direct lymphocyte involvement in CMML. Scoring systems like the modified Bournemouth score, the Spanish score and the Düsseldorf score for CMML I are clearly useful. However, within CMML II, only the Spanish Score was able to identify some patients at less risk. In conclusion, we have confirmed that thorough

examination of bone marrow smears with an accurate blast cell count is important for risk assessment of patients with CMML. The WHO classification distinction between CMML I and CMML II based on the medullary blast counts has significant prognostic value and may help in selecting appropriate treatment. Although this distinction does not reflect all pathophysiologic aspects of the disease, it allows the WHO classification to exploit an important cytomorphologic parameter which influences prognosis irrespective of other disease manifestations. It remains to be decided if it would be appropriate to shift myelodysplastic type CMML, i.e. WBC <12,000/μL, back into the MDS group, since these patients clearly have no proliferative features and only differ by the presence of more than 1,000 monocytes/μL. Since they have a better prognosis than RAEB I and RAEB II,[11,12] they should be regarded as a specific entity within MDS.

Authors' Contributions

UG: provided concept and design, performed cytologic examination, wrote the article; CS: contributed clinical patient data, helped with data assembly; SK: contributed clinical patient data; AK: data collection; AG: contributed clinical patient data, helped with data assembly; CA: performed cytology; RH, NG: critical review; JMB: performed reference cytology, critical review of the manuscript.

Conflict of Interest

The author reported no potential conflicts of interest.

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