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Research paper

Myelodysplastic syndromes without peripheral monocytosis but with evidence of marrow monocytosis share clinical and molecular characteristics with CMML

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ABSTRACT

MDS patients may present with monocytic marrow proliferation not fulfilling criteria for CMML. We analyzed MDS patients with or without a marrow monocytic proliferation by following up the amount of monocytic proliferation and characterizing their molecular profile. 315 MDS patients of Duesseldorf MDS registry were divided into two groups: A) 183 patients with monocytic esterase positive cells in marrow and monocytes between 101 and 900/µl in blood and B) 132 patients without monocytic esterase positive cells in marrow and monocytes in blood ≤100/µl. Twenty patients of each group were screened with regard to ASXL1, TET2, RUNX1, SETBP1, NRAS, and SRSF2 using Illumina myeloid panel. Group A patients were older, had significantly higher WBC, hemoglobin levels, neutrophils and platelets. CMML evolution rates were 4.9% and 1.5%, respectively (p = n.s.). TET2, NRAS and SRFS2 mutation frequencies were higher in group A and four patients had coexisting TET2 and SRFS2 mutation, which was shown to be characteristic but not specific for CMML.

MDS patients with marrow monocytic proliferation have a more CMML-like pheno- and genotype and develop CMML more often. Those patients could potentially be very early stages of CMML or represent a CMML-like myeloid neoplasma with marrow adherence of the monocytic cell population.

1. Introduction

Recently, the revised version of the World Health Organization classification of myeloid neoplasms and acute leukemia was published, chronic myelomonocytic leukemias (CMML) is now classified as mixed myeloproliferative/myelodysplastic neoplasms separated from myelodysplastic syndromes (MDS) per definition by the amount and percentage of monocytes in the peripheral blood [1]. CMML seems to be particularly difficult to classify [1–4]. Currently, it is diagnosed when certain criteria of other myeloid neoplasms can be excluded and the white blood count shows more than 10% monocytes (> 1000/µl). There are no specific marrow criteria for the diagnosis of CMML. Some patients with MDS present with an increased proportion of monocytic cells in the marrow (> 10% unequivocal monocytes or cells positive for esterase staining), but do not fulfill the criteria of CMML because the number of monocytes in the peripheral blood is too low. In contrast, some patients with marked monocytosis in peripheral blood have been identified to harbor reactive monocytosis in peripheral blood [5]. These aspects encouraged us to hypothesize that monocytosis in the bone marrow, rather than the peripheral blood, may be the pivotal criterion to establish the diagnosis of CMML. Malcovati and colleagues showed that concomitant mutations of TET2 and SRSF2 were highly predictive of a myeloid neoplasm characterized by myelodysplasia and monocytosis, including but not limited to, chronic myelomonocytic leukemia [6]. Cytogenetic abnormalities, recently divided into three risk categories [7], are present in 20–40% of patients with CMML [8–10]. Molecular alterations of ASXL1, TET2, SRSF2, RUNX1, NRAS and SETBP-1 are frequently found in CMML, without being specific for this entity [11–13].

Since they are markers of poor prognosis, mutations of ASXL1 [14,15], SETBP1 [16], RUNX1 [17] and NRAS have been included in the molecular update of the CMML prognostic scoring system (CPSS) [18].

We followed up the amount of monocytic proliferation and assessed

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the above-mentioned CMML-related molecular profile in MDS patients with or without monocytosis in the marrow. Owing to the lack of peripheral blood monocytosis, none of them fulfilled the WHO diagnostic criteria of CMML.

2. Methods

Our study included 315 patients from the Duesseldorf MDS registry, diagnosed between 1970 and 2017, who received best supportive care or disease specific therapy including allogeneic transplantation. The diagnostic procedures were the same as reported earlier [1,19,20]. Diagnoses were made adopted to the proposals of the WHO 2016 classification, including the enumeration of monocytes in the marrow, with or without alpha-naphthyl esterase staining [1,20]. The clinical data were gathered from the original patients' charts. Follow-up data were obtained from our outpatient department or by contacting the primary care physicians. Cytogenetic analyses at the time of diagnosis were performed at the Institute of Human Genetics and Anthropology, Heinrich-Heine University, Duesseldorf as was molecular screening of ASXL1, TET2, RUNX1, SETBP1, NRAS, and SRSF2 using the Illumina myeloid panel. These genes either have prognostic impact in CMML patients [18] or are mutated with a higher frequency in CMML (NRAS, TET2, and SRSF2) as compared to MDS [6,11,13,17]. The selection of patients, who were molecularly screened, was exclusively dependent on the availability of DNA material at time of diagnosis. Local ethics approval for this study and informed consent were obtained. Patients were censored at the date of last follow-up. Overall survival was calculated using the Kaplan-Meier method.

3. Results

3.1. Patients characteristics

We identified 183 MDS patients with ≥10% monocytes or monocytic esterase positive cells in the bone marrow and a peripheral blood monocyte count between 101 and 900/µl (group A), and 132 patients with < 10% monocytes or monocytic esterase positive cells in the bone marrow and a peripheral blood monocyte count ≤100/µl (group B). Patients in group A had a median monocyte count of 312 (104–900)/µl. A positive monocytic esterase staining of the bone marrow was available in 91%. For the other 9%, the monocyte proportion in the marrow was ≥10%. If monocytes were marked by positive esterase staining, no minimum percentage of monocytes was required (the median monocyte proportion in the marrow was 5% (0–42)). Group B included 132 patients with a median monocyte count of 40/µl (0–100). A negative monocytic esterase staining was available in 37%; all other patients had < 10% monocytes in the marrow.

Patients in group A were older on average than patients in group B (72 vs 67 years, p = 0.005). There was no difference in the proportion of males and females. Even though there were more patients with lymph node enlargement in group A (9% vs 4%), the difference was not statistically significant. The frequency of splenomegaly and hepatomegaly was similar in both groups. Patients in group A had significantly higher counts of total white blood cells, neutrophils, hemoglobin and platelets.

Patients in group B had a borderline significant higher mean medullary blast count 8% vs 6.3% (p = 0.055) and were more likely to have a diagnosis of MDS-EB (p = 0.023). Marrow hypocellularity assessed by histopathology was less frequent in group A (10.6% vs. 17.4%, p = n.s.). Median survival did not differ between the two groups. Patient characteristics are summarized in Table 1.

3.2. Disease evolution patterns

Of 183 patients in group A, 38 (20.8%) progressed to a higher risk MDS or AML, and 9 (4.9%) developed CMML as defined by the WHO.

Table 1
Patients Characteristics .

parameter	Group A	Group B	p
number of patients	183	132	
sex (male/female in%)	55/45	52/48	n.s.
age in years median (range)	71.7 (34.1–91.0)	67.4 (20.0 – 93.1)	0.005
hemoglobin in g/dl median (range)	9.6 (3.6–14.8)	9.2 (4.3–14.9)	0.009
platelets x 10^3/µl median (range)	143 (3–1350)	92 (3–676)	0.008
white blood cell count/µl median (range)	4000 (600–36600)	2500 (200–10500)	< 0.001
absolut neutrophile count/µl median (range)	1976 (40–21690)	1152 (28–6789)	0.001
monocytes/µl median (range)	312 (104–900)	40 (0–100)	< 0.001
LDH in U/l median (range)	187 (92–4680)	188 (17–837)	n.s.
medullary blasts in% median (range)	3 (0–29)	4 (0–29)	0.055
monocytes in BM in% median (range)	5 (0–42)	1 (0–7)	< 0.001
bone marrow cellularity (histology)	n = 98	n = 92	n.s.
hypocellular	10.6%	17.4%	
normocellular	44.9%	31.5%	
hypercellular	43.5%	51.1%	
bone marrow fibrosis	11% (9/85)	19% (15/81)	n.s.
lymph node enlargement	9%	4%	n.s.
splenomegaly	14%	14%	
hepatomegaly	15%	16%	
WHO—Classification in%			
MDS-SLD	5.0	5.3	
MDS-RS-SLD	8.4	6.8	
MDS with isolated del (5q)	4.5	3.8	
MDS-MLD	28.5	28.0	
MDS-RS-MLD	16.8	7.6	
MDS-EB 1	17.3	19.7	
MDS-EB 2	5	16.7	
RAEB-T	11.7	11.4	
RARS-T	2.8	0.8	
medullary blasts			
< 5%	65.9%	53.0%	
5–29%	34.1%	47.0%	p = 0.026
IPSS-R in%	n = 86	n = 60	
very low	18.6	3.3	
low	33.7	18.3	
intermediate	12.8	28.3	
high	19.8	23.3	
very high	15.1	26.7	
median survival in months	35.1	33.7	n.s.
disease evolution			
CMML	9 (4.9%)	2 (1.5%)	n.s.
RAEB or AML	38 (20.8%)	54 (40.9%)	0.001

Of 132 patients within group B, 54 (40.9%) progressed to a higher risk MDS or AML, and 2 developed CMML (1.5%).

The time to CMML diagnosis was quite variable: 4.1, 7.8, 10.3, 24.1, 39.0, 48.0, 53.8, 59.0 and 82.1 months in group A. Interestingly, the two patients in Group B developed CMML rather late (after 84.6 and 94.5 months, respectively).

3.3. Molecular screening

Of each group 20 patients, of whom DNA from first diagnosis was available, were screened for the presence of somatic mutations in ASXL1, TET2, RUNX1, SETBP1, NRAS, and SRSF2. In group B patients characteristics regarding WBC, monocytes in peripheral blood and bone marrow, hemoglobin, neutrophils, platelets, LDH, blast count in bone marrow and age did not differ between the whole cohort and the molecularly screened patients. In group A there was a significant difference between the absolute count of monocytes in peripheral blood with 366/µl in the not molecularly screened group and 560/µl in the screened group, and the monocyte amount in bone marrow, with 7.4% in the not