ABSTRACT:
Chronic myelomonocytic leukemia (CMML) is a rare de novo myeloid neoplasm that exhibits dysplastic and pro liferative features at presentation. The diagnosis is problematic with several specific controversial issues.

Aim: To analyze the cases with CMML diagnosed in the Hematology clinic, UMHAT “St. Marina”, Varna with assessment of risk, prognosis and survival.

Materials and methods: The results from cytology, flow cytometry, histology, and genetics are re-estimated. For the risk stratification the CPSS was used. The statistical analysis is performed using SPSS 19.

Results: Fifteen patients with CMML, 12 men and 3 women, with median age of 69.8 years were included in the study. According to the leukocyte count 12 were myeloproliferative (CMML/MP) and 3 myelodysplastic CMML (CMML/MD). The flow cytometry of peripheral blood and bone marrow was characterized by CD14, CD64, CD16 and CD56 expression. According to the histology of the bone marrow 2 cases were described as MDS, 1 as MDS/MPN, the rest as MPN with fibrosis in two of the cases. The cytogenetic risk was high in 5 patients and low in 10. According to CPSS one patient was with low risk, 3 with intermediate 1, 9 with intermediate 2 and 2 with high risk. Acute myeloid leukemia transformation occurred in 9 patients within median period of 13.1 months. The median survival after transformation was 2.5 months. The median survival in the whole group was 21.4 months.

Conclusion: CMML is an aggressive disease. The prognosis of patients with CMML is poor, with low survival and high risk of transformation. The therapeutic options are limited.

Keywords: Chronic myelomonocytic leukemia, risk stratification, survival

INTRODUCTION
Chronic myelomonocytic leukemia (CMML) is a clonal hematologic malignancy characterized by absolute peripheral monocytosis, ineffective hematopoiesis, and an increased risk of transformation to acute myeloid leukemia.

The French-American-British (FAB) group introduced the first formal definition of CMML in 1978 where CMML was one of the five subtypes of the myelodysplastic syndromes (MDSs). In addition to the initial classification, the FAB group sub-classified CMML into myelodysplastic (MD)-CMML and myeloproliferative (MP)-CMML according to the white blood cell (WBC) count (<13.0x10⁹/L and >13.0x10⁹/L, respectively) [1].

In 2001 the World Health Organization classified CMML within a novel category myelodysplastic syndromes/myeloproliferative neoplasm’s (MDS/ MPNs), containing hematologic malignancies with features overlapping MPNs and MDSs. CMML cases were further subdivided into CMML-1 (<5% peripheral blasts and promonocytes, <10% bone marrow blasts and promonocytes) and CMML-2 (5%-19% peripheral and 10%-19% marrow blasts and promonocytes) depending on the proportion of blasts in peripheral blood (PB) and bone marrow (BM) [2].

Diagnosis is based on cytology, flow cytometry, histology, and genetics. The bone marrow aspirate demonstrates features of dysplasia but, unlike MDSs, this is not absolutely required for the diagnosis of CMML [2]. An elevated ratio of myeloid to erythroid cells is often identified in the bone marrow, myeloblasts and promonocyte in the bone marrow and peripheral blood must be less than 20%. The morphological criteria, defining 4 monocytic subtypes in the bone marrow, were validated by Guasg et al [3]. Trephine histology shows hypercellularity, granulocytic hyperplasia, monocytosis, variable reticulin fibrosis, and may also detect other causes of monocytosis or additional pathology.

Flow cytometry can be applied to the diagnosis of CMML. Monocytes in CMML exhibit aberrant antigen expression, such as reduced HLA-DR and aberrant CD56 and CD2. A combination of monocytosis with 2 or more immunophenotypic aberrancies with 20% or more of marrow monocytes showing moderate CD14 expression was found 100% specific for CMML [4]. CMML patients demonstrate a characteristic increase in the fraction of CD14+ and CD16- cells which appeared a highly sensitive and specific diagnostic marker that rapidly and accurately distin-
guishes CMML from confounding diagnoses [5].

Cytogenetic abnormalities are found in less than 30% of patients with CMML with no specific aberration (+8, -Y, -7/7q, -20q, +21, der(3q)); trisomy 8 is the most frequent of these. Such et al. showed the strong prognostic impact of the cytogenetic findings and proposed a new CMML-specific cytogenetic risk classification [6].

Several CMML-specific prognostic tools have been developed in conjunction with the IPSS in MDSs that attempt to look at risk stratification of a CMML specific cohort. The most recent models are the CMML prognostic scoring system (CPSS) developed by the Spanish MDS cooperative group [7] and a model proposed by the GFM group (Groupe Francophone des Myélodysplasies) that is the first CMML specific model that incorporates ASXL1 mutations [8].

The aim of the study was to analyze the cases with CMML diagnosed in the Clinic of Hematology, UMHAT “St. Marina”, Varna with assessment of risk, prognosis and survival.

**PATIENTS AND METHODS**

Fifteen patients with CMML, diagnosed and treated in the Clinic of Hematology, UMHAT “St. Marina”, Varna for the period 2009 - 2015, were included in the study, 12 men and 3 women, with median age of 69,8 years. Diagnosis of CMML was made according to World Health Organization (WHO) criteria [2]. The results from cytology, flow cytometry, histology, and genetics were re-estimated. CPSS was used for the risk stratification.

The statistical analysis was performed using SPSS 19.

**RESULTS**

According to the leukocyte count 12 are CMML/MP and 3 CMML/MD. Thirteen of the patients were anemic, 5 with Hb lower than 70g/l. In nine of the cases thrombocytopenia was detected, 11 were with splenomegaly. JAK2V617F mutation was detected only in one patient. Treatment was performed mainly with Hydroxyurea. Cytarabine or 5+2 (Cytarabine + Idarubicin) was used in 4 cases, supportive care in two cases. Patient characteristics are presented in Table 1.

**Table. 1. Clinical characteristics of patients**

<table>
<thead>
<tr>
<th>No</th>
<th>WBC x 10⁹/l</th>
<th>Hb x g/l</th>
<th>Pltx 10⁹/l</th>
<th>PB Mo %</th>
<th>Spleen size/mm</th>
<th>BM biopsy</th>
<th>LDH</th>
<th>Treatment</th>
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<td>1</td>
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<td>89</td>
<td>43</td>
<td>15</td>
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<td>1032</td>
<td>Hydroxyurea</td>
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<td>2</td>
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<td>96</td>
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<td>170</td>
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<td>1010</td>
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<td>3</td>
<td>32</td>
<td>131</td>
<td>211</td>
<td>10</td>
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<td>76</td>
<td>95</td>
<td>28</td>
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<td>7</td>
<td>13.89</td>
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<tr>
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</table>

The flow cytometry of peripheral blood (PB) and bone marrow (BM) was characteristic for the malignant clone with the expression of CD14, CD64, CD16 and aberrant expression of CD56 (fig. 1).
Bone marrow biopsy was performed in 10 of the patients. According to the histology 2 of the cases were reported as MDS, 1 as MDS/MPN, 4 as MPN, 1-CML. In two of the cases fibrosis was described.

Cytogenetic abnormalities were detected in 40% of the patients (45XY -7, 45,X-Y, 47,XY+8, complex karyotype) (fig. 2a). The cytogenetic risk, determined according to the classification of the Spanish Group [6] was high in 5 patients (3 with trisomy 8, one with monosomy 7, one with complex karyotype) and low in 10 (one –Y, the rest with normal karyotype) (fig. 2b).

According to CPSS one patient was with low risk, 3 with intermediate 1, 9 with intermediate 2 and 3 with high risk (fig. 3). Acute myeloid leukemia (AML) transformation occurs in 60% of the patients within median period of 13,1 months. 6 from 9 of the transforming cases are intermediate 2 and high risk. One patient with low risk transformed into AML after 47 months (fig. 4a). AML transformation occurred in all cases with trisomy 8 (fig. 4b).
The mean survival in the whole group was 21.5 months (fig. 5a). The mean survival after transformation was 2.5 months (fig. 5b).

**DISCUSSION**

CMML is a rare de novo myeloid neoplasm. In our clinic, for the six years period CMML was confirmed only in fifteen patients. The diagnosis of CMML is usually problematic because of the heterogeneous morphological variables, difficult distinguish of reactive vs. clonal monocytosis, the overlapping morphology and phenotype of CMML and AML, especially in transforming CMML. All other causes of monocytosis, such as aggressive solid tumors, infectious and autoimmune disorders, must be excluded. Other
myeloid malignancies should be considered, with special attention on chronic myeloid leukemia, CMML with eosinophilia and rearrangements of PDGFRA or PDGFRB. Diagnosis CMML must be based on the precise interpretation of morphological, phenotypic and genetic features.

The results from our analysis confirm the aggressiveness of the disease. The prognosis of patients with CMML is poor, with a mean survival of only 21.4 months and high leukemic transformation rates of 60% with mean survival after transformation of 2.5 months. The prognostic value of trisomy 8 can be suggested, since it is the most frequent abnormality in CMML related to high cytogenetic risk, poor survival and high transformation rates [6]. Recently the prognostic impact of several mutations in CMML was studied and the independent prognostic relevance of ASXL1 gene mutations confirmed [8]. The combination of clinical and molecular information may be required to improve the accuracy of CMML prognostication.

The therapeutic options are limited. The results from the clinical trials with azacytidin are promising [9]. Several novel treatment approaches using JAK2 to MEK inhibition are now in clinical studies [10, 11].

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Please cite this article as: Micheva I, Chervenkov T, Ruseva C, Gercheva L. Chronic myelomonocytic leukemia - review and clinical experience of the Hematology Department UMHAT “St. Marina” Varna. J of IMAB. 2016 Jan-Mar;22(1):1091-1095. DOI: http://dx.doi.org/10.5272/jimab.2016221.1091

Received: 15/12/2015; Published online: 31/03/2016

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/J of IMAB. 2016, vol. 22, issue 1/