PROPOSED SCORING SYSTEMS FOR CHRONIC MYELOMONOCYTIC LEUKEMIA FROM THE PAST TILL PRESENT

MIHAELA GĂMAN1, ANA MARIA VLĂDĂREANU

1PhD candidate “Carol Davila” University of Medicine and Pharmacy, București, “Carol Davila” University of Medicine and Pharmacy, București

Keywords: Chronic myelomonocytic leukemia, prognosis, clinical and biological parameters, cytogenetics, molecular markers

Abstract: Chronic myelomonocytic leukemia (CML) is a clonal hematopoietic malignancy characterized by both myeloproliferative and myelodysplastic features. The factors predicting the course of this heterogeneous disease are poorly understood. Until a few years ago, they have relied on clinical and biological parameters. Recent reports highlighted the importance of cytogenetic and molecular characterization of CMLM for the identification of the prognostic factors, useful in establishing standardized therapeutic strategies.

Chronic myelomonocytic leukemia is a rare malignancy of the elderly, whose diagnosis requires persistent absolute monocytes in the blood (monocytes > 1 X 109/L). Due to its heterogeneous, clinical, hematologic, and morphologic features, CMLM classification has been always a subject of debate. In 1982, CMLM was initially classified as a subcategory of myelodysplastic syndromes (MDS) by the French-American-British (FAB) classification system. The diagnostic criteria included, at that point, persistent peripheral blood (PB) monocyte count > 1 X 109/L, bone marrow (BM) blast count less than 20%, PB blast count less than 5% and absence of Auer rods. However, CMLM did not fit entirely into this category. For this reason, in 1994, FAB classification based on the WBC count threshold of 13 X 109/L proposed two different CMLM subtypes: “myeloproliferative variant” (MP-CMMPL, WBC > 13 X 109/L) and “myelodysplastic variant” (MD-CMMPL, WBC < 13 X 109/L). Since the publication of the third edition of the WHO classification in 2001, several fundamental changes have occurred. Regarding CMLM, this was separated from MDS and assigned to a new category “myelodysplastic/myeloproliferative neoplasms” (MDS/MPN). Diagnosis criteria were modified as well: PB monocyte count of > 1 X 109/L, BM and PB blast and promonocyte count of < 20%, Auer rods, with two prognostic categories based on the percent of blasts: CMLM-I (blasts < 10% in BM and < 5% in PB) and CMLM-II (blasts 10–19% in BM or 5–19% in PB or presence of Auer rods). WHO revised classification continues to consider CMLM an “MDS/MPN” subtype along with the other three: juvenile myelomonocytic leukemia, “atypical chronic myeloid leukemia, BCR-ABL1-negative” and unclassifiable MDS/MPNs, only the first two are well defined.

The natural course of CMML is variable, with life expectancy ranging from 20 to 40 months in CMML-I patients and 15 months in CMML-II patients, but it varies between 1 and more than 100 months. Because of the clinical and haematological heterogeneity of CMML and the poor prognosis associated to this disease, different prognostic factors for a better risk stratification of these patients have been proposed. Analysis of prognostic factors is helpful to understand the biology of this disease and to develop risk-tailored treatment strategies.

A first attempt to develop a scoring system prognosis specific to CMML was made in 2002 by Onida, on a cohort of 190 patients, diagnosed with CMLM at the M.D. Anderson Cancer Center. Values for haemoglobin < 12 g/dl, absolute lymphocytes > 2.5 X 109/L, circulating immature myeloid cells, and bone marrow blasts > 10% were independently associated with shorter survival. The model identified four subgroups with median overall survival of 24, 15, 8, and 5 months for low, intermediate grade 1 and 2, and high risk patients. Although the presence of chromosomal abnormalities was associated with shorter survival, no specific abnormalities with prognosis value were identified. Later that year Gerning confirmed the independent prognostic value of a high lymphocyte count (>2.5 X 109/L) in CMML, after studying a group of 212 patients included in the Dusseldorf Registry. This was considered a unique association for CMLM, as the lymphocyte number was not an independent prognostic factor for other MDS patients. Other parameters evaluated for the prognostic impact in Gerning’s study were elevated LDH, medullary blasts > 10%, male gender, and haemoglobin < 12g/dl. Using Dusseldorf score system three subgroups of risk, not 4 were identified: high,
The C- terminal domain gives rise to the CBL protein resulting in degradation of different tyrosine kinases by ubiquitination. Mutations of the c-CBL gene are present at the level of a domain that functions as a linker between the tyrosine kinase binding domain and the RING finger domain. Breaks occurring at this level lead to the impossibility to degrade tyrosine kinases receptors and to increased cell proliferation. The highest frequency, 18.5%, was reported by Kohlmann in the same study.(12) Unlike TET2 mutations, the prognostic impact of CBL mutations is still unclear.

RUNX1 (Run-related transcription factor 1 gene), (formerly known as AML1) located on chromosome 21q22, encodes a subunit of a DNA core-binding factor, a regulatory transcription factor essential for normal hematopoiesis. The N-terminal runt domain dimerizes with CBFB and binds DNA, and by using the C-terminal domain, it acts as a transcriptional activator. RUNX1 regulates the expression of various genes involved in normal hematopoiesis including IL3, CSF2, and CD4. The loss of Runx1 in the hematopoietic compartment reduces lymphoid progenitors with an increase of myeloid progenitors and defective platelet maturation.

Using new research techniques, RUNX1 mutations (8%) were identified in 2008 by Gelsi-Boyer et al. According to their report, while ASXL1 is by far the most frequent mutated gene in CMML and it is more likely associated with MD –CMML variant, giving a poor prognosis and a high risk of acute transformation.(15)

EZH2, the Pcg Enhancer of Zeste Homolog 2, located on the 7q36 chromosome, encodes the catalytic subunit of the polycomb repressive complex 2, a highly conserved histone H3 lysine 27 methyltransferase that influences stem cell renewal by epigenetic modification.(16) Mutations are spread over the gene and consists of missense, nonsense and premature stop codons resulting in the loss of functions. In the study group (81 CMML cases) led by Kohlmann et al. in 2011, the incidence of this mutation was ~ 11%, but more important was the discovery of the poor outcome observed in the patients carrying EZH2 mutation.

Taking into account TET 2 mutational status, the cohort was also stratified into 3 prognostic groups: best survival for TET 2 mutated case and worst survival for EZH2 mutated cases. 3 years survival was of 33.9% for EZH2-mutated patients, 49.7% for EZH2/TET2 wild-type patients and 89.8% for TET2-mutated cases (P<0.001) (12).

TET2 and CBL mutations are mainly markers of myelomonocytic clonal proliferation; while ASXL1, RUNX1 and EZH2 mutations are associated with disease progression.

Conclusion: The search for novel molecular markers still continues, as well as exploring their prognostic relevance. All these studies incorporating clinical, biological parameters, cytogenetic findings, and new molecular markers are critical to further understand this heterogeneous disease. Future studies including a substantial number of patients are needed to validate and refine these prognostic systems scores, so that they can be used as a prognostic tool in the clinical management and therapy approach of CMML patients.
REFERENCES