REVIEW

OF

DISSERTATION WORK

of **Dr. Merlin Erol Efraim** on the topic: **"CLINICAL-BIOLOGICAL AND GENETIC MARKERS IN RISK STRATIFICATION IN PATIENTS WITH MYELODYSPLASTIC SYNDROME"** for awarding the educational and scientific degree **"Doctor"** in the field of education **7. Health and sports**, professional field **7.1 Medicine**, in the scientific specialty **"Hematology and blood transfusion"**

Scientific supervisor: **Assoc. Prof. Dr. Ilina Dimitrova Micheva, MD**

REVIEWER:

Prof. Dr. Valeria Ignatova Kaleva, MD

pediatrician, hematologist and pediatric oncohematologist,

Professor at the Department of Pediatrics, Medical University - Varna,

UMHAT "St. Marina "- Varna

By decision of the Chairman of the Scientific Jury and by order of the Rector of MU - Varna

№ P-109-303 / 16.07.21 I have been appointed to present this review.

Brief biographical and professional data of the dissertation:

Dr. Merlin Erol Efraim is a graduate of the `Nancho Popovich` High School of Natural Sciences and Mathematics in Shumen. She completed her medical education at the Medical University "Prof. Dr. Paraskev Stoyanov "- Varna in 2008. She acquired the specialty "Clinical Hematology" in 2015. From 2011 to 2015 she worked as a doctor in the Clinic of Hematology at the University Hospital "St. Marina "- Varna, and since 2016 - as an assistant in the Second Department of Internal Medicine at the Faculty of Medicine at MU" Prof. Dr. Paraskev Stoyanov "- Varna. She is a member of Bulgarian Medical Association of Hematology, Bulgarian Medical Association, European Hematology Association and the working group on myeloproliferative diseases.

1. Relevance of the problem

Myelodysplastic syndrome (MDS) is most common in elderly patients and is characterized by a variable clinical course. It includes a heterogeneous group of clonal hematopoietic disorders and

poses a number of challenges in terms of their diagnosis, clinical course and treatment, as well as in terms of creating and refining prognostic models for risk stratification.

Systemic approaches to risk prediction in patients with MDS have become an integral part of clinical behavior algorithms and a focus for continuous improvement. In recent years, new, disease-specific biomarkers have been studied, demonstrating increased prognostic accuracy and becoming increasingly accessible to actual clinical practice.

In the context of this trend, the study and analysis of clinical and biological characteristics of the disease in order to supplement the established classifications and scales for risk stratification in patients with MDS is extremely relevant and useful both in experimental terms and in clinical practice. There are not enough publications on this issue in our country.

2. Characteristics, volume and structure of the dissertation

The dissertation is developed in 211 pages and is illustrated with 28 tables, 82 figures and one appendix. The style is very good, clear and with a correct discussion of the data and results.

The content is properly structured and balanced in the individual parts.

Presented by introduction (2 pages), literature review (58 pages), purpose, tasks and working hypotheses (1 page), materials and methods (4 pages), results (70 pages), discussion (23 pages), conclusion (2 pages), contributions (1 page), list of publications related to the dissertation (1 page), bibliography (31 pages) and appendices (1 page). The bibliography contains 243 Latin titles.

2.1. Literature review

The literature review defines the importance of risk stratification in patients with MDS and provides up-to-date and detailed information related to epidemiology, pathogenesis, risk factors, diagnostic criteria, clinical course, classification, stratification scales and prognostic factors in MDS.

The first part of the literature review presents in detail the available classification systems for patients with MDS, as well as the established scales for their risk stratification.

The second part presents additional risk factors related to the patient that are relevant to the risk stratification. The available comorbidity scales, the clinical frailty scale, the role of ECOG status, and age are described in detail.

The literature review concludes with a clear presentation of the factors that play a role in determining the prognosis in patients with MDS. The lack of clinical studies in Bulgaria on the importance of both types of factors (related to the disease and the patient) is *a reason* for Dr. Efraim to conduct such a study.

2.2. Purpose, tasks and working hypothesis

The aim of the dissertation is formulated precisely and clearly: `To study and analyze in patients with MDS the influence of disease-related (clinical-biological and genetic) and the patient-*related* factors (age, ECOG and comorbidity) on risk stratification, survival and the risk of transformation into acute myeloid leukemia (AML) '.

To achieve this goal, the doctoral student has formulated 6 main tasks. The last task involves *formulating* factors with favorable and unfavorable prognosis for survival in patients with MDS and in practice is an approbation of the working hypothesis, which assumes that: "Adding additional factors related to the patient to the established prognostic scales in MDS can prove to be key *for* more accurate risk stratification, survival and transformation risk."

2.3. Materials and methods

For the purposes of the scientific study, Dr. Efraim retrospectively analyzed 219 patients with MDS over 18 years of age, diagnosed and treated at the Clinic of Clinical Hematology at the University Hospital "St. Marina "- Varna for a period of 10 years (May 2010 - May 2020).

Study methods include retrospective analysis of demographic, clinical, biological, cytogenetic and molecular data, as well as patient affiliation to classification systems (FAB, WHO2008 and WHO2016) and risk stratification (IPSS, IPSS-R, WPSS), comorbidy indices (CCI, HCT-CI, MDS-CI, ACE-27), Clinical Vulnerability Scale (CFS) and ECOG status.

Laboratory tests are divided into two categories: routine (blood count, differential blood count , chemistry and iron metabolism) and specialized (sternal puncture with myelogram, cytogenetic and flow cytometric analysis of bone marrow aspirate, bone marrow biopsy and molecular test in JAK and internal tandem duplication of the FLT3 gene).

The statistical methods are optimally selected and allow processing of the expected results.

2.4. Results

The results of the study follow the sequence of tasks and are structured in 6 sections. They are illustrated with 28 tables and 82 figures.

The first section presents the results of the analysis of the main characteristics of patients - distribution by age and sex, classification and risk stratification systems, scales for comorbidity and "frailty" and laboratory data.

In the second section, an analysis of patient survival is made according to demographic data, classification and risk stratification systems, clinical-biological and cytogenetic parameters. A detailed analysis of the indicators of the complete blood count and their significance for survival - hemoglobin, leukocytes, ANC, ALC and platelets. The influence of the biochemical parameters -

LDH and serum iron, as well as the number of cell lines with dysplasia, the percentage of myeloblasts in the bone marrow and cytogenetic aberrations is presented in detail.

The third section details the distribution and median survival of patients relative to ECOG, CFS, CCI, HCT-CI, MDS-CI, and ACE-27. Within the section, survival is compared against the above-mentioned classification systems and risk stratification scales for MDS.

The fourth section analyzes the relationship between the risk assessment scales and the comorbidity and 'frailty' scales in patients with MDS after their comparison in Task 3.

The fifth section includes data related to the transformation of MDS into AML and analyzes the survival of patients before and after the transformation. The main clinical and biological indicators with respect to the transformation and survival of the patients are determined. The frequency of transformation in relation to the scales for risk stratification and the classification systems is also determined.

The last section presents the prognostic factors associated with favorable and unfavorable prognosis in terms of survival.

2.5. Discussion

This section of the dissertation follows the logic of the study and adequately comments on the results obtained. Within 23 pages, a detailed comparative analysis of both the doctoral student's own results and those reported by other authors on the relevant issues *has been* conducted.

2.6. Conclusion

The conclusion is clear and concise. *It* includes a summary of the most important results of the dissertation in favor of clinical hematology practice.

2.7. Conclusions

The dissertation ends with eleven specific, clearly formulated conclusions that correspond to the tasks.

Contributions

I accept the four contributions with original and the four contributions with confirmatory character, which support the significance of the dissertation.

The abstract is 100 pages. It fully meets the requirements of the Law for the development of the academic staff and objectively and adequately reflects the main results and the scientific contributions of the dissertation.

I do not find any omissions in the documentation attached by Dr. Merlin Erol Efraim.

Critical notes

There are no grounds for significant critical remarks.

Publications and research

The list of scientific publications includes 3 articles, two of which were published in 2021. Dr. Efraim is the first author in two of the articles. The scientific activity during the period of preparation of the dissertation work is in compliance with the normative requirements.

Conclusion:

The peer-reviewed dissertation is an author's work that addresses a current problem in hematology and is characterized by originality and practical applicability. The doctoral student demonstrates in-depth theoretical knowledge, professional skills in hematology, as well as qualities for independent research.

I give my positive assessment of the presented dissertation and *propose to* the members of the esteemed Scientific Jury *to* award the educational-scientific degree "Doctor" in the scientific specialty "Hematology and Blood Transfusion" *to* Dr. Merlin Erol Efraim.

Date: 15.08.2021.

Varna

Reviewer: ....

Prof. Dr. Valeria Kaleva, MD