

OPINION

From: Assoc. Prof. Dr. Veselina Goranova-Marinova, MD, Ph.D

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External member of the scientific jury according to order

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Subject: Procedure for obtaining the scientific and educational degree of doctor

Field of higher education: 7. "Health and sport"

Professional field: 7.1. "Medicine"

Doctoral program: "Hematology and blood transfusion" 03.01.39

Author: Dr. Merlin Erol Efraim, Assistant in the Department of Hematology, Second Department of Internal Medicine, Faculty of Medicine, Medical University – Varna

Form of doctoral studies: self- study doctoral program

Topic: Clinical-biological and genetic markers in risk stratification in patients with myelodysplastic syndrome

Supervisor: Assoc. Prof. Dr. Ilina Dimitrova Micheva, Ph.D

- 1. General presentation of the procedure.** The presented set of materials on paper and electronic media is in accordance with the procedure for acquisition of "Doctor" degree in Medical University-Varna, the Regulations of MU-Varna for the development of the academic staff and includes all necessary documents. The orders for enrollment and deduction, the protocols of extended department councils and the passed doctoral minimum exam are presented, which reflect all stages of the doctoral's development, including the Dissertation and the Abstract. The stages of the doctoral program have been observed, there is no change in the initial topic and the supervisor. The study was approved by the Commission on Scientific Ethics of MU-Varna. A list and copies of the publications related to the dissertation are attached to the set of materials. The total number of publications submitted for review is 3, in two of which Dr. Merlin Efraim is a leading author. Criticism of Dr. Merlin Efraim is the fact that none of the publications is in a journal, referenced and indexed in the scientific databases Scopus or Web-of-Science.

However, according to the presented list of publications on the topic, Dr. Merlin Efraim has the required number of points required for the educational and scientific degree "Doctor" according to the MU-Varna and the regulations for its application. ***The doctoral procedure has been followed.***

- 2. Presentation of the doctoral student.** Dr. Merlin Efraim graduated in medicine at the Medical University - Varna in 2008. She has a specialty in clinical hematology since 2015. Since then she has been an assistant at the Hematology Section, Second Department of Internal Medicine, Faculty of Medicine, Medical University - Varna. From 2008 to 2010 she worked at Emergency Department in Varna. Speaks English, Turkish and Russian. She has >10 years of experience in the field of clinical hematology. The list of participations and publications shows that Dr. M. Efraim's research interests are focused on doctoral studies. ***The doctoral student has theoretical knowledge, practical experience, additional qualifications and focused scientific and practical interests in the field of doctoral studies.***

- 3. Relevance of the topic and knowledge of the problem.** In her dissertation, Dr. M. Efraim develops an important, topical and significant problem of modern clinical hematology, namely the detailed prognostic assessment of patients with MDS. MDS is a heterogeneous group of diseases that are diagnosed more often, especially in patients > 70 years, have a multifaceted clinical manifestation, variable evolution and prognosis, as well as limited opportunities for therapeutic response. In an attempt to predict the evolution of the disease and the outcome of treatment, detailed risk stratification is extremely important. Dr. Merlin Efraim objectively points out that the existing established prognostic score systems - IPSS (*Greenberg P et al, 1997*), its revised version - IPSS-R (*Greenberg P et al, 2012*) and the World Health Organization-based prognostic system- WPSS (*Malcovati L et al, 2007*) largely reliably determine the risk of progression, transformation into acute leukemia and patient survival. Dr. M. Efraim points out that they underestimate the importance of the factors on the part of the patient: general condition, concomitant diseases and quality of life, which modify the prognosis, treatment choice and survival of patients. According to Dr. Efraim and her supervisor, there is currently no assessment of the prognostic and informative value of the factors on the part of the patient in the complex prognostic approach of the patient with MDS. This gives a scientific basis for the doctoral student to develop the present dissertation. ***The topic of the dissertation is with important clinical significance.***

- 4. Knowledge of the scientific problem.** The presented scientific hypothesis suggests that the analysis of some additional clinical and biological factors may be important for the stratification of risk, survival and risk of transformation into AML in patients with MDS. The analysis of additional prognostic factors related to the patient is necessary to clarify their role in the assessment of patients with MDS at the time of diagnosis. ***The author***

knows the scientific problem in depth, can formulate a scientific hypothesis and conduct an analysis, the results of which would improve the patient's prognostic assessment of the diagnosis, the choice of treatment, the risk of transformation into AML and the expected survival.

5. **Characteristics and evaluation of the dissertation.** The dissertation is developed on 211 pages. It contains 28 tables and 82 figures. 243 literature sources were cited, purposefully selected. The obligatory sections of the scientific work are professionally developed, and an acceptable ratio between them is observed. A clear and accurate, grammatically correct Bulgarian language is used.

5.1 Literature review. The literature review is set out on 58 standard pages, in-depth and focused on the scientific problem. Much of it propaedeutically presents the nature of the disease, its pathogenesis, classification systems and risk stratification and concludes with a review of the known prognostic factors discussed in the literature. Objectively, data from numerous studies on the prognostic role of the factors on the part of the patient, along with the factors on the part of the disease, are clearly indicated, and it is clearly stated that their significance is in the process of clarification. The literature review concludes with a reasoned basis for the analysis of the influence of disease-related (clinical-biological and genetic) and patient-related factors (age, ECOG and concomitant diseases) on risk stratification, survival and risk of transformation into AML and *allows the formulation of a clear goal and scientific hypothesis*. A critical remark to the literature review is the very thorough review of the definition, classification systems and risk-stratification systems. They are validated, generally accepted and could be listed, for example, in an annex.

5.2 Purpose and tasks. The aim of the dissertation is to study and analyze the influence of disease-related factors (clinical-biological and genetic) and patient-related factors (age, ECOG and comorbidities) on risk stratification, survival and risk of transformation into AML. *It is precisely and clearly formulated and logically set 6 main tasks.*

5.3 Material and methods section. The Material and Methods section is presented on 8 standard pages. The dissertation analyzed retrospectively 219 patients for a 10-year period (2010-2020), diagnosed, treated and followed at the Clinic of Clinical Hematology, University Hospital "St. Marina", Second Department of Internal Medicine, Medical University of Varna. The inclusion and exclusion criteria are precisely formulated. The test methods are described in detail and are appropriately selected in accordance with the guidelines for the diagnosis, treatment and follow-up of patients with MDS. Along with the patient's demographic data and the data necessary for the diagnosis of the disease (routine and specialized), the type and

number of concomitant diseases, the general condition of the patient and the prognostic significance of the systems for determining the comorbid index (CFS, CCI, MDS-CI, HCT-CI, ACE-27). A study was performed on the JAK-2 mutation in 17 patients, as well as on the carrier of FLT-3 ITD in 29 patients. The prognostic significance of these factors was analyzed by the Kaplan-Maier method with Log rank test, and the significance of prognostic factors - with Cox-regression analysis. It is noteworthy that in calculating the survival of patients depending on the derived risk factors, the indicator "average survival" was used. Typically, in large retrospective series, such as Dr. Efraim's research, the "median survival" indicator is used to assess survival as more accurate and more informative. However, the methods used allow reliable statistical analysis on a large number of patients. *I accept the section "Material and methods", with the critical note made.*

5.4 The "Results" section is presented on 73 standard pages. The presentation of the section is detailed and is presented in an overview of tables, figures, graphs and diagrams. The sequence of the set tasks is logically followed. The comparative analysis of the studied contingent by demographic characteristics, distribution by classification systems and risk stratification systems, general condition, levels of important laboratory parameters and genetic markers confirms the characteristic distribution of the disease. The same groups of parameters are assessed by Dr. Efraim in a prognostic aspect using the already mentioned indicator "average overall survival". The results obtained confirm their critical importance for risk assessment in patients with MDS. Cox - regression analysis selects % of myeloblasts in bone marrow, age, platelet levels and serum iron levels as independent prognostic factors. Dr. Efraim did not find a statistically significant difference in the survival of patients with MDS depending on the scales for comorbidity and frailty, but ECOG and comorbidity model survival in each of the classification categories and risk groups of MDS. Dr. Efraim confirms the significantly shorter survival after transformation in AML, as well as the significantly higher risk of transformation in the RAEB and RAEB-2 categories as well as in high and very high risk groups. The doctoral student does not establish a correlation between the transformation risk and the comorbidity and frailty index. The results end with the implementation of task 6, which presents the risk profile of the patient with MDS according to favorable and unfavorable prognostic factors. In addition, the dissertation of Dr. Efraim contains interesting data on the role of fibrosis in the bone marrow for transformation and prognostic risk, the significance of the JAK-2 mutation and FLT-3-ITD, which are subject to further study. *As a result of important clinical significance, I note the data for CFS > 5 as an unfavorable prognostic factor ACE-27 = 0-1 as a blogo-favorable prognostic factor. I accept the results without remarks.*

- 5.5 Discussion section.** In 23 standard pages the doctoral student analyzes the obtained own results, discusses their significance and compares them with those of other author teams. The established differences with the data from other scientific developments, the author explains with arguments and specific facts. The data from Dr.Efraim's dissertation on the role of MDS-CI coincide with the data from the world literature on the greatest importance of this scale in patients at low risk for IPSS-R and WPSS, as well as the role of CFS as an independent prognostic indicator in analysis against IPSS-R. There is a clear clinical justification in comparison with the literature data on the need for additional assessment of the patient to the diagnosis to accurately determine the prognosis, the risk of transformation into AML and survival. ***I accept the "Discussion" section without remarks.***
- 5.6 The conclusions** are 11 and clearly follow the set goals and objectives and are logically formulated according to the results obtained. The most important from a clinical point of view are conclusions 6, 7, and 8, which show that concomitant diseases and the general condition of patients with MDS modify their prognostic risk. I agree with the conclusions formulated in this way.
- 5.7 The bibliography** includes 243 literary sources, which do not contain citations of Bulgarian authors, which I point out as a critical note. The analyzed scientific publications after 2015 are > 30% of the total number. These data testify to the urgency of the problem and the great research interest on the topic in recent years.
- 5.8 Assessment of the contributions of the dissertation.** Dr. Efraim's dissertation ends with the presentation of contributions that have a scientific as well as a strong scientific-applied nature. Four of the contributions are original and four are confirmatory. I accept the contributions presented.
6. **Personal participation of the doctoral student.** The doctoral student has a personal participation in the formulation of the scientific idea, the collection of the material and the design of the research. Her participation in the statistical processing of the data and the analysis of the obtained results is personal. Conclusions and contributions were also presented with the participation of Dr. Efraim. ***The doctoral student has mainly personal participation in the development of the dissertation.***
7. **Abstract.** The abstract contains 100 pages, gives a complete idea of the dissertation and fully reflects the individual sections. The figures and tables are selected specifically and present the necessary data.
8. **Conclusion.** The dissertation work of Assistant Dr. Merlin Erol Efraim meets the requirements of the Regulations for its implementation and MU-Varna for awarding the

scientific and educational degree "Doctor". The topic of the dissertation has not been developed in Bulgaria, and some of the problems in it are still the subject of discussion internationally. The contributions of the dissertation have a scientific and strongly scientific-applied character, which is a good basis for integrating the scales for comorbidity and frailty of patients with MDS to risk stratification systems in order to improve the prognostic assessment in these patients. The dissertation of Dr. Merlin E. Efraim shows the qualities for analysis and synthesis of scientific information, the ability to formulate conclusions and scientific hypotheses. Scientific knowledge and practical skills in the scientific specialty "Hematology and blood transfusion" are evident. I give my positive assessment of the dissertation on "Clinical-biological and genetic markers in risk stratification in patients with myelodysplastic syndrome" and invite the esteemed scientific jury to vote "for" the award of scientific and educational degree "Doctor" of Dr. Merlin Erol Efraim.

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Prepared an opinion:

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