

PhD Thesis Evaluation Report

By Assoc. Prof. Maria Nikolaeva Simeonova, MD, PhD,

Department of Medical Genetics, Medical University - Pleven

of a dissertation for awarding the educational and scientific degree of Doctor,

Professional field: 4.3 Biological sciences, Doctoral program: Genetics

Author: Valentina Dimitrova Miteva MD,

Form of doctoral studies: Independent study

Department : Medical Genetics, MU - Varna

Topic: Cytogenetic and molecular cytogenetic markers in patients with multiple myeloma – prognostic Significance.

Scientific supervisors: Prof. Iliana Dimitrova Micheva, MD, PhD

Assoc.Prof. Trifon Georgiev Chervenkov, MD, Ph.D.

General presentation of the proced

The PhD Thesis Evaluation Report was prepared on the basis of the presented abstract and dissertation work. The latter has 123 standard pages, 39 figures, 12 tables and 2 appendices. The bibliography covers 206 literary sources, 5 in Cyrillic and 201 in Latin. The dissertation and the abstract are structured according to the rules for preparing this type of scientific work, but there is an imbalance between the individual sections. For example, the literature review is much larger than the own results and their discussion, as well as Material and methods. The evidence material testifies to very good skills of the PhD student. Reading the dissertation leaves a good overall impression of a dissertation.

Actuality of the topic

The dissertation is dedicated to a current topic - malignant disease, which is a serious health problem, not only in Bulgaria, but also in the world. Multiple myeloma (MM) is a neoplastic disease with clonal proliferation of plasma cells. As a result, their accumulation in the bone marrow is observed, leading to multiple damages to various organs. Almost all patients with MM have the so-called precursor asymptomatic conditions. The risk of progression depends on the presence or absence of cytogenetic abnormalities. The deletion of the short arm of

chromosome 17 - del(17), the translocation t(4;14), and t(14;20), and the multiplication of the long arm of chromosome 1 - gain (1q) are considered high-risk. That is why genetic analysis, with the most commonly used conventional cytogenetic and fluorescent in situ hybridization (FISH), is of primary importance for diagnosis and therapy. In the dissertation, the doctoral student successfully focused on this type of research in order to analyze the type, frequency and prognostic significance of chromosomal abnormalities in Bulgarian patients with multiple myeloma referred to the Laboratory of Medical Genetics, MU-Varna.

Knowledge of the problem and appropriateness of the goal and tasks

The literature review, in my opinion, is structurally too extensive, although informative. It is divided into chapters, in view of the stages of scientific research. The systematization of the literature data in the review shows that the doctoral student knows the problem and can analyze the cited literature. It would be good, at the end of the review, to make a summary to show the logical justification of the purpose and tasks of this dissertation work.

Purpose and tasks

The purpose is formulated briefly and clearly. In order to achieve it, 7 main tasks are set to be solved. They are well formulated and adequate to the intended purpose.

Research methodology

The study included 110 patients, aged 38 to 91 years, referred for genetic analysis to the Laboratory of Medical Genetics from the Clinical Hematology Clinic, UMBAL St. Marina, Varna, for a period of 5 years. All patients were examined with two main techniques – conventional cytogenetic and molecular cytogenetic analysis with FISH on bone marrow material. Patients were divided into 3 groups based on MM ISS. All subjects with MM were selected based on established inclusion and exclusion criteria, through analysis of data from medical records. The study was approved by the Research Ethics Committee at the University of Varna.

The methodology applied in the dissertation work, with the use of established methods for cytogenetic research and molecular cytogenetic research (FISH), is modern and allows achieving the goal and answering the tasks. Very well are presented: the methodical stages of research; the methods used, with their very detailed principles and laboratory techniques, some with modifications. The doctoral student shows good theoretical and practical training and professional experience. I appreciate the personal work that the author has invested in learning and applying the cytogenetic and molecular genetic methods. Appropriate statistical methods for analysis and evaluation of results, software programs and online-based databases are properly used.

Results and discussion

The results are presented sequentially as the study itself followed in 3 main stages. Refined sub-steps are included. The first main stage is "*Characterization of patients by various features*". The second is "*Conventional Cytogenetic Studies*" and the Third: "*Molecular Cytogenetic Study*". Development stages show the following final summaries: The disorders found, even in the small number of patients, show their importance for therapy and the course of the disease. This confirms the need for Cytgenetic analysis, possibly combined with FISH. Based on the data found, it can be considered that numerical and structural chromosomal abnormalities are likely to be an important prognostic factor, especially in combination with some of the laboratory ones. The visualization of the results is of very good quality. Figures and tables are informative and include statistical analysis.

Conclusions

I accept the conclusions drawn. They are specifically worded in a clear scientific style. Seven conclusions were made, reflecting the stages and sub-stages of the study and are a response to the tasks set.

Contributions.

I accept the contributions and the self-assessment of the doctoral student. For me, an important confirmatory contribution is the application of conventional cytogenetic method and FISH analysis as routine methods in order to distinguish low- and high-risk patients with MM.

Abstract The abstract represents an independent scientific work and is a good certificate for the doctoral student. It is prepared according to the requirements and reflects the main results and conclusions reached in the dissertation work. Dr. Miteva's publication activity meets the requirements for the educational and scientific degree of Doctor .

CONCLUSION

The dissertation work of Valentina Miteva, MD contains scientific and clinical-applied results, which are a contribution to Bulgarian science. The dissertation meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Rules for its Implementation and the Rules for the conditions and procedure for acquiring academic degrees and occupying academic positions at Medical University – Varna were met. The doctoral student has theoretical knowledge and professional skills for the scientific specialty "Genetics". It demonstrates opportunities for independent conduct of scientific research. Due to the above, I give my positive assessment of the conducted dissertation research and propose to the

honorable scientific jury to award the educational and scientific degree Doctor to Valentina Dimitrova Miteva, MD in the doctoral program Genegics.

09/07/2023
MD, PhD,

Assoc. Prof. Maria Simeonova,

A handwritten signature in blue ink, appearing to read 'M. Simeonova', is written over the printed name of the signatory.