

*Chairman of the Scientific Jury,  
Determined by Order No. R-109-347/07/03/2023  
To the Rector of  
Medical University "Prof. Dr. Paraskev Stoyanov" - Varna*

## ***REVIEW***

From: Associate Professor Antonio Ivanov Antonov, MD, Ph.D  
Scientific specialty: 03.01.39 Hematology and blood transfusion  
Institution: Medical University – Pleven  
Address and contacts:  
Postal address: Hematology Clinic, UMBAL "Sveta Marina" Pleven, "Bulgarian Aviation" street  
Email address: [aantov@abv.bg](mailto:aantov@abv.bg)  
Tel. 08 8 8 74 46 11

**of a dissertation for the award of an educational and scientific degree "doctor"**

**Field of higher education:** 4. Natural sciences, mathematics and informatics  
**Professional direction:** 4.3. Biological Sciences  
**Doctoral program:** "Genetics"  
**Author:** Dr. Valentina Dimitrova Miteva  
**Form of doctorate:** regular form of study  
**Scientific organization:** Medical University "Prof. Dr. Paraskev Stoyanov" - Varna

**Topic:** "Cytogenetic and molecular-cytogenetic markers in patients with Multiple Myeloma - prognostic significance"

**Scientific supervisors:** Prof. Iliana Dimitrova Micheva, MD, Ph.D.  
Assoc. Prof. Trifon Georgiev Chervenkov, MD, Ph.D.

### **1. General presentation of the procedure and the PhD student**

The presented set of documents and materials by Dr. Valentina Dimitrova Miteva in paper and electronic media is complete and meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the part for the acquisition of the ONS "Doctor" of the Regulations for its application to Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

The abstract is well written, structured and illustrated.

*The documents and materials are well-formed and fulfill the necessary requirements.*

### **2. Relevance and dissertationability**

Multiple myeloma is one of the main hematologic diseases that requires long-term hospital treatment. It typically affects older patients. In clinical aspect, it leads to multi-organ damage, causing permanent disability to the patient and shorter life expectancy. The treatment process is complex, continuous and long-lasting, radically changing the life of patients and their relatives. Thus, the overall care of the patient becomes a significant medical, social and ethical problem.

In recent years, we have seen remarkable progress in the unraveling the molecular mechanisms of its development. On the other hand, we note significant variations in the clinical course and the response to treatment, with seemingly identical diagnoses. With the introduction of many modern methods and technologies into real practice, we have established the enormous genetic heterogeneity of Multiple Myeloma. It predetermines the individual progress and development of each patient. It is specific dynamics in the genome that lead to evolution from a premalignant state to an active, progressive and later resistant tumor process. Moreover, this dynamic has been found to affect the effectiveness of some groups of antitumor drugs. Thus, the individual genetic profile becomes important as a major factor in determining the degree of risk.

The present dissertation summarizes and analyzes the type, frequency, and prognostic significance of chromosomal abnormalities in newly diagnosed multiple myeloma patients at a large university clinic.

*Guided by the above, I believe that regardless of the multitude of publications in this field, the chosen topic of the dissertation work is relevant and will lead to interesting conclusions with subsequent practical contributions.*

### **3. Structure of the dissertation:**

The dissertation is designed in a classic style and contains the mandatory: introduction ; literature review ; purpose and objectives; materials and methods; results of the conducted scientific research; analysis of results ; discussion ; conclusion.

The contents cover 123 pages with 12 tables and 39 figures included. Tables and figures are clear, well adapted and explained, with proper citation of the relevant authors.

The bibliography is a total of 206 titles in Bulgarian and Latin. A significant part of them are from the last 10 years.

#### **4. Literature review:**

Due to the nature of the topic, the initial part of the review begins with an outline of the basic understanding of Multiple Myeloma, with significant attention given to current staging systems. The cited literature on familial predisposition is also of interest. In more detail, understandably so, the second part presents the type and types of basic genetic abnormalities. The review concludes with a statement of the current diagnostic markers presented more generally, without citing the strictly accepted criteria. Finally, new generation biomarkers have been announced, which are about to play a leading role in the diagnosis and follow-up processes.

***I believe that the literature review is well structured and corresponds to the topic of the dissertation work. In it, Dr. Valentina Miteva presents and systematizes the current data on cytogenetic abnormalities in Multiple Myeloma.***

#### **5. Purpose and tasks:**

The main objective is a direct continuation of the dissertation topic. It is formulated specifically and clearly. To achieve it, it is necessary to carry out 7 research tasks including:

- 1) grouping of patients with Newly Diagnosed Multiple Myeloma (NDMM) by stages ;
- 2) establishing the frequency and structure of the detected chromosomal aberrations ; 3) analyzes of the chromosomal aberrations established by conventional cytogenetics and their prognostic significance ; 4) analyzes of FISH-detected chromosomal aberrations and their prognostic significance; 5) analysis of the ratio between bone marrow plasma cells and cytogenetic results ; 6) analysis of survival compared to cytogenetic results ;
- 7) comparative analysis of survival curves depending on the staging system ;

***I accept the formulated goal and research tasks as optimally structured.***

#### **6. Methodology of the dissertation work:**

The material and methods are described clearly, concretely and reflect a high professional level. A total of 110 newly diagnosed multiple myeloma patients aged 38 to 91 years over a 5-year period (2016-2020) were retrospectively included in the study.

Laboratory methods for standard karyotyping and locus-specific FISH are detailed. Software, on-line databases and statistical programs providing reliable and precise analysis are used.

***I believe that this chapter of the dissertation is presented in detail and comprehensively.***

## **7. Results:**

The description of the results follows the sequence of the set research tasks. They are presented in detail, accompanied by well-illustrated figures and tables. Patients were initially grouped by age and sex, and later by ISS and R-ISS. It is interesting from a practical point of view, the results of task 3) with 86% success in standard karyotyping. It is necessary to note the low number of patients examined with the combination of CG and FISH. Also surprising is the FISH analysis for the deletion in chromosome 17 del(17)(p13) in 67% of the group of newly diagnosed multiple myeloma patients.

Results for overall survival in different ISS and R-ISS stage were significant.

*I accept the described results as adequate to the set goals and tasks, but it is necessary to note the low number of patients.*

## **8. Discussion:**

The discussion begins with a comparison of the obtained results for an abnormal karyotype (20%) with those described in the literature, ranging from 18% - 66%. Later, the data from similar scientific studies are presented, summarizing close to the obtained results. Especially important are the concluding words emphasizing the need for the combination of CG and FISH analysis to obtain the optimal genetic evaluation.

*The discussion of the thesis reflects the importance of genetic abnormalities as a determining prognostic factor.*

## **9. Conclusions:**

The conclusions are based on the relevant results as a response to the tasks. They establish correspondence of the data from the conducted study with those described in the literature. They demonstrate again that there is a statistically significant difference in median survival depending on the cytogenetic finding. They did not find (probably due to the small number of patients) a significant difference in median survival between patients with hyperdiploid and non-hyperdiploid karyotypes and with chromosomal abnormalities according to ISS stage. They confirmed a statistically significant difference in survival compared to ISS stage, but not to R-ISS stage.

## **10. Contributions of the dissertation:**

Contributions are formed as expected in 2 groups. The first group Contributions of a confirmatory nature are set out and formulated well. Contributions of an applied nature are also important and clear.

As a recommendation, it is good to note that the opportunity to compile an optimized practical approach of sequential FISH analysis depending on the frequency of genetic abnormalities in newly diagnosed multiple myeloma patients is missed.

*I accept the contributions formulated by the author.*

**11. Conclusion:**

*The dissertation submitted for review on the prognostic significance of cytogenetic and molecular genetic markers in patients with newly diagnosed multiple myeloma is practically important and up-to-date. It meets the scientometric criteria of the regulation for academic development of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.*

*I make a recommendation to the colleagues of the Scientific Jury to award Dr. Valentina Dimitrova Miteva the educational and scientific degree "Doctor".*

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assoc. prof. A. Antonov, MD, Ph.D.