**MEDICAL UNIVERSITY – Pleven**
Saint Kliment Ohridski 1 Street 5800 Pleven

# STANDPOINT

**by assoc.prof. Vanya Slavcheva Popova, MD, PhD**

Department of Nephrology, hematology and gastroenterology, MU- Pleven

Head of hematology clinic UMHAT "Dr. G. Stranski"-Pleven

**About:** Dissertation work of **Dr. Vladimir Todorov Gerov** affiliated with Department of Hematology, Faculty of Medicine MU- Varna for the scientific and educational degree of "Doctor of Education and Science" in Area 7. Healthcare and sports, Professional field 7.1. Medicine, doctoral program "Hematology and Blood Transfusion".

Topic of dissertation:**"Biomarkers for assessment of bone disease in multiple myeloma"**

**Scientific supervisor:** Prof. Ilina Dimitrova Micheva, Phd, MD Procedure for acquiring the degree "Doctor of Education and Science"

By order № P 109- 141/09.04.24 of the Rector of Medical University -Varna, I have been appointed as a member of the Scientific jury for the defense of dissertation work for awarding the educational and scientific degree "Doctor" of Dr.Vladimir Todorov Gerov. At the first remote meeting, I was proposed and elected to write an opinion following the current procedure. All stages of the Procedure have been observed and complied with the requirements of the Development of Academic Staff in the Republic of Bulgaria Act (DASRBA ) and the Rules for the development of academic staff at MU-Varna.

The following documents are presented:

- Dissertation - electronic and paper variant
- Abstract - electronic and paper variant
- List and copies of publications and reports related to the dissertation – electronic variant

Brief details of the candidate's professional biography :

Dr.Vladimir Todorov Gerov graduated in the Medical University of Varna in 1988. Chronologically, the professional excellence of the PhD candidate passes through the positions of a physician at the Emergency Medical Service, GP at the Outpatients conulting rooms, Shumen, until 1992, when he began working at the Hematology Clinic of the "St. Marina" UMBAL Varna. Since 2014 Dr. Gerov

has been reassigned to the Department of Stem Cell Transplantation dedicated to the Hematology Clinic. In 1995 Dr. Gerov obtained a specialty in internal medicine, and two years later a specialty in

Clinical Hematology. In 2006 he completed second higher education in the "Health Management" master's program at the MU-Varna University and has a master's degree in Health Management. He has conducted specializations in the hematology and transplantation departments in France, Croatia and Germany. Since 2017 Dr. Gerov is a part-time assistant at the Second Department of Internal Medicine, Department of Hematology, MU Varna. Dr. Vladimir Gerov is a member of the Bulgarian Medical Association, the Bulgarian Scientific Society of Hematology and the European Society for Bone Marrow Transplantation. Fluent in written and spoken French and English.

Thematic relevance of the dissertation: Multiple myeloma belongs to the group of mature B-cell neoplasms. It is characterized by malignant proliferation of plasma cells in the bone marrow and production of monoclonal antibodies or parts thereof. Not infrequently, one of the reasons for identifying the disease among the rich palette of proliferative disorders of plasma cells is the clinically apparent bone disease. The pathobiochemical mechanisms driving abnormal bone remodeling are the subject of intensive research given the serious complications that impair the quality of life of patients with multiple myeloma. Referring to the statement that "the severity of the bone disease is proportional to the tumor mass and the number of osteolytic bone lesions", the PhD candidate has create a working hypothesis on the basis of which dynamic monitoring of the serum biomarkers sclerostin, Dkk-1, sRANKL, osteopontin is based , periostin and the possibility of the latter being applied in clinical practice as predictive factors related to the course of the disease and the effect of the treatment.

In the literature review section, the PhD candidate has made a thorough review of the scientific problem. Up-to-date data on the incidence of the disease and the observed downward trend in mortality worldwide as a result of the introduction of new highly effective therapeutic regimens are presented. The complex molecular interactions between myeloma cells and the bone marrow environment, the role of some known and some understudied proteins in bone remodeling processes are briefly and clearly outlined. As a summary of the literature review, the PhD candidate indicated the increasing need to enrich knowledge related to "clarifying the role of various molecules involved in the regulation of osteoclasts, osteoblasts and osteocytes and the possibility of using them in clinical practice to monitor myeloma bone disease and the effect of the treatment.

The aim of the dissertation is clearly formulated "To assess the role of the bone biomarkers sclerostin, Dkk-1, sRANKL, osteopontin and periostin for the development of bone disease in newly

diagnosed patients with multiple myeloma and to follow-up their dynamics during the course of treatment". To realize it, the Dr. Gerov has set himself 8 research tasks.

A total of 74 individuals were included in the study, of which 41 newly diagnosed patients with multiple myeloma and a control group of 33 healthy volunteers. The methods section clearly describes the stages of the study. To realize the set goal and related tasks, the PhD candidate used standard diagnostic laboratory and imaging methods, whole-body low-dose computed tomography to assess bone damage and specific immunosorbent assay (ELISA) to study bone biomarkers (sclerostin, Dkk-1 , sRANKL, osteopontin, periostin). The analytical reliability of the method for each of the studied biomarkers is presented in tabular form. The programs GraphPad Prism, version 8.0.2 for Windows, USA and IBM SPSS Statistics v. Adequate methods of analysis and comparison of variables have been skillfully applied.

The results are presented systematically and comprehensively in tables, figures, graphs and follow the sequence of the tasks. The relationship between demographic, clinical and laboratory characteristics and bone biomarkers (sclerostin, Dkk-1, sRANKL, osteopontin and periostin) in control and patient groups was analyzed. The association between suppressed bone marrow osteoblastic activity, serum Dkk-1 and sclerostin levels in untreated multiple myeloma patients was confirmed. Similar results were reported for sRANKL, osteopontin and periostin, increased osteoclast activity and advanced disease stage. According to the author's data, serum concentrations of the biomarkers sRANKL, OPN, and PON are dynamic and change even with minimal bone damage seen in active disease. Based on his own results, the doctoral student confirms the importance of bone biomarkers as relevant serum markers reflecting the effect of the applied treatment and their predictive role for the outcome of the disease. Based on the performed ROC-analysis and logistic regression analysis, the author confirms the high diagnostic reliability of the serum biomarkers Dkk-1, sRANKL, osteopontin sclerostin and periostin and the possibility of the latter two predicting the progression of myeloma bone disease.

In the discussion section, the doctoral student argued the obtained results, comparing them with the results and data of other author groups. The lack of differences in the serum levels of Dkk-1 and Scl depending on the demographic characteristics, the author logically explains with the fact that most of the participants in the study were in physiological menopause, and the age range for both groups is significantly narrower compared to that quoted by other sources. In accordance with the data of other authors' collectives, elevated serum levels of sRANKL and PON were found in patients with untreated myeloma disease. Undoubtedly, in the absence of studies on the relationship between bone marrow infiltration by plasma cells and inhibitors of the Wnt signaling pathway (Scl and Dkk-1), the

reported results enrich the knowledge of the disease. The sensitivity of imaging methods for visualizing bone damage in MM patients and their limited role in assessing therapeutic effect are discussed.

An essential merit of the dissertation work is the formulated conclusions and contributions of an applied and original nature, which reflect the essence of the scientific development.

The bibliography includes 424 sources, one of which is from a Bulgarian collective.

The author has published part of the results in two refereed journals with a total impact factor of 9.7.

The results were reported at 5 scientific forums, three of which outside our country.

The abstract is prepared according to the requirements.

In conclusion, the presented dissertation work of Dr. Vladimir Gerov meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its Application and the Regulations of the MU-Varna for awarding the educational and scientific degree "Doctor" in the scientific specialty "Hematology and blood transfusion".

I confidently give my positive assessment to Dr. Vladimir Gerov and believe that he is a well-rounded professional, possesses the necessary qualifications and competence for an independent scientific activity. I propose to the colleagues of the Scientific Jury to vote "positively" and to award of the educational and scientific degree "Doctor" to Dr. Vladimir Gero...



Pleven

20.May.2024

Prepared the opinion:

assoc.prof Vanya Slavcheva Popova MD, PhD