

STATEMENT

by **Prof. Ivan Stefanov Ivanov, MD,**

Department of Pediatrics "Prof. Ivan Andreev". MF, MU-Plovdiv

on the Ph.D. thesis for the award of the educational and scientific degree 'doctor'

in the professional field 7.1. Medicine

on the doctoral program in Pediatrics 03.01.50

Author: Dr. Petya Petkova Markova

Form of doctoral studies: full-time

Department: Department of Pediatrics "Prof. Ivan Andreev", Medical faculty, Medical University of Plovdiv

Topic: Monitoring of renal function in children undergoing chemotherapy

Scientific supervisors: Prof. Dr. Maria Spasova, MD, and Prof. Dr. Polina Miteva-Shumnalieva, MD

1. General presentation of the procedure and the doctoral student

Dr. Petya Markova graduated with full honors and the "Key to Knowledge" award from her secondary education in the specialty "Biotechnology" and with an excellent grade of 5.94 from her medical education. She already has 19 years of experience as a doctor, starting at the Central Emergency Service in 2006, and since 2008, she has been working at the Pediatrics Clinic of the University Hospital "St. George", Plovdiv - initially in the Intensive Care Unit, and since 2016 - in the specialized structure of pediatric gastroenterology and nephrology. She obtained a specialty in pediatrics in 2014, and pediatric nephrology - in 2016. Since 2020, she has also been an assistant at the Department of Pediatrics "Prof. Ivan Andreev", Faculty of Medicine, Medical University of Plovdiv.

I have known Dr. Markova since her first days in the department. She is distinguished by intelligence, thoroughness, resilience and determination, which qualities make her a reliable colleague and a successful doctor introducing innovations. After her specialization in pediatric nephrology, conducted mainly under Prof. Polina Miteva's guidance at the Specialized Pediatric Hospital "Prof. Ivan Mitev", Sofia, Dr. Markova managed to modernize pediatric nephrology in our department. This dissertation is a step in this direction.

A full set of documents is presented in accordance with the Regulations for Academic Development of MU-Plovdiv.

The dissertation is 167 pages long, of which 48 are a literature review. The bibliography contains 247 literary sources, of which 5 are by Bulgarian authors in Cyrillic. The dissertation is illustrated with 63 figures and 29 tables. It is written in correct Bulgarian.

2. Relevance of the topic to contemporary medicine

The subject of the dissertation is the nephrotoxicity of contemporary chemotherapy in pediatric oncology. The topic is quite relevant for the following reasons:

- Acute kidney injury (AKI) is often detected during and after chemotherapy.
- Chronic kidney injury is a frequent permanent complication after some medications, e.g. in 20-50% after cisplatin or ifosfamide. It is of increasing importance in relevance to the increasing survival rate in pediatric oncology.
- The diagnosis of AKI by serum creatinine level and by oliguria is late (after 48 hours), only in severe lesions (over 50% non-functioning nephrons) and with low sensitivity for tubular damage.
- There are new urinary biomarkers for AKI, whose application in pediatric oncology seems promising, but has not been well studied yet.

3. Knowledge of the problem

Dr. Markova demonstrates a very good knowledge of the problem under investigation in the thesis. In the literature review, she displays modern concepts of AKI in childhood, scientific studies on nephropathy in oncology, data on nephrotoxicity of chemotherapy. Special attention is paid to the new biomarkers NGAL, KIM-1, IL18, L-FABP, as well as AKI in the context of pediatric oncology.

4. Research methodology

The aim of this dissertation is to monitor renal function in children undergoing chemotherapy. Three types of studies were conducted in children with solid tumors and malignant hemopathies aged 0 to 18 years, treated at the Pediatrics Clinic of the University Hospital "St. George", Plovdiv: a retrospective study of 213 patients, a cross-sectional study of 40 children with a total of 116 chemotherapy cycles and a prospective study of 28 children who completed their treatment with nephrotoxic medications at least one year ago. Up-to-date laboratory methods, functional indicators and statistical methods were applied, which allowed achieving the set goal and obtaining an adequate answer to the tasks that must be solved in this Ph.D. thesis.

5. Characteristics and evaluation of the dissertation work and contributions

In the retrospective study, Dr. Markova established important facts regarding AKI in pediatric oncology: She found a high frequency of AKI - 44.1%. It is mainly due to chemotherapeutical nephrotoxicity and is most commonly of mild degree. Infections and tumor lysis syndrome are less common causes of AKI, but it is more severe.

In the cross-sectional study, the doctoral candidate proves that NGAL, which is appreciated as an early biomarker for subclinical AKI in a number of hypoxic conditions, does not have such diagnostic value in relation to AKI due to nephrotoxic chemotherapeutics. In this etiological group of AKI, NGAL is found increased only after several courses due to cumulative nephrotoxicity. The role of the estimated glomerular filtration rate (eGFR) as a marker for early diagnosis of drug nephrotoxicity is not confirmed in this study, while such a role is established in relation to indicators of tubular damage - fractional excretion of phosphates (FeP %) and renal threshold for phosphates (Imp/GFR).

The prospective study identified chronic kidney disease in 11 of 28 children, with microalbuminuria being the most common pathological abnormality (found in 10 children).

proving the leading role of tubulopathy in kidney damage. The frequency of ultrasound abnormalities is also high, being found in 11 of the children in this group.

Based on her own study, Dr. Markova proposes an algorithm for monitoring kidney function during and after chemotherapy, which includes correction of the chemotherapy dose according to the estimated glomerular filtration rate.

With this dissertation, Dr. Markova draws attention to kidney health as one of the important determinants of the quality of life of children who have undergone chemotherapy. The in-depth dissertation research indicates the leading role of tubular damage and focuses the attention of treating physicians on its prevention and monitoring. On this basis, I define the results of this dissertation as important for daily practice and as an important stage in the direction of better renal health after chemotherapy in childhood.

I accept without reservation the contributions of this dissertation listed by Dr. Markova. The critical evaluation of the so-called new urinary markers and the proposition of phosphate excretion as a more informative indicator for AKI are important contributions of supranational importance.

6. Assessment of the publications and personal contribution of the doctoral student

The results of this work and the related literature review have been published in three articles in a journal referenced in Scopus, and have been reported at three Bulgarian and one international scientific forum.

Personally, I am convinced that this work is entirely done by the doctoral candidate. Through it, she demonstrates in-depth knowledge of pediatric nephrology and general pediatrics, as well as of scientific research methods. The constant striving for a pathogenetic explanation of the results and for her own verification of the literature data is impressive.

I have no critical comments on this thesis. I would suggest in case of future activities on long-term follow-up of patients after chemotherapy, indicators of general somatic and mental health and quality of life be added. This may help measuring the relative share of renal health in the overall assessment.

7. Abstract

It is 75 pages long and reflects the main results achieved in the dissertation.

CONCLUSION

The dissertation contains scientific and applied results that represent an original contribution to science and meet the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation and the Regulations for Academic Development of Medical University of Plovdiv.

The dissertation shows that the doctoral student Dr. Petya Petkova Markova possesses in-depth theoretical knowledge and professional skills in the scientific specialty of pediatrics, demonstrating qualities and skills for independent conduct of scientific research.

Due to the above, I confidently give my positive assessment of the conducted research, presented by the above-reviewed dissertation, abstract, achieved results and contributions, and **I propose to the esteemed scientific jury to award the educational and scientific degree of 'doctor' to Dr. Petya Petkova Markova in the doctoral program in pediatrics.**

19.3.2025

Author of the statement:

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