Review of the NSA "Doctor"

REVIEW

From: Assoc. Dr. Boryana Emanuilova Avramova, Ph, Department of Pediatrics, Medical University - Sofia,

on the dissertation for the award of the educational and scientific degree 'Doctor' professional field - 7.1. Medicine, doctoral programme - 'Paediatrics' 03.01.50

Author : Petya Petkova Markova

Form of the PhD: full-time

Department: Pediatrics „Prof. Dr. Ivan Andreev", Medical Faculty, Medical University - Plovdiv

Subject: Monitoring kidney function in children undergoing chemotherapy

Scientific supervisor: Prof. Dr. Marya Spasova, MD, MU – Plovdiv;

Prof. Dr. Polina Miteva-Shumnalieva, MD, MU – Sofia

1. General presentation of the procedure and the PhD student

The submitted set of materials on paper/electronic media is in accordance with Art. Section. Acquisition of Educational and Scientific Degree "DOCTOR" and Scientific Degree "DOCTOR OF SCIENCES" at MU-Plovdiv; Regulations of MU-Plovdiv of 28.01.2021 and includes the following documents:

- Application to the Rector of MU-Plovdiv for the disclosure of the procedure for the defense of a dissertation

- CV in European format with the doctoral student's signature

- a notarized copy of a diploma of higher education

- orders for enrolment in a doctoral programme, for dismissal with the right to defend

- an order to conduct an examination from the individual plan and a corresponding pro-certificate for passing the examination or the doctoral minimum in the specialty

- an order for an examination from the individual plan and a corresponding record of passing the examination or the doctoral minimum in the specialty

- the minutes of the departmental council for the preliminary discussion of the doctoral thesis and the decisions taken on the opening of the procedure and on the composition of the scientific jury

- dissertation

- abstract

- list of scientific publications on the subject of the thesis

- copies of scientific publications

- list of participations in scientific forums

- declaration of originality and authenticity of the attached documents

The PhD student has attached 3 publications in full text, 3 presentations at national forums, 1 at an international forum and 1 participation in a project.

All attached documents are in compliance with the requirements.

2. Brief biographical data about the PhD student

Dr. Petya Petkova Markova was born in Chirpan on 2.01.1981. She graduated from Medical University - Plovdiv in 2006. She obtained her specialty "Pediatrics" in 2014

at Medical University - Plovdiv and pediatric nephrology and hemodialysis in 2016 at Medical University Sofia.

Consecutively worked in the Children's Emergency Room at the University Hospital "St. George" in Plovdiv from 02.10.2006 to 29.05.2008, in EAD Plovdiv from 29.05.2008 to 01.08.2008, in the Clinic of Pediatrics and Genetic Diseases at the University Hospital "St. George", from 01.08.2008 - in the Intensive Care and Resuscitation Unit until 2016 and in the Department of Gastroenterology and Nephrology until now.

She is enrolled as a full-time doctoral student at the Department of Pediatrics with the enrollment order N P-2374/17.12.2021.

3. Relevance of the topic and appropriateness of the set goals and objectives

The chosen scientific topic is devoted to the renal impairment in children who are treated with chemotherapy for oncological diseases. Due to the significant advances in recent decades in the treatment of patients with cancer and the increase in the long-term survival of these patients, especially in childhood, the quality of life is increasingly important, which is very much determined by the prevention of chronic complications of therapy. These include renal complications related to the cancer or its treatment.

Acute kidney injury (AKI) is one of the common complications during chemotherapy, leading to increased hospital stay, treatment costs, mortality, and decreased functional capacity of the patient. Its occurrence during treatment may also become a reason for changing the therapeutic plan, substituting one drug for another, excluding strategic cytostatics from further therapy or changing the timing of administration of individual therapeutic cycles.

Chronic renal complications of chemotherapy greatly impair the quality of life of survivors of childhood cancer and the development of additional complications and new causes of morbidity and mortality from non-oncological causes.The study of the factors influencing the occurrence of acute and chronic kidney injury in pediatric oncology patients in relation to the chemotherapy, the introduction of new and rapid diagnostic tests, as well as the regular follow-up of affected patients according to a modern algorithm, will lead to early diagnosis and prevention of severe complications in children undergoing anticancer treatment.

The presented thesis is the first attempt for such a study in Bulgaria, with practical significance and significant contribution to the Bulgarian medical literature and practice.

In the realization of this study, the dissertator set well-formulated tasks that meet the aim of the dissertation - analysis of the incidence, characteristics and type of UTI in children with cancer from one clinic over a period of 5 years; monitoring the dynamics of urinary NGAL as an early marker of UTI in children undergoing chemotherapy; study of the role of classical markers of UTI - creatinine and GFR as markers of UTI in pediatric oncology; Establish the importance of markers of proximal tubular injury - fractionated phosphate excretion and renal phosphate threshold as early markers of nephrotoxicity; Analysis of the incidence of chronic kidney disease (CKD) in children who had chemotherapy more than one year ago, and the role of NGAL as a marker of chronic kidney disease; Establishment of an al-gorithm for monitoring renal function in children treated with nephrotoxic drugs.

4. Knowledge of the problem

In all sections of the thesis a good knowledge of the problem, a very thorough knowledge of the current advances in the diagnosis and follow-up of oncological patients with renal impairment, as well as of the methods for conducting such a study (collection and statistical processing of the material, interpretation of results and formulation of conclusions) are evident.

The presented literature material of more than 50 pages with citation and creative discussion of the publications of more than 210 Bulgarian and foreign authors shows a very thorough study of all available literature data and elaborations on the topic and a critical evaluation of all the results of similar studies conducted to date.

5. Research methodology

The chosen methodology of the research allows achieving the set goal and obtaining answers to the problems solved in the dissertation.

Statistical methods of the data processing are very precisely selected.

6. Characteristics and evaluation of the dissertation

Literature review

The literature review together with the introduction is laid out over 53 pages. It is very detailed, competently designed and based on 219 cited references. Of these, 5 are by Bulgarian authors and 214 by foreign authors. The literature used is sufficiently recent - 130 of the cited publications are from the last ten years, which is more than 50%. The technical presentation was corrected after the remark during the internal defense of the dissertation.

The review presents in great detail the current concepts of acute and chronic kidney injury in general and specifically in patients undergoing chemotherapy for cancer - hematological and solid tumors, including historical development, etiology, clinical manifestations, methods of diagnosis, specific effect of different cytostatics, etc. Структурата на обзора корелира с поставените цел и задачи. Все още има стилистични и граматични грешки, но са значително по-рядко отколкото преди корекциите.

The **goal** is precisely formulated.

To achieve it, 6 clearly formulated **tasks** are set, and the stages in the study follow their implementation.

The **design** of the study is selected and adapted to the objectives of the development. It includes a retrospective study of hospitalized patients in the Pediatric Clinic of "St. George" Hospital for the period 2016-2020 with an analysis of medical records in accordance with the standards and criteria for anonymity and ethics and the requirements of the hospital in terms of medical records; a cross-sectional study including 40 children undergoing chemotherapy with nephrotoxic drugs in the Department of Pediatric Oncohematology of the Pediatrics Clinic of ""St. George" Hospital. A prospective study on a group of 28 children who completed their treatment with nephrotoxic drugs at least one year ago for analysis and evaluation of the occurrence of chronic kidney disease. For all three groups of patients, inclusion and exclusion criteria for their selection were specified.

Section "Materials and Methods"

The study material includes an impressive number of patients for a single center, divided into retrospectively and prospectively evaluated, 213 and 68, respectively, which increases the significance of the results and allows for a precise conduct of the study.

The study methods were well selected and described in detail: clinical assessment, standard laboratory and imaging tests, determination of urinary NGAL levels, functional tests - glomerular filtration rate, determination of the degree of acute kidney injury, determination of the stage of chronic kidney disease and markers of proximal tubular injury.

The statistical methods of analysis used in the study are well described. Statistical processing of the results was performed using SPSS v.23 statistical software.

Methods of descriptive statistics were applied, and data for qualitative, unmeasured variables are presented by absolute frequencies and relative proportions (number, %). Quantitative variables were described by main central tendency parameters (Mean ± standard error of the mean - SEM), statistical variance (standard deviation - SD) and 95% confidence interval (95% CI). Quantitative indicators that do not follow a normal distribution are described by median and interquartile range (IQR). The Kolmogorov-Smirnov test was used to assess the normality of distribution of the variables analyzed. When testing hypotheses of non-significant factors, the χ^2 test for multiple tables and Fisher's exact test for 2x2 tables were applied. In the analysis of quantitative variables in independent groups not following a normal distribution, the Mann-Whitney U test was applied. Comparison of quantitative data between two dependent groups was performed using Mann-Whitney U test for dependent samples for variables that do not follow a normal distribution. The Kruskal-Wallis test was used to compare more than two independent groups for variables that do not follow a normal distribution. $P<0.05$ was taken as the significance level of the null hypothesis.

Graphical presentation of the results was implemented using Microsoft Excel 2016.

The study was approved by the Ethics Committee of the Medical University - Plovdiv (Protocol №6/07.10.2021).

Section "Results"

The results obtained after the statistical analysis of the data are described in great detail on 86 pages. They are divided into subsections that follow the objectives of the dissertation, with a summary of the results obtained after each section. They are illustrated with 27 tables and 62 graphs and figures, which gives additional clarity to the description and confirms the reliability of the material.

Each group of results (6 in total) is followed by a summary and discussion, which also includes an analytical evaluation and comparison with the literature data. The summaries are very detailed and give a clear idea of the depth of the study presented.

There are 10 very precise **conclusions**, a number adequate to those generally accepted for this type of clinical study, which are consistent with the results obtained and meet the stated aim and objectives. Based on the study, it was found that among children treated for cancer, the incidence of Acute Kidney Injury was quite high at 44.1%, with chemotherapy-induced drug nephrotoxicity and tubulopathy as the leading causes. Classical markers of UU (serum creatinine and eGFR) have low sensitivity in children with cancer. A large percentage of children have hyperfiltration associated with hypermetabolic state during chemotherapy cycle. A very important finding of the study is that NGAL is not indicative for the diagnosis of UU resulting from nephrotoxic cytostatics.

The markers of tubular injury (FeF % and Tmp/GFR) have high sensitivity for the diagnosis of drug-induced nephrotoxicity from chemotherapeutics, and the tubulopathy that occurs is reversible in more than 50% of cases, but it remains chronic in about one-third of children.Patients should be followed up for tubulopathy both during and after therapy.

When assessing renal function in pediatric oncology, the use of body weight-based GFR formulas is recommended.

A very detailed management algorithm for the diagnosis of renal impairment resulting from treatment with nephrotoxic cytostatics in children with cancer has also been derived.

7. Contributions and Significance of the Development for Science and Practice

Overall, the thesis has made a significant contribution to our knowledge of the nephrotoxicity of chemotherapy in children with cancer. The distribution of this type of complications by patient groups and by drugs, the diagnostic methods and their relevance for the assessment of the degree of kidney damage have been studied and very well described. This is a major contribution to the Bulgarian medical literature and practice. It is also the first detailed analysis of these complications in paediatric patients in Bulgarian medical literature.

The PhD student has indicated 3 groups of contributions of general, original and confirmatory nature. The first group of contributions is very important for Bulgarian medical science and practice - the original ones concerning the pediatric population in Bulgaria. For the first time in Bulgaria a study on the incidence of UTI among children treated for oncological diseases has been performed and the drug nephrotoxicity of chemotherapeutics has been studied, as well as for the first time a long-term follow-up for chronic kidney injury of children undergoing chemotherapy has been performed. These are contributions of great importance to pediatric oncologists, as they provide clear and easy access to the investigation and follow-up of children treated with chemotherapy for renal function impairment. The proposed algorithm can also be used for even greater convenience. The remaining two groups of contributions are of an original and general and confirmatory nature, as the original contribution – the created algorithm, could also be in the group of significance for Bulgarian practice.

I accept all the indicated contributions, but their significance is primarily in the field of Bulgarian medical literature and practice and of applied significance. The indicated contributions to Bulgaria can and should be introduced into practice in pediatric oncology clinics, as well as the indicated markers for renal damage to be used in the diagnosis and monitoring of each patient treated with chemotherapy.

I recommend that the doctoral candidate continue her research in this direction, enriching it with new studies on the effect of different types of oncological therapies (chemo-, immuno- and targeted therapy) on renal function.

8. Evaluation of the publications on the dissertation work

The results of Dr. Markova's research work are reflected in 3 publications in the journal Pediatrics, two of which are on the topic of the dissertation work from 2023 and 2024, which is related to the intensive research work on the topic of nephrotoxicity of chemotherapy and markers for diagnosis in children with cancer. Also impressive is a report presented at an international forum - the 56th annual meeting of the European Society of Pediatric Nephrology in Valencia in 2024, on the topic "Role of urinary NGAL as a marker of nephrotoxicity in children undergoing chemotherapy", with first author P. Markova. It is also important to note that the author is also a participant in a project on the same topic - Scientific Project No. NO-07/2021 - topic "Study of NGAL in urine as a marker for kidney damage in cancer patients undergoing chemotherapy". In all publications and

communications on the topic of the doctoral studies, Dr. Markova is the first author, proof that the dissertation work is her personal work.

9. Personal participation of the doctoral student

The dissertation work of Dr. Petya Markova is an independent work of high scientific value and practical significance. I hope that the presented contributions will be taken into account by interested individuals and institutions, who will assess their benefit for patients with oncological diseases treated in childhood.

I can categorically state that when analyzing the dissertation work, it is seen that it is the work, above all, of the doctoral student, supported and guided by her scientific supervisors, leading specialists in the field of pediatric oncology and pediatric nephrology and hemodialysis in Bulgaria. The formulated contributions and obtained results of the study are, above all, the personal merit of Dr. Petya Markova.

10. Abstract

The abstract is presented according to the requirements and reflects the main results achieved in the dissertation.

11. Recommendations for future use of the dissertation contributions and results

I believe that the presented dissertation work is up-to-date, contains scientific and applied results that represent an original contribution to pediatric oncology in Bulgaria. I recommend that the dissertation candidate continue her work on this topic, building on current and new discoveries in this field, for the benefit of increasingly successful treatment and ensuring a good quality of life for children with oncological diseases.

CONCLUSION

The dissertation work contains scientific, scientifically applied and applied results that represent an original contribution to science and meet all the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria (ADSRB), the Regulations for the Implementation of the ADSRB and the relevant Regulations of MU -

Plovdiv. The presented materials and dissertation results fully comply with the specific requirements of MU - Plovdiv.

The dissertation work shows that the doctoral student Dr. Petya 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.

03/24/2025 **Reviewer:**

Sofia Assoc. Prof. Dr. Boryana Avramova, MD