

Review

by Prof. Dimitrichka Duceva Bliznakova, MD, PhD

Medical University "Prof. Paraskev Stoyanov"- Varna

Chairman of the Scientific Jury assigned by order of the Rector of Medical University- Varna
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Subject:

Doctoral thesis for the award of the educational and scientific degree "Doctor of Philosophy"

in the field of higher education 7. Health and Sports,

professional field 7.1. Medicine,

doctoral program "Pediatrics",

by **Hristina Yaneva Hristozova, MD,**

doctoral fellow at the Department of Pediatrics, Faculty of Medicine,

Medical University "Prof. Paraskev Stoyanov" - Varna

on the topic ***"Quality of life after treatment of malignant hematopathies and solid tumors in childhood"***,

with scientific supervisors:

Prof. Valeria Ignatova Kaleva, MD, PhD,

Prof. Paraskeva Mancheva Draganova, MD, DSc

- Hristina Yaneva Hristozova was born on 25.04.1970. She completed her secondary education at the Second Mathematical High School "Dr. Petar Beron" - Varna. In 1994, she graduated from medicine with honors at the Medical University "Prof. Paraskev Stoyanov" - Varna.

Professional development:

- She obtained a specialty "Pediatrics" in 2001.
- Specialty in "Oncology" in 2006.
- Specialty " Pediatric Clinical Hematology" in 2009.
- Since 1995, she has been working consecutively in the First Pediatric Clinic and Pediatric Emergency Center of the University Hospital "St. Marina" - Varna.
- Since 2001, she has been part of the team of the " Clinic of Pediatric Clinical Oncology and Hematology" University Hospital "St. Marina" - Varna.
- acquired qualifications: Abdominal Ultrasound, Palliative Care and Stem Cell Transplantation. In 2014, she completed a specialization in the Pediatric Oncology Clinic at the St. Anna Children's Hospital, Vienna.
- In 2014, she completed a Master's degree in Public Health and Health Management at the Pleven Medical University.

Academic development:

- In 2005, he won a competition for an assistant professor in pediatrics at the Department of Pediatrics, Faculty of Medicine, Medical University - Varna;
- Since 2006, he has been an assistant professor at the Department of Clinical Medical Sciences, Faculty of Dental Medicine, Medical University - Varna.

Scientific interests:

- Pediatric malignant diseases;
- Quality of life after treatment of malignant diseases in childhood

Publications:

- Has 20 publications;
- Over 90 participations in scientific forums: conferences, congresses.
- Co-author of the Clinical Guide "Behavior in Neuroblastoma in Children".

Membership in professional organizations: Bulgarian Medical Union, Bulgarian Pediatric Association (BPA), Bulgarian Society of Hematology, Bulgarian Medical Association of Pediatric Hematology and Oncology, European Society of Pediatric Oncology (SIOPE).

He speaks Russian and English.

The presented thesis "Quality of life after treatment of malignant hematopathies and solid tumors in childhood" examines one of the important and current problems in the field of pediatric oncohematology. In addition to diagnosing and treating these socially significant diseases, the quality of life of patients is extremely important. More and more attention is paid not only to physical, but also to mental health.

Analyzing diseases in the field of pediatric oncohematology, an extremely important conclusion is that over the past four decades, significant success has been noted in the treatment of pediatric oncological diseases worldwide. The basis of this progress are improved diagnostic capabilities, a complex individualized risk-stratified therapeutic approach, as well as the successful management of side effects of the treatment. High long-term survival is reported in children with malignant hematopathies and solid tumors. In Europe, an average of 12,000 children annually complete successful treatment for oncohematological diseases and it is predicted that their number after 2020, in total for Europe and the USA will exceed 1 million. It is extremely important to know that the life expectancy of survivors of these diseases is increasingly approaching that of the general population. The largest relative share is of young adults who have survived cancer. Among them are numerous side effects of the treatment. Some of them affect the health status even during active treatment and can become chronic, others appear years after the completion of treatment. In addition to somatic impairments, there are psychological and social problems. All of the above creates prerequisites for impaired quality of life of patients who have survived malignant hemopathies and solid tumors in childhood. This requires long-term follow-up and comprehensive care after treatment in order to achieve optimal quality of life for survivors of these diseases.

The presented work contains 235 literary sources, of which 5 in Cyrillic and 230 in Latin. The work is illustrated with 19 tables, 27 figures and 2 appendices.

The literature review is thorough and competently written. The individual parts address issues such as:

- Health, quality of life and health-related quality of life. Quality of life measurement tools. Generic and cancer-specific questionnaires;
- Quality of life after childhood cancer and determinants of quality of life. The importance of individual domains of quality of life is described: physical health, sexual function and fertility, appearance and figure, social relationships, friendships, family and loved ones, starting a family, psychological state, fears, anxiety, insecurity and depression, cancer-related post-traumatic stress, cognitive impairment, spiritual environment, resilience. The role of age at diagnosis, as well as age at the time of assessment, is taken into account. Employment with social and economic independence of patients who have experienced childhood cancer is an important factor for their quality of life;
- Role of long-term follow-up of survivors of childhood malignant disease.

The goal of the work is set clearly and precisely and includes assessing the quality of life in patients who have undergone treatment for malignant hematopathies and solid tumors in childhood, as well as the factors that influence it.

The tasks are properly structured. They meet the set goal: study of the available literature, use of appropriate methods for assessing the quality of life, comparison of the quality of life of children with malignant hematopathies with those with solid tumors. Indicators related to the demographic characteristics of patients with malignant disease, the treatment performed and clinical data from follow-up and their impact on the quality of life are considered.

The hypothesis meets the set goal and tasks.

Material and methods

The study included patients with malignant hematopathies and solid tumors, diagnosed and treated at the Clinic of Pediatric Clinical Hematology and Oncology the University Hospital (CPCHO) "St. Marina" - Varna. Patients over 18 years of age are monitored in the CPCHO. The study started after receiving permission from the Research Ethics Committee at the Medical University of Varna and was carried out for 2 years in the period March 2020 - February 2022. The inclusion and exclusion criteria were clearly and precisely formulated. 52 patients were included in the study.

The following methods were used: documentary method, sociological methods (generic questionnaire for assessing the quality of life of the WHO - WHOQOL BREF 26), clinical and laboratory methods, statistical methods (descriptive, correlation analysis, one-factor analysis of variance).

Results

Patients who were diagnosed and successfully completed treatment for malignant hematopathies and solid tumors in childhood at the CPCHO for the period 2000-2021 at the time of the study are 159. Of these, 91 are registered for follow-up at the CPCHO and are

identified as potential participants. 52 of them were included in the study for the period 2020-2022. The results analyze: demographic data of the participants, data on the malignant disease in childhood and the treatment performed, side effects of treatment, follow-up monitoring of the participants, assessment of quality of life by diagnoses with a questionnaire. The participants in the study were diagnosed with a malignant disease in childhood at different ages from 8 months to 17 years and 6 months, with a peak of 4-6 years of age and puberty. The participants are divided into two main groups: a group of survivors of malignant hematopathies and a group of survivors of solid tumors.

Discussion

The discussion is complete and detailed and covers all the results obtained. It is reported that the majority of those who completed treatment for the period 2000-2021 and who were 18 years old at the time of the study were observed at the CPCHO, but a significant part of them dropped out of observation over time. The reasons reported are the lack of interest of the families and the underestimation of the seriousness of the disease, the desire to forget what they experienced. The role of the COVID 19 epidemic, which limited planned hospital visits, is also reported. The participants are aged 18-32 years (adolescents and young adults), than in the population. The majority of the participants have secondary education. In the studied group, 38.5% are employed. The participants who are single predominate. In the two groups of participants: malignant hemopathies and solid tumors, no difference by gender was found. The number of patients treated for malignant hematopathies is approximately three times higher than those treated for solid tumors. The high success rate of treatment for malignant hematopathies, mainly including chemotherapy, and the established lasting relationship and trust between the team of pediatric oncologists, patients and their families, which is a major reason for adherence to dispensary monitoring, are discussed. The relative proportion of patients who survived ALL is higher in the present study. The participants treated for solid tumors are significantly fewer than those who survived malignant hematopathies. The largest proportion of survivors of solid tumors is in patients with Wilms tumor, which is associated with the good prognosis of the disease. In the study group, there are 4 participants who survived bone tumors: two with Ewing sarcoma and two with osteosarcoma. Complex surgical interventions and impaired physical activity justify considering these patients together when assessing the quality of life. The group with "other tumors" included two germ cell tumor survivors, one with neuroblastoma and one with hepatoblastoma. Survivors of hematological neoplasms were stratified into an intermediate risk group, and survivors of tumors were mainly in a low risk group. Current internationally accepted treatment protocols were used. The results of chemotherapy treatment and its side effects were reported. Over 50% of the participants received intrathecal applications of cytostatics and steroids, due to the tendency of malignant hematopathies to spread via the cerebrospinal fluid into the CNS. Intrathecal therapy was not applied to survivors of solid tumors. In 1/3 of the patients, radiotherapy was performed, after which late side effects were discussed. In patients with solid tumors, postoperative chemotherapy was often applied.

Patients were followed up for an average of 10 years after the end of treatment, which provides a good opportunity to analyze their quality of life. There was no evidence of significant deviations in the height of the survivors. Some patients had an increased BMI, which was most likely related to reduced motor activity and increased caloric intake. Changes in appearance (scars, stretch marks, hair growth) were also found. When looking for complications from the treatment, a higher percentage of cases received cardiotoxic chemotherapy was found.

Orthopedic complaints are also common, especially in survivors of osteosarcoma and Ewing's sarcoma. Endocrinological problems were also reported in 9.6% of the patients followed up, including menstrual cycle disorders, adrenal adenoma, autoimmune thyroiditis, and impaired uric acid metabolism. Problems with the digestive system were also observed. Psychiatric problems are of extremely important importance. Among the survivors in the group, they account for 7.7%.

The results of the quality of life assessment with the WHOQOL-BREF 26 questionnaire were reported. The highest score was for the "Physical" domain and the lowest for the "Psychological" and "Relationships" domains. The score in the "Environment" domain was slightly higher than the score in the "Psychological" and "Relationships" domains. The quality of life assessments by diagnosis were also analyzed. The highest score in the "Physical" domain was for participants with hematological neoplasias and participants with Wilms' tumor. In the "Psychological" domain, the highest score was for participants who had survived acute myeloblastic leukemia. The highest score in the "Relationships" and "Environment" domains was for survivors of acute myeloblastic leukemia, and the lowest score was for survivors of non-Hodgkin's lymphoma.

Conclusions

Nine conclusions were formulated. They are a correct and accurate summary of the results obtained. They relate to the quality of life in patients who have survived malignant hematopathies and solid tumors. The relationship of the survivors' quality of life assessments in the areas of "Physical", "Psychological", "Relationships" and "Environment" with indicators related to the type and group of oncological disease, risk group, demographic characteristics of the survivors (marital status and occupation), changes in appearance and figure due to treatment, BMI and the presence of late side effects was reported.

The contributions are structured in two groups: three of a scientific-theoretical nature and three of a scientific-applied nature.

Extremely valuable contributions to clinical practice are:

- The study of the quality of life of survivors of malignant hematopathies and solid tumors in childhood is the first of its kind in Bulgaria;
- The reliability of the WHOQOL-BREF questionnaire has been established as a tool for quantitative assessment of the quality of life in patients who have survived malignant hematopathies and solid tumors;
- Indicators related to the demographic characteristics of the patients, the malignant disease and the treatment performed, clinical data from the follow-up observation, correlating with the quality of life of the survivors, which can be used to identify patients at risk and take appropriate measures for complex care during their follow-up.
- This questionnaire is applicable both for clinical practice and for scientific research

Conclusion

The doctoral thesis of Hristina Yaneva Hristozova, MD "Quality of life after treatment of malignant hematopathies and solid tumors in childhood" examines one of the current problems in the field of pediatric oncohematology in recent years. The data from the study show good

adaptation of survivors of treatment of malignant hematopathies and solid tumors with a pronounced high score in the areas: "Physical" and slightly below the average value of the scores in the areas "Environment", "Psychological" and "Relationships". The following recommendations are given:

- Assessment of quality of life should become a mandatory part of the long-term follow-up of survivors of malignant hematopathies and solid tumors;
- After the completion of treatment, each survivor should receive a summary of the treatment performed and the complications obtained.
- Long-term follow-up care should gradually move from pediatric oncohematology clinics to centers for the long-term observation of adult survivors with oncohematology diseases.
- The follow-up team should include, in addition to oncologists and specialists from other fields, a psychologist and a social worker.

The doctoral work of Hristina Yaneva Hristozova, MD, reminds us of the words of Fullar: "Theory is a treasure, the key to which is good clinical practice".

With a clear goal and specific tasks, the implementation of the dissertation topic meets modern requirements. An extremely difficult and risky contingent is covered – patients who have experienced oncohematological diseases. The main goal is to shed light on the future of these patients and improve their quality of life, which requires an individual approach to treatment and medical examination. Follow-up must be carried out in certain centers, provided with highly qualified medical personnel.

The doctoral thesis fully meets 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 on the terms and procedures for acquiring scientific degrees and occupying academic positions at MU-Varna.

I propose to the esteemed Scientific Jury to award the educational and scientific degree "Doctor of Philosophy" to Hristina Yaneva Hristozova, MD.

05.05.2025

Varna

Reviewer:

Prof. Dr. Dimitrichka Bliznakova, MD, PhD

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