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CURRENT TRENDS IN EARLY INVESTIGATION AND THERAPEUTIC RETINOBLASTOMA: A COMPREHENSIVE ANALYSIS OF DIAGNOSTIC STRATEGIES AND THERAPEUTIC OPTIONS

Maria Julia Santana Santos Cotta
Faculdade Dinâmica do Vale do Piranga (FADIP)
Ponte Nova - MG
https://orcid.org/0009-0004-8873-1752

Anna Carolina de Oliveira Carone Bissoli
Universidade Estácio de Sá (UNESA)
Rio de Janeiro - RJ
https://orcid.org/0009-0000-1319-9053

Luiza de Sant Anna Petrucci
Universidade Feevale
Novo Hamburgo - RS
https://orcid.org/0009-0007-9375-1653

Valkíria Moreira Climaco de Aguiar
Centro Universitário FAMETRO
Manaus - AM
https://orcid.org/0009-0006-7783-3213

Ana Beatriz Piscopo Pereira
Centro Universitário FAMETRO
Manaus - AM
https://orcid.org/0009-0007-5091-1151

Ana Laura Romanini Perego
Pontifícia Universidade Católica de Campinas (PUC-Campinas)
Campinas - SP
https://orcid.org/0009-0009-4874-6155

Victoria Cristina Farani Vieira
Fundação Técnico Educacional Souza Marques (FTESM)
Rio de Janeiro - RJ
https://orcid.org/0009-0000-8012-9565

Bárbara Lopes Ramalho
Centro Universitário de Adamantina (UNIFAI)
Adamantina - SP
https://orcid.org/0009-0004-9611-2054

Carolina Gama Arndt
Pontifícia Universidade Católica de Minas Gerais (PUC-MG)
Betim - MG
https://orcid.org/0009-0002-3491-4823

Tainah Berbeti Pacheco de Lacerda Lage
Universidade Vila Velha (UVV)
Vila Velha - ES
https://orcid.org/0009-0002-5965-4597

Laura Melo Costa
Faculdade Ciências Médicas de Minas Gerais (FCMMG)
Belo Horizonte - MG
https://orcid.org/0009-0003-9695-4051

Kathleen Priscila Correia Coelho
Universidad Nacional de Rosario
Rosário - Argentina

Abstract: Objective: To evaluate the effectiveness of early detection of retinoblastoma and current therapeutic options in the regression of ocular tumor. Methods: A bibliographic review was carried out through searches in the PubMed Central (PMC) database. 141 articles were identified. In the end, 18 articles were selected. Results: The studies analyzed suggest that retinoblastoma has been the target of significant advances in early diagnosis, offering hope for improvements in therapeutic options for young patients. The implementation of diagnostic modalities and the search for new drugs that expand therapeutic options are essential for less invasive management, aiming to provide a better quality of life for these patients. Conclusion: Despite advances, significant improvements are needed in investigation, accessibility and image analysis tools.

Keywords: retinoblastoma, early diagnosis, treatment, quality of life, ocular neoplasia, pediatrics.

INTRODUCTION

Retinoblastoma (RB) is the most common primary intraocular malignancy in children, although it is a rare disease. It can present bilaterally or multifocally, being hereditary in around 25% of cases, characterized by the presence of germline mutations in the RB1 gene. Most of the time, the unilateral or unifocal form does not have a hereditary origin. A common presenting feature of retinoblastoma is leukocoria (white pupillary reflex), often accompanied by strabismus. Early diagnosis of this disease is essential, as it helps preserve children's vision, eyes and lives. It is essential to increase awareness among healthcare professionals, especially in early identification of symptoms, in order to save the vision and lives of these children who have potentially treatable conditions. Additionally,

primary care physicians must receive training in managing treatment-related side effects during follow-up (Gupta N. et al., 2020).

The expression, clinical significance and molecular mechanism of the miR-204 gene in RB tissues are fundamental to understanding this disease. Retinoblastoma occurs predominantly in both eyes and is often associated with multiple lesions. The possibility of intracranial and systemic metastases is a serious threat, especially if the tumor continues to grow and eventually ruptures the eyeball. However, effective and early treatment may allow affected children to maintain partial visual function and enjoy longer survival. Therefore, it is crucial to investigate molecular biological markers that can enable early diagnosis of retinoblastoma, understand the molecular signaling mechanisms underlying the development of the disease, and identify therapeutic targets that can inhibit its occurrence and progression (Ding & Lu, 2018).

Despite continuous improvements in treatment methods, the therapeutic effect of retinoblastoma in most children is limited, often affecting both visual function and quality of life (Khedekar A. et al., 2019). Therefore, it is essential to study the specific pathogenic mechanism of retinoblastoma and investigate the molecular biological markers and therapeutic targets related to its occurrence and development. The miR-204 gene has been observed to play a role in the proliferation and apoptosis of retinoblastoma cells and may be involved in its pathogenesis. The miR-204 gene may become a new biological index for early diagnosis, prognostic assessment and molecular therapy of retinoblastoma (BELSON P.J. et al., 2022).

Therefore, studying the specific pathogenic mechanism of RB and investigating the molecular biological markers and therapeutic targets closely related to the occurrence and development of RB is important for the early diagnosis and molecular therapy of RB. The effects of the miR-204 gene on the proliferation and apoptosis of RB cells were observed, it may be involved in the occurrence and development of RB. The miR-204 gene can inhibit proliferation. Therefore, miR-204 may become a new biological index for early diagnosis, prognosis assessment and biotherapy of RB (Ding & Lu, 2018).

The main objective of this review is to evaluate the effectiveness of early investigation of retinoblastoma and current therapeutic alternatives in the regression of the ocular tumor. We aim to explore recent advances in early diagnosis, analyze available treatment options and estimate the impact of treatment on the quality of life of children diagnosed with retinoblastoma, a rare ocular tumor that predominantly affects the pediatric population.

METHODOLOGY

This is a bibliographic review developed according to the criteria of the PVO strategy, an acronym that encompasses the population or research problem, variables and outcome. This approach was used to develop research around the following guiding question: "What are the advances in early diagnosis, treatment and quality of life qualification in children affected by retinoblastoma, a rare ocular tumor?". In this context, according to the parameters mentioned, the population or problem addressed by this research refers to early childhood patients who seek an early diagnosis, aiming to increase the life expectancy and quality of life of these children.

The search for articles was carried out by searching the PubMed Central (PMC) database. We use descriptors in combination with the Boolean term "AND": Retinoblastoma and Early Diagnosis. Initially, 141 articles were identified, which were subsequently subjected

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to strict selection criteria. The inclusion criteria covered articles in English published between 2019 and 2023, which addressed the themes relevant to this research. Review and meta-analysis studies were considered, as long as they were available in full. Duplicate articles, those available only in abstract form, as well as those that were not directly related to the research proposal were excluded. In the end, 18 articles were selected to compose the present study.

DISCUSSION

DIAGNOSIS OF RETINOBLASTOMA

Retinoblastoma (RB), a rare ocular tumor that predominantly affects children, has been the target of significant advances in early diagnosis, offering hope for improvements in therapeutic options and quality of life for these young patients. This literature review critically addresses recent innovations, highlighting challenges and progress that directly impact the clinical approach to this pediatric cancer.

In the RB diagnosis scenario, the search for innovative methods is constant. The red reflex test, although widely used, has limitations, being sensitive to the examiner's competence and susceptible to external interference. Leukocoria, a prevalent clinical manifestation in RB, is detected in a large proportion of diagnosed children, as evidenced by studies such as that by Uddin et al. (2020) and Munson M.C. et al. (2019).

Given these limitations, the use of digital photographs, captured by parents, has been integrated as a screening tool. Applications such as CRADLE and MDEyecre, based on artificial neural networks, emerge as promising strategies to identify leukocoria autonomously, providing earlier detection. Despite the challenges related to the sensitivity and specificity of these tools, the reduction in time to diagnosis is notable, as evidenced by Jabir A.R. et al. (2022).

In addition to image-based screening strategies, genetic diagnostic methods have stood out. Genetic analysis, as addressed by Zhang Z. et al. (2020), presents a specific approach for the early detection of RB, contributing to the understanding of associated genetic variants. Non-invasive prenatal diagnosis (NIPD), as explored by Gerrish A. et al. (2020), demonstrates effectiveness when using maternal cfDNA to identify fetuses with retinoblastoma.

When comparing screening approaches, it is noted that image-based methods have significant advantages, especially in terms of accessibility and ease of implementation. However, the sensitivity and specificity of these tools require continuous improvement, highlighting the need for more research, as highlighted by Jabir A.R. et al. (2022).

Genetic analysis, although robust in its ability to identify genetic variants, faces challenges related to widespread availability and accessibility. The global disparity in time to diagnosis, as evidenced by Mattosinho C.C.D.S. et al. (2019), highlights the urgent need for educational strategies and public awareness to improve early detection, especially in developing countries.

Implementation of diagnostic imaging modalities such as fetal ultrasound and magnetic resonance imaging (MRI) plays a crucial role in screening and staging retinoblastoma. MRI, in particular, not only contributes to tumor diagnosis and staging, but is also vital in detecting metastases and post-treatment monitoring. Neuroimaging emerges as an essential tool, reinforcing the need for a deep understanding of imaging findings in the pediatric context (ORMAN G.; HUISMAN T.A.G.M., 2022).

The introduction of telemedicine as an integral part of the multidisciplinary approach at King Hussein Cancer Center (KHCC)

in Jordan highlights an innovative strategy to optimize time to diagnosis and improve clinical outcomes. International collaboration, especially with centers of excellence in developed countries, appears to be a replicable model for other developing countries. This approach not only accelerates decision-making in the treatment of retinoblastoma, but also contributes to reduced mortality and improved ocular preservation rates (YOUSEF Y.A. et al., 2021).

Comparatively, genetic analysis, although essential for high-risk families, faces availability and accessibility challenges. While imaging strategies, especially MRI, provide a comprehensive view of the tumor and its staging, telemedicine emerges as a key player in streamlining the diagnostic process. Public awareness and education, mentioned in previous studies, remain crucial to reducing the mean time to diagnosis, especially in regions with limited resources. Combining these approaches, from genetic testing to imaging strategies and innovative telemedicine models, offers an integrated and holistic perspective to optimize the diagnosis and treatment of retinoblastoma.

TREATMENT

The treatment of retinoblastoma (RB) is multifaceted, adapting to the child's age, laterality and severity of the disease. Different modalities such as chemotherapy, brachytherapy, external beam radiotherapy, enucleation, and intra-arterial chemotherapy (IAC) are chosen based on these variables. Recent studies highlight the complexity in choosing therapy, with specific considerations to avoid significant side effects, especially in young children.

Research by Zhang, Y., et al. (2023) highlights the evolution of therapeutic strategies for infant patients with RB presenting retrobulbar invasion. The study emphasizes the transition from intra-arterial therapy to systemic chemotherapy due to the high risk of local side effects associated with intrathecal therapy. This change highlights the importance of therapeutic adaptation to mitigate specific risks in more vulnerable population groups.

On the other hand, Zheng, W., et al. (2022) emphasizes the need for less invasive therapeutic strategies. Enucleation, although effective, is considered a more destructive option in ophthalmology. The study suggests exploring alternatives such as photothermal therapy (PTT) and photodynamic therapy (PDT) due to their non-invasiveness, limited side effects and effective temporal-spatial control. This innovative path points to the search for less aggressive, but effective treatments, aiming to preserve ocular function and reduce tumor recurrence.

Wang, K. et al. (2020) addresses a promising approach using GD2-specific chimeric antigen receptor T lymphocytes, membrane glycosphingolipid, antigen

which is associated with tumor cells. The combination with local release of interleukin (IL)-15 and an injectable hydrogel revealed efficacy in eliminating RB tumor cells without compromising the mouse's vision. This research highlights innovative advances in personalized immune therapy, paving the way for more precise and less invasive strategies.

RB treatment continues to be predominantly based on chemotherapy, being considered the gold standard. However, recent research presented by Munson M.C. et al. (2019) and Bowman R.J.C. et al. (2020) explore alternative and innovative approaches, introducing new horizons in the management of this condition.

Munson MC et al. (2019) highlights the use of topotecan in the form of a hydrogel, an approach that allows for the slow and prolonged release of the therapeutic agent

in RB tumor tissues. This strategy aims to achieve a more efficient and prolonged antitumor effect, minimizing side effects. The application of new formulations and vehicles for chemotherapy represents a promising area of research, seeking to optimize treatment efficacy and improve the quality of life of pediatric patients.

Bowman R.J.C. et al. (2020) focuses on the comparison between intra-arterial chemotherapy (IAC) and intravenous chemotherapy (IVC) in cases of cavitary RB. The results suggest that IAC is more effective, reducing tumor thickness significantly more than IVC. This finding is crucial, providing insights into the appropriate choice of therapeutic approaches based on specific tumor characteristics. The scarcity of literature on the topic, as highlighted by the study, highlights the need for more research in this specific field.

The study by Huo Y. et al. (2019) takes a unique perspective by exploring international travel to obtain medical treatment for retinoblastoma. The observed phenomenon, with a significant proportion of cases in Europe followed by Africa and Asia, highlights the disparity in access to treatment. The absence of reported cases in North America or Oceania suggests significant variations in treatment opportunities in different regions of the world. Discussion raises questions about equity in access to medical care for serious pediatric conditions.

Comparison between studies highlights the complexity of retinoblastoma treatment and the need for diverse approaches. While Munson M.C. et al. (2020) proposes a specific formulation to improve the effectiveness of chemotherapy, Bowman R.J.C. et al. (2020) highlights the importance of the route of administration. Finally, Huo Y. et al. (2019) sheds light on global issues of access to treatment, highlighting significant challenges in some regions of the world. The convergence of these perspectives contributes to a more comprehensive and integrated understanding of the retinoblastoma treatment landscape.

Comparison between studies highlights the need for a personalized approach in the treatment of retinoblastoma. The choice between invasive and non-invasive therapies, as highlighted by Zhang, Y., et al. (2023) and Zheng, W., et al. (2022), reflects the complexity of disease management. While Zhang, Y., et al. (2023) highlights the importance of adapting therapy based on age and individual characteristics, Zheng, W., et al. (2022) suggests that less invasive therapies may offer viable alternatives.

The innovative approach of Wang, K. et al. (2020) with the use of GD2-specific T lymphocytes highlights the growing importance of personalized immune therapy. The combination with local delivery of IL-15 and an injectable hydrogel represents a promising strategy that aims for efficacy without compromising visual function. This variety of approaches highlights the complexity of retinoblastoma treatment, encouraging continued research to improve efficacy and reduce adverse impacts, especially in pediatric populations.

The complexity of RB treatment is evidenced by the need for individualized approaches, considering several factors, such as the stage of the disease, presence of metastases, results of genetic tests and the psychosocial situation of the family (ANCONA-LEZAMA D. et al., 2020). Initial response to treatment also plays a crucial role in determining long-term strategies, emphasizing the importance of judicious choice of initial therapy to avoid unnecessary toxicities.

The Global Retinoblastoma Presentation Study highlights the disparity in access to treatment between developed and underdeveloped countries (FABIAN I.D. et al.,

2022). The estimated three-year survival rate for children diagnosed with retinoblastoma in underdeveloped countries is approximately 50%, while in developed countries, death from retinoblastoma is a rare event. The availability of more sophisticated treatments and investigative resources, such as MRI and focal therapies, is significantly limited in poorer countries. The data suggest not only differences in medical infrastructure, but possibly a more biologically aggressive form of the disease in children from low-income countries.

The effectiveness of enucleation, especially in unilateral cases without extraocular metastasis, is evidenced by the ability to cure 85-90% of patients (CRUZ-GÁLVEZ C.C. et al, 2022). However, the complexity of treatment increases in bilateral cases or with metastasis, requiring a more diversified approach. Conservative treatment, which includes several modalities such as intravenous chemotherapy, transpupillary thermotherapy, laser, photocoagulation, brachytherapy, external beam radiotherapy and local chemotherapy, is indicated in specific situations for ocular preservation.

In addition to traditional approaches, there is a search for new drugs that can expand therapeutic options, considering the toxicity associated with current therapies. Preliminary research has identified compounds, such as survivin inhibitors, antiapoptotic proteins, methyltransferase and kinesin proteins, that may play a role in the management of RB (CRUZ-GÁLVEZ C.C. et al, 2022). The search for more effective and less toxic therapies highlights the constant evolution in the field of retinoblastoma treatment.

FINAL CONSIDERATIONS

Retinoblastoma is the most prevalent primary intraocular neoplasm in children and can manifest unilaterally or bilaterally. Leukocoria is a characteristic present in most cases, giving vital importance to the eye test and the attentive monitoring of parents in the face of changes in photographic images. To improve tracking, applications have been developed that optimize the early detection of this signal. Additionally, genetic diagnostic methods have demonstrated prominence, although their accessibility is still limited. It is concluded, therefore, that, despite the progress made, there remains a need for significant improvements in research, access and image analysis tools for retinoblastoma.

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