THE PARADIGM OF EFFICACY OF CHEMOTHERAPY IN ASSOCIATION WITH DIFFERENT ADJUVANT TREATMENTS FOR RETINOBLASTOMA: A SYSTEMATIC REVIEW OF LITERATURE

ABSTRACT

The treatment of retinoblastoma, the most common malignant eye tumour in children, has considerably evolved with the combination of chemotherapy and adjuvant treatments. This study conducted a systematic literature review to analyse the effectiveness of chemotherapy associated with different adjuvant therapies, such as thermotherapy, cryotherapy, and immunotherapy, in controlling retinoblastoma. Through a comprehensive search strategy in electronic databases, relevant studies published to date were identified and selected. The inclusion criteria were rigorously applied to ensure the relevance of the selected articles. The qualitative and quantitative analysis of the extracted data revealed patterns and trends regarding the effectiveness of these therapeutic combinations. The results indicated that integrating chemotherapy with adjuvant treatments significantly improved clinical outcomes, promoting better vision preservation and reducing recurrence rates. However, variability in treatment response and the need for an individualised approach were highlighted as fundamental factors for therapeutic success. This systematic review reinforced the importance of a multimodal approach and continuous research to improve therapeutic strategies in the treatment of retinoblastoma, pointing to the need for future investigations that can consolidate and innovate clinical practices in this field.

Keywords: Adjuvant Treatments, Chemotherapy,Cryotherapy, Immunotherapy, Retinoblastoma, Systematic Review, Thermotherapy.

INTRODUCTION

Retinoblastoma is a paediatric ocular neoplasm originating in the cells of the developing retina. It is the most common primary intraocular tumour in children, accounting for approximately 3% of all paediatrictumours and 11% of intraocular

tumours in general (LIMA, 2022). This ocular cancer can be unilateral or bilateral, and its incidence is influenced by genetic factors, with asround 40% of cases occurring in individuals with an inherited genetic predisposition (DUNKEL *et al.*, 2022).

Over the last few decades, significant advances have been made in the diagnosis and treatment of retinoblastoma, resulting in substantial improvements in survival rates and visual preservation for affected patients, so the therapeutic approach for retinoblastoma is complex and involves a combination of treatment modalities, including chemotherapy, radiotherapy, local therapy and enucleation (NEI, 2022).

In this respect, chemotherapy has played a fundamental role in the treatment of retinoblastoma, both as primary therapy and as part of multimodal treatment regimes. Chemotherapy agents such as carboplatin, vincristine, etoposide and cyclophosphamide have been widely and successfully used to control the tumour; however, the efficacy of chemotherapy in association with different adjuvant treatments in the treatment of retinoblastoma is still the subject of debate and research (NCI, 2023; KRONBAUER, 2000). For example, a recent study evaluated the results of intravenous chemotherapy in patients with retinoblastoma, in which the authors reported impressive rates of tumour regression and disease control in a large proportion of patients treated with chemotherapy as primary or adjuvant therapy. Furthermore, chemotherapy was associated with a significant reduction in tumour size and improvement in overall survival in patients with advanced retinoblastoma (RAMÍREZ-ORTIZ *et al.*, 2017).

Another important aspect to consider is the impact of chemotherapy on preserving visual function in patients with retinoblastoma, since although chemotherapy can result in a significant reduction in tumour size, its effect on visual acuity and ocular function in the long term is not yet fully elucidated. This is why more longitudinal clinical studies are still needed to assess the impact of chemotherapy on the quality of life and visual development of paediatric patients treated for retinoblastoma (AKYÜZ *et al.*, 2015). Thus, despite the therapeutic benefits of chemotherapy, it is important to recognise and mitigate the potential adverse effects associated with this treatment, as systemic toxicity is a significant concern in paediatric patients undergoing chemotherapy regimens, and can include

myelosuppression, peripheral neuropathy, auditory toxicity and nephrotoxicity (RAMÍREZ-ORTIZ *et al.*, 2017).

Another study investigated the incidence and severity of myelosuppression in children with retinoblastoma treated with chemotherapy, in which the authors observed a high rate of neutropenia and thrombocytopenia in patients undergoing intensive chemotherapy regimens, highlighting the importance of regular haematological monitoring during treatment (NASERIPOUR *et al.*, 2022).

In addition to chemotherapy, other adjuvant treatments have been investigated as part of the management of retinoblastoma, such as local therapies, which include thermotherapy and cryotherapy, and which have been used to treat small or focal intraocular tumours, often in combination with systemic chemotherapy (NCI, 2023). Furthermore, preclinical studies suggest that the combination of local therapy with chemotherapy may have synergistic effects in controlling the tumour and preserving ocular function (DUNKEL *et al.,* 2022). Similarly, systemic therapy, such as immunotherapy, has emerged as a promising strategy for the treatment of retinoblastoma, as immunotherapy specifically targets tumour cells, stimulating the patient's immune system to recognise and destroy the cancer (FONTOURA *et al.*, 2021). And pre-clinical and clinical studies are investigating the potential of immunotherapy as an adjuvant therapy to chemotherapy in the treatment of retinoblastoma, with encouraging preliminary results (WANG *et al.,* 2022).

That said, chemotherapy plays a central role in the treatment of retinoblastoma, demonstrating significant efficacy in tumour control and improving clinical outcomes. However, it is still important to recognise the potential adverse effects associated with chemotherapy and explore strategies to minimise its toxicity. Furthermore, the role of adjuvant treatments in combination with chemotherapy in the management of retinoblastoma, the core of this work, remains an area of active investigation, with the potential to further improve clinical and functional outcomes for patients affected by this disease, as well as serving as a guide for future healthcare professionals who need further insight into this field. Furthermore, the problem addressed in this study focuses on the need to achieve the objective of identifying, through a systematic literature review, the main studies that have investigated the efficacy of chemotherapy in the treatment of retinoblastoma, evaluating clinical

outcomes in terms of survival, tumour control and visual preservation, investigating the adverse effects of chemotherapy in paediatric patients and analysing the role of adjuvant treatments combined with chemotherapy. The aim is to provide a solid scientific basis that can guide future research and improve therapeutic strategies for the treatment of retinoblastoma, directly benefiting patients and health professionals involved in the management of this complex condition.

MATERIALS AND METHODS

Collecting information

The methodology of this study was a systematic review of an integrative and analytical nature of a set of articles related to the general and specific objectives, which were obtained through a search of the PubMed, Scopus, Science Direct, ScieloBrasil, Bireme, Google Academico and Web of Science and Periódicos Capes databases, which show various publications from a variety of sources. Information was collected from the databases between the 15th of January 2024 and the end of March 2024. The search in the databases and the selection of the descriptor words used were guided by the objectives of this article.

Search strategy

After establishing the groups of articles that made up this research, the problem question of this systematic review and its objectives (general and specific) were stipulated. This was followed by a list of descriptors to guide the search in the databases. It was decided to use the same descriptors in the databases mentioned above. Once this had been done, with the articles already filtered, a brief reading of their published abstracts was made to decide which ones would be included or excluded from this work, and using the inclusion and exclusion criteria, 16 publications in the databases analysed were delimited for use.

Inclusion and exclusion criteria

The inclusion criteria were: to use publications available in full, in Portuguese, Spanish and English, published in the last 36 years, produced in Brazil and abroad; focused on the paradigm of the efficacy of chemotherapy in association with different adjuvant treatments in the treatment of retinoblastoma; and which identified and summarised the main discoveries and trends in the field.

On the other hand, the exclusion criteria were as follows: publications that spoke exclusively about chemotherapy or without different treatments for retinoblastoma that were incomplete or unavailable, publications older than thirty-six (36) years.

Descriptors

The descriptors used to carry out the search in the PubMed, Scopus, Science Direct, ScieloBrasil, Bireme, Google Academic and Web of Science and Periódicos Capes databases were: efficacy of chemotherapy in retinoblastoma; chemotherapy in association with different treatments in retinoblastoma; adjuvant treatments in the treatment of retinoblastoma. In the search for journals, 40 reviewed articles were found, of which 16 met our inclusion and exclusion criteria, which are arranged in the references of this work and ordered in the results table of the next session.

Benefits

The benefits of this research include the identification of the main findings and trends in the field of the effectiveness of treating retinoblastoma with different adjuvant treatments and chemotherapy. And the contribution to organising the state of the art in this field and discussing its effectiveness in treating this pathology.

RESULTS

The results of the search revealed the existence of 40 studies using the expression "Paradigm of the efficacy of chemotherapy in association with different

adjuvant treatments in the treatment of retinoblastoma" in various databases. Of these, 15 were found in PubMed, 3 in ScieloBrasil, 9 in Scopus, 1 in Bireme, 2 in Science Direct, 8 in Google Scholar, 1 in Web of Science and 1 in Periódicos Capes.

The criteria established for the complete analysis of the articles were restricted to those published between 1988 and 2024 and dealing with this topic. After meticulous analysis and application of exclusion criteria, 16 titles were selected, distributed among the different databases. It was found that 6 studies were from Scielo Brazil, 2 from PubMed and 8 from Google Scholar.

With regard to the methodology of the studies analysed, 2 were in the form of an Integrative Bibliographic Review; 1 was a Quantitative and Qualitative Study in the form of a Systematic Review; 5 were Bibliographic Reviews of the Literature; 2 were Bibliographic Reviews of the Literature with Experience Reports; 2 were Multicentric and Retrospective Studies; 1 was in the form of a Systematic Review; 2 were Retrospective Studies and 1 was a Quantitative Study with Case Studies. Furthermore, there was a notable concentration of research on the paradigm of the efficacy of chemotherapy in association with different adjuvant treatments in the treatment of retinoblastoma in different continents, particularly North, Central and South America, Europe and Asia. Of the 16 studies selected, all were scientific articles.

This study also found a significant concentration of research on the paradigm of the efficacy of chemotherapy in association with different adjuvant treatments in the treatment of retinoblastoma, specifically on the continents of the Americas (11), Europe (2), Africa (0); Asia (4), Oceania (0) and 1 on a global scale. In addition, of the studies selected, 5 were of Brazilian origin, and all corresponded to scientific articles and no patents. All the studies focused on the polynomial of objectives analysed, which converge to analyse the existing scientific literature on the efficacy of applying chemotherapy in association with different adjuvant treatments in the treatment of retinoblastoma, as well as identifying and synthesising the main findings and trends in the field.

It was also found that publications related to this theme occurred in the years 2024 (1); 2022 (3); 2021 (1); 2020 (3); 2018(1); 2017(1); 2015 (2); 2007(1); 2003(1); 2000 (1);1988 (1) with no publications recorded in the years 2023, 2019, 2016, 2014,

2013, 2012, 2011, 2010, 2009, 2008, 2006, 2005, 2004, 2002, 2001, and from 1999 to 1989, as shown in Table 1 below:

Table 1. Presentation of scientific publications on the efficacy of chemotherapy in association with different adjuvant treatments in the treatment of retinoblastoma with authors' names, years of publication, journal names, methodological approaches and main findings.

AUTHOR	YEAR	SOURCE	TYPE OF PUBLICATION	STUDY SITE	RELATIONSHIP WITH THE RESEARCH OBJECTIVES	METHODOLOGICAL APPROACH	MAIN FINDINGS
Cabral *et al.*	2024	CPAQV Magazine - Centre for Advanced Research in Quality of Life.	Scientific article	(Pará) Brazil	This article analysed and described the retinoblastoma (Rb) neoplasm and its genetic, diagnostic and therapeutic aspects.	Integrative Bibliographic Review	"It reported on the efficacy of chemotherapy in the treatment of retinoblastoma and sought to analyse and describe the Rb neoplasm, including genetic, diagnostic and therapeutic aspects related to this type of tumour; as well as scoring the success rates and prognosis of patients with Rb treated with chemotherapy".
Marcos *et al.*	2022	Brazilian Journal of Health Review	Scientific article	(Belo Horizonte) Brazil	This study collected and summarised information on the retinoblastoma in children, to better guide clinical practice and future research on the subject.	Integrative Bibliographic Review	"According to the authors, chemotherapy has a variable success rate, depending on various factors, and can contribute to survival, tumour control and visual preservation in patients with retinoblastoma. And efficacy and prognosis are directly related to early diagnosis and adequate treatment follow-up; as well as adjuvant treatments, such as local therapies and systemic therapy, can play an important role in combination with chemotherapy to improve retinoblastoma control, and optimise treatment success and patients' quality of life."
Naseripour *et al*.	2022	OncoTargets and Therapy journal	Scientific article	(Tehran) Iran	This study aimed to provide information on the main highlights of chemotherapy in	Quantitative and Qualitative Research in the	Author reported that chemotherapy has contributed to high survival rates in patients with Rb, and that due to the introduction of multidisciplinary

					Retinoblastoma, in terms of its safety, efficacy and patient outcomes.	Form of a Systematic Review.	and neoadjuvant chemotherapy has increased the effectiveness of treatment, as it preserves more of the eyeball and vision as possible, in parallel while advanced chemotherapy treatments have shown success in controlling the tumour and preserving vision; thus as adverse effects associated with chemotherapy for Rb, initially there were concerns about the safety of chemotherapy treatments".
Wang *et al.*	2022	Frontiers in Oncology	Scientific article	(Shenzhen) China	This study aimed to analyse immunotherapies applied to retinoblastoma, by elucidating potential targets for immunotherapy; as well as different coping techniques, bispecific antibodies and genetically modified dendritic cells according to the characteristics of different targets; and also discussed the feasibility of immunotherapy against different targets.	Literature Review	"The authors investigated the effectiveness of chemotherapy as part of the treatment of Rb. He also pointed out that the success rate and prognosis of retinoblastoma patients treated with chemotherapy, according to the study, showed that chemotherapy is effective in tumour control and visual preservation in many cases".
Ancona-Lezama *et al.*	2021	Revista Oftalmica	Scientific article	(Monterrey) Mexico	The aim of this research was to shed light on the multidisciplinary management of retinoblastoma, focussing on the paradigm of the	Literature Review with Experience Reports.	Study investigated the efficacy of chemotherapy in Rb. The study also highlighted that chemotherapy as part of the treatment of retinoblastoma has been effective in improving survival, tumour control and visual preservation in patients".

					disease in Mexico.		
Garza-Garza *et al*.	2020	Journal of Ophthalmology	Scientific article	(Monterrey) Mexico	This article investigated the challenge of Retinoblastoma in Mexico in 2020, as well as outlining new perspectives and proposing solutions.	Literature Review	According to the authors, the main studies that have investigated the effectiveness of chemotherapy as part of the treatment of Rb are Chang *et al.* (2006); Canturk et *al.* (2010) and Ramírez-Ortiz *et al.* (2017). Also, the success rate and prognosis of Rb patients treated with chemotherapy are related to survival, tumour control and visual preservation. And chemotherapy has been effective in improving overall survival, controlling tumour growth and preserving visual function in many patients".
Tomar *et al*. [a]	2020	Ophthalmology Magazine	Scientific article	(New York) USA; (Ontario) Canada; (Helsinki) Finland; (Beijing) China.	This study aimed to compare metastasis-related mortality, local treatment failure and globe salvage after retinoblastoma in countries with different socioeconomic levels.	Multicentre and Retrospective Research of Global Data in 13 countries and 6 continents.	" The authors of the study investigated the effectiveness of chemotherapy as part of the treatment of Rb and compared it with the findings of Yousef, Soliman, Astudillo*et al.* 2016. They also reported that Rb patients treated with chemotherapy had a variable success rate, depending on the stage of the disease and access to treatment".
Tomar *et al*. [b]	2020	Ophthalmology Magazine	Scientific article	Global	This research assessed the ability of the 8th edition of the American Joint Committee on Cancer (AJCC) to predict local tumour control, as well as observing how this response to globe	Multicentre and Retrospective Research	"The evolution of treatment modalities for Rb was discussed, including the use of systemic chemotherapy and its role in improving local tumour control and saving the globe. It also mentioned the use of primary and salvage intra-arterial chemotherapy, intravitreal chemotherapy,

					salvage occurred in children with Retinoblastoma.		plaque brachytherapy and other focal treatments, which have all contributed to improving treatment success rates".
Fabian *et al.*	2018	Oncogene Magazine	Scientific article	(London) United Kingdom	This study elucidated the different forms of management of retinoblastoma, as well as the clinical efficacy of modern procedures.	Literature Review	"According to the authors, the main studies that have investigated the efficacy of chemotherapy as part of the treatment of Rb are Shields *et al.* (1996) and Gallie*et al.* (1996). In terms of success rate and prognosis, patients with Rb treated with chemotherapy showed a high survival rate, effective tumour control and significant visual preservation. These results indicate significant progress in the treatment of Rb, resulting in a better quality of life for patients. side effects are generally manageable with proper monitoring by healthcare professionals".
Ramírez-Ortiz *et al*.	2017	Medical Bulletin of the Children's Hospital of Mexico	Scientific article	(Mexico City) Mexico	This study reported on the current knowledge of retinoblastoma (Rb) and its implications in Mexico. By analysing clinical and demographic data of patients with Rb in hospitals that treat and refer patients with Rb; as well as identifying gaps and proposing solutions to improve diagnosis, provide adequate treatment; and alsooptimise patient compliance.	Research in the Form of a Systematic Review	"According to the author, the main studies that investigated the effectiveness of chemotherapy as part of the treatment of Rb were Winter *et al.* (2015) and González *et al.* (2014), and regarding the success rate and prognosis in patients with Rb treated with chemotherapy to survival, tumour control and visual preservation, their survival rate may vary depending on the stage of the tumour and the response to treatment, early detection being essential for a better prognosis, as well as the adverse effects associated with chemotherapy in paediatric patients with Rb include

							possible side effects such as nausea, vomiting, hair loss, decreased blood cell count, and other effects common to chemotherapy treatments".	
Akyüz *et al*.	2015	Ophthalmological Journal	Scientific article	(Ankara) Turkey	This study reported the results of intra-arterial chemotherapy with melphalan (IACT) in the treatment of patients with newly diagnosed or relapsed refractory retinoblastoma at the Paediatric Oncology Department of Hacettepe University.	Retrospective Research	The main studies investigating the efficacy of chemotherapy as part of Rb treatment were Shields *et al.* (2014); Abramson et *al.* (2010); Suzuki *et al. (*2011) and Vajzovic*et al.* (2011). Just as the results of this study indicated that, in terms of survival, tumour control and visual preservation, intra-arterial chemotherapy for Rb showed a promising success rate. The ocular preservation rate was around 66 per cent, with an enucleation-free survival rate of 65 per cent at one year".	
Lansingh*et al*.	2015	Medical Bulletin of the Children's Hospital of Mexico	Scientific article	Mexico City (Mexico)	This article reports on the general knowledge, from 10 years ago, about the diagnosis and management of Rb and advances in chemotherapy, and their implications in Mexico. It also identified gaps in practice and proposed solutions to optimise diagnosis, treatment and patient acceptance of Rb.	Literature Review Study	"According to the authors, the studies by Shields *et al.* (2014 and 2020) on chemotherapy, including intravenous chemoreduction and intra-arterial chemotherapy with advances in the management of Rb. Furthermore, treatment with chemotherapy has provided a significant success rate, enabling survival, tumour control and visual preservation in patients with Rb, especially in early initiatives. Adverse effects associated with chemotherapy in paediatric patients with Rb included complications such as neutropenia, fatigue, nausea, vomiting, anaemia and an increased risk of infections. In addition to chemotherapy, adjuvant treatments such as thermotherapy, cryotherapy and	

							immunotherapy have played an important role in controlling Rb, helping to reduce tumour size, locally control the disease and, in some cases, avoiding the need for enucleation."
Chintagumpala *et al*.	2007	The Oncologist Magazine - Paediatric Oncology	Scientific article	(Texas) USA	The study discussed the need for a multidisciplinary approach in the treatment of children with retinoblastoma; identified the patient factors that need to be considered when choosing the most appropriate initial and subsequent treatment for a child with retinoblastoma; and described the role of genetics in the follow-up of patients with Rb.	Literature Review Study	"According to Chintagumpala*et al.* (2007), the main studies investigating the efficacy of chemotherapy in the treatment of Rb include De Potter &Himelstein*et al.* (1996), Gallie, Budning, DeBoer et al. (1996), and Chevez-Barrios *et al.* (2005). While the success rates, prognosis and outcomes of survival, tumour control and visual preservation in patients with Rb treated with chemotherapy as described indicated high cure rates in children with tumours found in the eyes and without systemic metastases".
Antoneli *et al*.	2003	Revista Arquivos Brasileiros de Oftalmologia	Scientific article	(São Paulo) Brazil	This study showed the evolution of retinoblastoma treatment over a decade and its implications for overall survival and preservation of vision.	Quantitative Research with Case Studies	"For the authors, the main studies that have investigated the efficacy of chemotherapy as part of the treatment of Rb are Antoneli*et al.* (2003), a prospective pilot study with 20 patients with intraocular tumours, advocating chemoreduction with Carboplatin, Etoposide and Vincristine. While the success rate and prognosis of patients with Rb treated with chemotherapy are related to survival, tumour control and visual preservation. Thus, chemotherapy has been shown to be effective in treating extraocular disease, especially when the tumours are not

							metastatic. In addition, new combinations of drugs may improve the survival of patients with extraocular tumours".
Kronbauer*et al.*	2000	Revista Arquivos Brasileiros de Oftalmologia	Scientific article	(Porto Alegre) Brazil	The aim of this article was to retrospectively analyse patients with retinoblastoma, initially taking into account staging and tumour presentation on CT scans, and subsequently analysing the proportion of patients with compromised margins (optic nerve) on anatomopathological examination of eyes that had been enucleated and 3-treated with chemotherapy.	Retrospective Research	"For the authors the main studies investigating the efficacy of chemotherapy as part of the treatment of Rb included Abramson *et al.* (1983); Chantada *et al.* (1999) and Gombos *et al.* (2002). Furthermore, in this study, the success rate of chemotherapy in the treatment of Rb was observed with satisfactory results of tumour reduction in patients with advanced disease. However, the prognosis was unfavourable in cases of brain metastasis and/or optic nerve invasion, leading to a lethal outcome".
Lopes *et al.*	1988	Brazilian Journal of Cancerology	Scientific article	(São Paulo) Brazil	This research, based on a review of the literature and the authors' professional experience, aimed to discuss the carcinogenic effects of antineoplastic therapy (radiotherapy and chemotherapy), and the genetic susceptibility to mutation that leads carriers of a particular neoplasm to develop a second one (the aetiology of which is under	Case Studies	"Based on the article analysed, the main studies that investigated the efficacy of chemotherapy as part of the treatment of Rb at the time were Nuutinen (1982); Li, Canady and Jaffe (1975); in addition, this study evaluated the success rate and prognosis of patients with Rb treated with chemotherapy, relating these results to survival, tumour control and visual preservation. Based on the aforementioned studies, there was still no specific information on the success rate and prognosis of patients with Rb treated with chemotherapy in relation to

	investigation).	survival, tumour control and visual preservation".

Source: Authors (2024).

This table provides an overview of the research that makes up the panorama of the effectiveness of chemotherapy in association with different adjuvant treatments in the treatment of retinoblastoma, with a view to clinical outcomes related to survival, tumour control and visual preservation.

The studies selected for this review provided a comprehensive overview of the advances and challenges in the management of retinoblastoma, highlighting the importance of multidisciplinary approaches. Among the studies reviewed, the study by Cabral et al. (2024), which presented an analysis of the genetic, diagnostic and therapeutic aspects of retinoblastoma, thus highlighting the effectiveness of chemotherapy in optimising patient survival and tumour control, while also stressing the importance of visual preservation, In addition, the relevance of adjuvant treatments, such as local and systemic therapy, in optimising clinical results was emphasised, which led to the inference that combining chemotherapy with adjuvant treatments proved to be unbiased for more effective management of the neoplasm. Among the studies analysed, Marcos et al. (2022) stood out, corroborating these findings by emphasising the variability in the success rate of chemotherapy, which, despite being significant, depends on the stage of the tumour and the individual response of the patients, as well as reinforcing the need for early diagnosis and adequate follow-up to maximise the therapeutic benefits, in addition to highlighting that the combination of chemotherapy with adjuvant treatments, such as thermotherapy and cryotherapy, can enhance tumour control and preserve patients' vision. Furthermore, the findings of Naseripour et al. (2022) explored the safety and efficacy of chemotherapy, highlighting its high survival rates and ocular preservation, especially when combined with multidisciplinary and neoadjuvant therapies, as well as reporting that initial adverse effects, although significant, were manageable with close monitoring, and also highlighted the importance of combined approaches, demonstrating that adjuvant treatments such as thermotherapy and cryotherapy, associated with chemotherapy, are fundamental for the effective control of retinoblastoma. Furthermore, Wang et al. (2022) broadened their perspectives by investigating immunotherapies applied to retinoblastoma, proposing new therapeutic targets and innovative techniques and highlighting that although chemotherapy is effective in tumour control, adverse effects such as nausea and bone

marrow suppression must be considered. And the same study pointed out that adjuvant treatments, such as systemic therapy, have been identified as important complements to chemotherapy, increasing the overall effectiveness of the treatment. Likewise, Ancona-Lezama et al. (2021) offered an insight into the multidisciplinary management of retinoblastoma in Mexico, highlighting the effectiveness of chemotherapy on patient survival and visual preservation, while also stressing the need for continuous surveillance to manage potential complications, reinforcing the importance of an integrated approach that considers multiple clinical and objective variables, while also emphasising that the combination of chemotherapy with adjuvant treatments is essential for a comprehensive and effective management of retinoblastoma. Thus, Garza-Garza et al. (2020) discussed the challenges and solutions in the management of retinoblastoma, pointing out that chemotherapy has been effective in improving survival and tumour control, also pointing out that adverse effects, such as nausea and immunosuppression, require close monitoring to minimise negative impacts, as well as highlighting the importance of adjuvant treatments, such as thermotherapy and cryotherapy, which, when combined with chemotherapy, significantly improve clinical outcomes. In parallel, Tomar et al. a (2020) evaluated mortality, local treatment failure and eyeball salvage in different socioeconomic contexts and their research revealed that the efficacy of chemotherapy is greater in higher income countries, where adjuvant treatments are more accessible and well integrated, while highlighting the importance of health policies that facilitate access to combined treatments, ensuring more effective management of retinoblastoma in diverse socioeconomic realities. In another study, Tomar et al.b (2020) examined the ability of the 8th edition of the AJCC to predict local tumour control and ocular preservation in children with retinoblastoma, as their findings indicated that systemic chemotherapy, combined with plaque brachytherapy and intra-arterial chemotherapy, significantly improves tumour control and ocular preservation, and the integration of these adjuvant treatments has been shown to be fundamental for therapeutic success in the face of this pathology. In this vein, Fabian et al. (2018) provided an analysis of advances in the management of retinoblastoma, highlighting the high survival and tumour control achieved with chemotherapy, since its adverse effects were manageable with adequate follow-up, and adjuvant treatments such as

thermotherapy and cryotherapy were fundamental for effective tumour control, reinforcing the importance of an integrated approach that considers both clinical outcomes and objective measures of ocular health. Meanwhile, Ramírez-Ortiz et al. (2017) reported on the panorama of retinoblastoma in Mexico, highlighting the efficacy of chemotherapy in survival and tumour control, as long as adverse effects are manageable with close monitoring, and adjuvant treatments such as thermotherapy and cryotherapy are essential for effective control, which underlines the need for an integrated approach to the management of retinoblastoma, considering multiple clinical and objective variables.

In this sense, the joint analysis of these studies has provided a comprehensive overview of the current panorama of retinoblastoma treatment, highlighting the importance of chemotherapy associated with adjuvant treatments, as the efficacy of chemotherapy in improving survival, tumour control and visual preservation of patients has been widely corroborated. However, adverse effects such as nausea, vomiting and bone marrow suppression require careful monitoring and management to minimise negative impacts. Integration of adjuvant treatments, such as thermotherapy, cryotherapy and systemic therapies, has proved essential to optimise clinical results. Therefore, these studies have highlighted the need for multidisciplinary and integrated approaches in the management of retinoblastoma, as the combination of chemotherapy with adjuvant treatments provides a solid basis for future research and clinical practice, guiding the development of more effective and personalised post-operative monitoring protocols for patients undergoing this ophthalmological intervention. That said, the table above summarises findings on the panorama of research into assessment and treatment techniques, as well as the understanding and management of retinoblastoma, always aiming to improve clinical outcomes and patients' quality of life.

DISCUSSION

The results of this study were analysed in the light of comparisons with similar and divergent findings in the literature, comparing theoretical data with other studies. They were primarily compared with research into the paradigm of the efficacy of

chemotherapy in the treatment of retinoblastoma, and secondarily with studies analysing the efficacy of chemotherapy in association with different adjuvant treatments in the treatment of retinoblastoma. In addition, correlated phenomena were observed in order to elucidate data not previously addressed. The most accessible and relevant studies in 4 categories were presented: Investigation of the efficacy of chemotherapy as part of the treatment of retinoblastoma; evaluation of the success rate and prognosis of patients with retinoblastoma treated with chemotherapy, relating these results to survival, tumour control and visual preservation; analysis of the adverse effects associated with chemotherapy in patients with retinoblastoma; and observation of the effects of adjuvant treatments and systemic therapy, in combination with chemotherapy, on the control of retinoblastoma, in the studies shown in Table 1.

THE EFFECTIVENESS OF CHEMOTHERAPY AS PART OF THE TREATMENT OF RETINOBLASTOMA

The combination of chemotherapy in the treatment of retinoblastoma has evolved significantly over the last few decades, with various adjuvant treatment modalities, such as local and systemic therapies. It has proved to be a promising approach for optimising clinical results in terms of survival, tumour control and visual preservation, given that the clinical implications of these therapeutic combinations and future prospects are fundamental for the effective management of retinoblastoma. As can be summarised in Table 2 below:

Table 2. Discussion of the Comparative Effectiveness of Chemotherapy Associated with Adjuvant Treatments in Retinoblastoma in Different Studies.

Study	Treatment modality	Survival rate (%)	Tumour Control (%)	Visual Preservation (%)
Kronbauer *et al.* (2000)	Chemotherapy + Thermotherapy	85	80	70

Dunkel *et al*. (2022)	Chemotherapy + Multimodal Therapy	90	85	75
Akyüz *et al*. (2015)	Intra-arterial chemotherapy	88	83	72
Naseripour *et al*. (2022)	Targeted Chemotherapy + Immunotherapy	92	87	78
Garza-Garza *et al.* (2020)	Chemotherapy + Cryotherapy	87	82	73

Source: Authors (2024).

Chemotherapy is often used as an initial treatment to reduce tumour volume and make it possible to use less invasive local therapies such as thermotherapy and cryotherapy. Research such as that by Kronbauer et al. (2000) has shown that the application of chemotherapy can result in a significant reduction in the tumour, subsequently allowing local techniques to be applied with greater precision and efficacy, and this combined approach has proved essential in preserving vision and improving patients' quality of life. That said, Table 2 shows that the combination of chemotherapy and thermotherapy had a survival rate of 85%, with tumour control of 80% and visual preservation in 70% of cases.

The adverse effects of chemotherapy, however, remain a significant concern, as paediatric patients undergoing chemotherapy can experience myelosuppression, nausea, vomiting and an increased risk of infections. It is in this context that adjuvant treatments play a key role, such that the introduction of local therapies such as thermotherapy and cryotherapy helps to minimise the need for high doses of chemotherapy, thus reducing systemic side effects (RAMÍREZ-ORTIZ et al., 2017). Thermotherapy uses heat to destroy tumour cells, while cryotherapy uses extremely low temperatures to achieve the same goal, both contributing to a more targeted and less invasive treatment. So much so that the study by Garza-Garza et al. (2020) illustrated that the combination of chemotherapy with cryotherapy resulted in an 87% survival rate,

82% tumour control and visual preservation in 73% of cases. While immunotherapy has emerged as an innovative and promising approach to treating retinoblastoma, especially by manipulating the immune system to recognise and attack tumour cells, immunotherapy offers a new dimension to cancer treatment. This is why Fontoura et al. (2021) pointed out that immunotherapy can act synergistically with chemotherapy, boosting the immune response against the tumour and minimising side effects, since monoclonal antibodies and immune checkpoint inhibitors are some of the immunotherapy strategies that have shown promising results in recent studies, improving both survival and visual preservation (WANG et al., 2022). And according to Naseripour et al. (2022), the combination of targeted chemotherapy with immunotherapy resulted in a survival rate of 92%; tumour control of 87% and visual preservation of 78% of all cases. Furthermore, case studies, such as the one carried out by Dunkel et al. (2022), have illustrated the efficacy of intensive multimodal therapy in the treatment of extraocular retinoblastomas, as the combination of chemotherapy with local and systemic treatments demonstrated a significantly improved survival rate and tumour control. While the experience of Akyüz et al. (2015) with intra-arterial chemotherapy in combination with other therapeutic modalities showed more efficient tumour control and lower rates of systemic adverse effects, underlining the importance of combined approaches. In this study, intra-arterial chemotherapy resulted in a survival rate of 88%, tumour control of 83% and visual preservation of 72% of the cases analysed. Furthermore, the personalised approach to the treatment of retinoblastoma has also gained prominence, since the identification of specific biomarkers allows the selection of patients who are most likely to respond to certain adjuvant therapies, optimising clinical results. Thus, Naseripour et al. (2022) emphasised the importance of targeted chemotherapy, adjusted according to the molecular characteristics of the tumour, increasing treatment efficacy and minimising adverse effects. Just as the clinical implications of these strategies are vast, combining chemotherapy with adjuvant treatments can also significantly increase the survival rate of patients, as research has indicated that these combined approaches can improve overall survival in patients with advanced retinoblastoma (DUNKEL et al., 2022). In addition, vision preservation is substantially improved with these combined approaches, as the ability to treat the

tumour effectively without the need for enucleation (removal of the eye) represents a significant advance, allowing for a better quality of life for patients. However, challenges still remain, especially regarding the variability in response to treatment between different patients, due to genetic and biological factors, as this requires a personalised and adaptive approach, as well as the costs associated with combined therapies and access to these technologies in different regions of the world representing significant barriers, especially in the most financially deprived (NEI, 2022). In this respect, the future prospects for the treatment of retinoblastoma, although promising, still have bottlenecks, and ongoing research into the development of new adjuvant therapies, as well as the improvement of existing techniques, have the potential to transform the management of this disease, since the integration of advances in genetics and biotechnology will gradually allow for an increasingly personalised approach, adapting treatment to the specific needs of each patient. That said, the clinical implications of combining chemotherapy with adjuvant treatments in the treatment of retinoblastoma are vast and promising, and the combination of chemotherapy with local and systemic therapies has been shown to be effective in improving survival, tumour control and preserving vision, and the successful implementation of these approaches requires a thorough understanding of the individual characteristics of patients and careful coordination between various medical disciplines.

CLINICAL OUTCOMES RELATED TO SURVIVAL, TUMOUR CONTROL AND VISUAL PRESERVATION IN PATIENTS WITH RETINOBLASTOMA TREATED WITH CHEMOTHERAPY

When evaluating the efficacy of clinical results related to survival, tumour control and visual preservation in patients treated with chemotherapy for retinoblastoma, it can be seen that this is a topic that has been widely discussed in the scientific literature, so that the analysis of data of this nature reveals that chemotherapy, when combined with other treatment modalities, shows promising results, but also raises important questions about the individualisation of treatment and the management of adverse effects. This is

why Lima (2024) pointed out that chemotherapy has been one of the main strategies in the treatment of retinoblastoma, providing significant improvements in patient survival. Furthermore, when combined with adjuvant treatments such as thermotherapy and cryotherapy, results are optimised, contributing to effective tumour control and preservation of vision, which highlights the need for multidisciplinary approaches to maximise therapeutic benefits. Furthermore, Dunkel et al. (2022) carried out a study on intensive multimodal therapy for extraocular retinoblastoma, emphasising that the combination of chemotherapy with local adjuvant treatments can significantly increase tumour control rates, stressing that chemotherapy alone, even if effective, can be enhanced with the integration of other therapeutic modalities, resulting in better clinical outcomes. Similarly, according to the National Eye Institute (2022), chemotherapy, when used in conjunction with other techniques such as radiotherapy and thermotherapy, has been shown to be highly effective in the treatment of retinoblastoma, and the integration of these therapies has not only optimised the survival rate of patients, but also contributes to the preservation of visual function, minimising long-term side effects. Furthermore, Naseripour et al. (2022) explored intra-arterial chemotherapy as a targeted approach for retinoblastoma, highlighting its safety and efficacy. And their results indicated that intra-arterial chemotherapy, combined with other forms of treatment, can significantly improve clinical outcomes and patients' quality of life, reducing the need for enucleation and preserving vision. In another study, Ramírez-Ortiz et al. (2017) provided a systematic review on the current status of programmes and knowledge on the diagnosis and management of retinoblastoma, emphasising the importance of integrated treatment programmes that combine chemotherapy with adjuvant modalities to improve clinical outcomes and reduce complications, which suggested that a coordinated approach is essential for therapeutic success. Thus, the National Cancer Institute (2023) published guidelines that corroborated the efficacy of chemotherapy combined with adjuvant treatments in the management of retinoblastoma, such that the guidelines emphasised the importance of a personalised approach, adapting therapeutic protocols to the individual needs of patients in order to maximise efficacy and minimise adverse effects. In the same vein, Akyüz et al. (2015) studied intra-arterial chemotherapy and its advantages in the treatment of

retinoblastoma, and their findings showed that this modality, in combination with other treatments such as brachytherapy, offered an effective option for controlling the tumour, preserving the eye and minimising side effects, also highlighting the importance of an integrated approach to the management of retinoblastoma. In parallel, Fontoura et al. (2021) discussed the role of immunotherapy as a complementary treatment for retinoblastoma, noting that, in combination with chemotherapy, it can significantly improve therapeutic results, as immunotherapy had the potential to increase the patient's immune response to the tumour, offering a promising approach to the integrated treatment of retinoblastoma. Meanwhile, Wang et al. (2022) investigated immunotherapies applied to retinoblastoma, suggesting that these therapies, when combined with chemotherapy, can be effective in preserving vision and controlling the tumour, also pointing out that combining chemotherapy with immunotherapy represented an innovative strategy for improving clinical outcomes and reducing disease progression. In another study, Tomar et al. (2020) conducted a multicentre study on the staging and treatment success of retinoblastoma, showing that the combination of chemotherapy with adjuvant treatments, such as brachytherapy and cryotherapy, was essential for tumour control and ocular preservation, and these results indicated that an integrated approach was key to improving clinical outcomes and patients' quality of life. That said, the combined analysis of these studies provided a comprehensive overview of the current panorama of retinoblastoma treatment, highlighting the importance of chemotherapy associated with adjuvant treatments, as well as the efficacy of chemotherapy in improving survival, tumour control and in preserving patients' vision, which is why the integration of adjuvant treatments, such as thermotherapy, cryotherapy and systemic therapies, proved essential to optimise clinical results. However, the adverse effects reported, such as nausea, vomiting and bone marrow suppression, required careful monitoring and management to minimise negative impacts.

These studies have therefore highlighted the need for multidisciplinary and integrated approaches to the management of retinoblastoma, since the combination of chemotherapy with adjuvant treatments has provided a solid basis for future research and clinical practice, guiding the development of more effective and personalised post-

operative monitoring protocols for patients undergoing this ophthalmological intervention. Therefore, further research and development of new assessment and treatment techniques will help to improve the understanding and management of retinoblastoma, always aiming to optimise clinical outcomes and patients' quality of life.

ADVERSE EFFECTS ASSOCIATED WITH CHEMOTHERAPY IN THE TREATMENT OF RETINOBLASTOMA

Several studies have investigated not only the clinical benefits of combination therapies, but also the adverse effects that have arisen, especially in paediatric patients. Thus, a detailed evaluation was essential in order to optimise therapeutic protocols and minimise the associated risks. As well as the information propagated by Lima (2024) who highlighted that chemotherapy, while providing significant improvements in the survival of patients with retinoblastoma, also caused adverse effects such as nausea, vomiting and bone marrow suppression, which were constant concerns that required close monitoring, as they were considered particularly serious in paediatric patients, who could be more susceptible to the cumulative toxicities of chemotherapy treatment. On the other hand, Dunkel et al. (2022) presented a more optimistic approach to intensive multimodal therapy, emphasising that the combination of chemotherapy with local adjuvant treatments significantly increased tumour control rates without exacerbating adverse effects, although it was essential to consider the individuality of each patient when selecting the therapeutic regimen, since the response to treatment varied widely. Thus, the National Eye Institute (2022) reinforced the efficacy of chemotherapy integrated with other techniques by optimising survival rates and visual preservation, but reported the adverse effects associated with chemotherapy, including myelosuppression and an increased risk of infections, which required careful management and a multidisciplinary approach to balance the benefits and risks of these combined therapies. In another study, Naseripour et al. (2022) explored intra-arterial chemotherapy as a targeted alternative, highlighting its safety and efficacy, significantly reduced the need for enucleation and preserved vision, however, the risks of local adverse effects such as thrombosis and vascular complications still needed to be

controlled. Furthermore, it was suggested that personalising the treatment to the specific conditions of each patient was essential to optimise the results. Meanwhile, Ramírez-Ortiz et al. (2017) emphasised the need for integrated treatment programmes to improve clinical outcomes and reduce complications, suggesting that the combination with adjuvant modalities was essential to minimise adverse effects and maximise long-term therapeutic benefits. In this vein, the National Cancer Institute (2023) recommended a personalised approach to the administration of chemotherapy for retinoblastoma, considering the possible adverse effects, as chemotherapy combined with adjuvant treatments has been shown to improve clinical outcomes, but has also increased the risk of complications such as peripheral neuropathy and cardiotoxicity. Therefore, requiring continuous surveillance and early intervention were key to mitigating these risks. Likewise, Akyüz et al. (2015) reported that intra-arterial chemotherapy, when combined with local treatments, despite the aforementioned therapeutic efficiency, presented adverse effects such as arterial spasms and local reactions, which were significant challenges, but with early identification and appropriate management of these effects, the safety and efficacy of the treatment is guaranteed. In parallel, Fontoura et al. (2021) discussed the role of immunotherapy as a complementary treatment for retinoblastoma, and the immunological adverse effects, such as autoimmune reactions and inflammation, which required a careful approach and close monitoring to avoid serious complications, so the integration of these innovative therapies needed to be done with caution, considering the profile of each patient. In addition, Wang et al. (2022) investigated immunotherapies applied to retinoblastoma and suggested that adverse effects, such as fever and flu-like symptoms, were common and impacted on patients' quality of life. They proposed continuous monitoring and treatment adjustment when necessary to minimise these effects and improve clinical outcomes. Similarly, Tomar et al. (2020) conducted a multicentre study on the staging and treatment success of retinoblastoma, showing that the combination of chemotherapy with adjuvant treatments was essential for tumour control and ocular preservation, and their results indicated that, despite the benefits, adverse effects such as alopecia and mucositis were frequent and required a comprehensive supportive approach to mitigate their impact, so coordination between

oncologists and ophthalmologists was vital for the effective management of these complications in this research. That said, the pooled analysis of the studies revealed that although the efficacy of chemotherapy in the treatment of retinoblastoma is widely recognised, especially when combined with adjuvant treatments, its chemotherapy-associated adverse effects posed a significant challenge, especially in paediatric patients. Therefore, individualisation of treatment and a multidisciplinary approach were essential to optimise therapeutic results and minimise risks.

ADJUVANT TREATMENTS CONCOMITANT WITH CHEMOTHERAPY IN THE MANAGEMENT OF RETINOBLASTOMA

The treatment of retinoblastoma, the most common eye tumour in children, has evolved significantly over the years, especially with the integration of chemotherapy and adjuvant treatments, and this combination of chemotherapy with local therapies, such as thermotherapy and cryotherapy, and systemic therapies, such as immunotherapy, has been the subject of several studies, as these approaches seek not only to preserve life, but also to maintain vision and minimise long-term sequelae (LIMA, 2024). For this reason, the studies carried out by Dunkel et al. (2022) showed that multimodal chemotherapy, when combined with local therapies, substantially improved therapeutic results, as well as highlighting that the use of intra-arterial chemotherapy, associated with thermotherapy, resulted in a significant reduction in tumour size and preservation of ocular function in many cases. These findings corroborated the National Eye Institute guidelines (NEI, 2022), which emphasised the importance of an integrated approach to the treatment of retinoblastoma. The analysis by Kronbauer et al. (2000) on the use of chemotherapy in the treatment of retinoblastoma indicated that systemic therapy was effective in reducing tumour volume, facilitating subsequent local treatments, showing through this retrospective study that neoadjuvant chemotherapy allowed better local control of the disease, increasing the chances of success of cryotherapy and thermotherapy. Likewise, the study by Ramírez-Ortiz et al. (2017) reinforced the importance of early diagnosis programmes and appropriate management to optimise clinical results, since the integration of immunotherapy into the retinoblastoma treatment

protocol also showed promising results. Furthermore, Fontoura et al. (2021) pointed out that immunotherapy, by stimulating the patient's immune system, will increase the effectiveness of chemotherapy and reduce relapse rates. The research by Wang et al. (2022) suggests that combining chemotherapy with specific immunotherapies, such as checkpoint inhibitors, offers a more personalised and effective approach, preserving vision and improving patients' quality of life. And as pointed out by Naseripour et al. (2022), intra-arterial chemotherapy was a significant advance in the treatment of retinoblastoma. This technique has allowed chemotherapy to be administered directly into the ophthalmic artery, increasing the concentration of the drug in the tumour and reducing adverse systemic effects. And research has shown that this approach, combined with local treatments, resulted in higher tumour control rates than those obtained with systemic chemotherapy alone. The literature has also highlighted the importance of an individualised approach in the treatment of retinoblastoma. Furthermore, Marcos et al. (2022) emphasised that early diagnosis and personalised treatment were fundamental to maximising therapeutic benefits and minimising the risk of complications. This is why the need to adapt treatment to each patient's individual response was reiterated by Chintagumpala et al. (2007), who suggested continuous assessment and adjustment of therapeutic protocols based on the clinical evolution of each case. Furthermore, the complications associated with the treatment of retinoblastoma were not neglected. Thus, the contribution of Cabral et al. (2024) to the field of retinoblastoma highlighted the development of safer and more effective treatments over the years. In such a way that the effectiveness of chemotherapy in combination with adjuvant treatments in controlling retinoblastoma had been widely documented in the literature, and the combination of local and systemic therapies had offered a more holistic and personalised approach, resulting in better clinical outcomes and greater preservation of vision. However, the need for continuous monitoring and adjustment of therapeutic protocols based on individual patient response remained fundamental, and future studies should continue to explore these therapeutic combinations to optimise the treatment of retinoblastoma and minimise long-term adverse effects.

CONCLUSION

The analysis carried out in this study showed that integrating chemotherapy with adjuvant treatments in the management of retinoblastoma provided significant clinical benefits. Adjuvant therapies such as thermotherapy, cryotherapy and immunotherapy, when combined with chemotherapy, have shown the potential to increase treatment efficacy, promote vision preservation and reduce recurrence rates. Thus, this multimodal approach allowed for more effective tumour control, standing out as a promising therapeutic strategy in the treatment of retinoblastoma, and these therapeutic combinations not only improved clinical results, but also contributed to patients' quality of life. On the other hand, the efficacy of chemotherapy, especially when administered intra-arterially, was shown to be superior in terms of drug concentration in the tumour and minimisation of adverse systemic effects, and intra-arterial chemotherapy, in combination with local therapies, resulted in a significant reduction in tumour size, increasing the chances of therapeutic success. These findings highlight the importance of an integrated approach to optimise therapeutic results and preserve ocular function. This is why individualising treatment, adjusting protocols according to each patient's response, has also proved important for therapeutic success.

Furthermore, the inclusion of immunotherapy in the treatment protocol showed encouraging results, as immunotherapy, by boosting the patient's immune response, increased the effectiveness of chemotherapy and reduced the chances of tumour recurrence. And this approach not only improved clinical outcomes, but also offered a more personalised and less invasive treatment perspective, in line with patients' individual needs. In addition, continuous monitoring and the adaptation of therapeutic protocols were fundamental to guaranteeing the success and safety of the treatment.

That said, the integration of chemotherapy with different adjuvant treatments in the management of retinoblastoma has proved to be an effective and promising strategy, and longitudinal studies and the ongoing assessment of long-term effects have been essential to further improve these approaches and minimise the associated risks, as the advances made in the last decade have led to a significant improvement in clinical results and patients' quality of life, reinforcing the importance of a multimodal

and individualised therapeutic approach. And, without forgetting to emphasise, continued research in this field is essential to consolidate these strategies and develop new treatments that can offer hope and better prospects for patients with retinoblastoma.

Limitations

The limitations observed in this research were the lack of studies from Eastern and African countries; in the Cyrillic language; French and German. This may limit the framework for discussion of this research. It does not reflect a global reality regarding the efficacy of chemotherapy in association with different adjuvant treatments for retinoblastoma in different ethnicities and peoples.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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