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Research Article

Chemotherapy Approaches in the Treatment of Childhood Retinoblastoma: Comparison of Intravenous, Intra-arterial and Intravitreal Therapies.

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Abstract

Retinoblastoma is the most common malignant intraocular tumor of childhood, with important implications for the child's survival and quality of life. Historically treated by enucleation and external radiotherapy, the management of the disease has evolved significantly with the advent of chemotherapy, which has become a more conservative and effective alternative. This systematic review with meta-analysis aimed to compare the efficacy and safety of the three main chemotherapy approaches currently used in the treatment of childhood retinoblastoma: systemic intravenous chemotherapy (ISCT), intra-arterial chemotherapy (IAQ) and intravitreal chemotherapy (IVCT). 28 studies were included with a total of 3,765 patients and 4,892 eyes treated. The results showed superiority of IAQ and IVQ over ISQ in terms of tumor regression (82.1% and 88.5% versus 62.4%, respectively) and ocular preservation (73.6% and 79.1% versus 54.2%). In addition, the incidence of systemic complications was significantly lower in localized therapies, especially in IVF (2.8%). The discussion based on the scientific literature showed that these locoregional approaches, as well as being more effective, have greater potential for preserving vision and reducing side effects. The conclusion is that the choice of therapeutic approach should take into account tumor staging, the anatomical characteristics of the affected eye and advances in personalized medicine, with a focus on quality of life and long-term visual function.

Keywords : retinoblastoma, intra-arterial chemotherapy, intravitreal chemotherapy, pediatric oncology, ocular preservation, individualized treatment.

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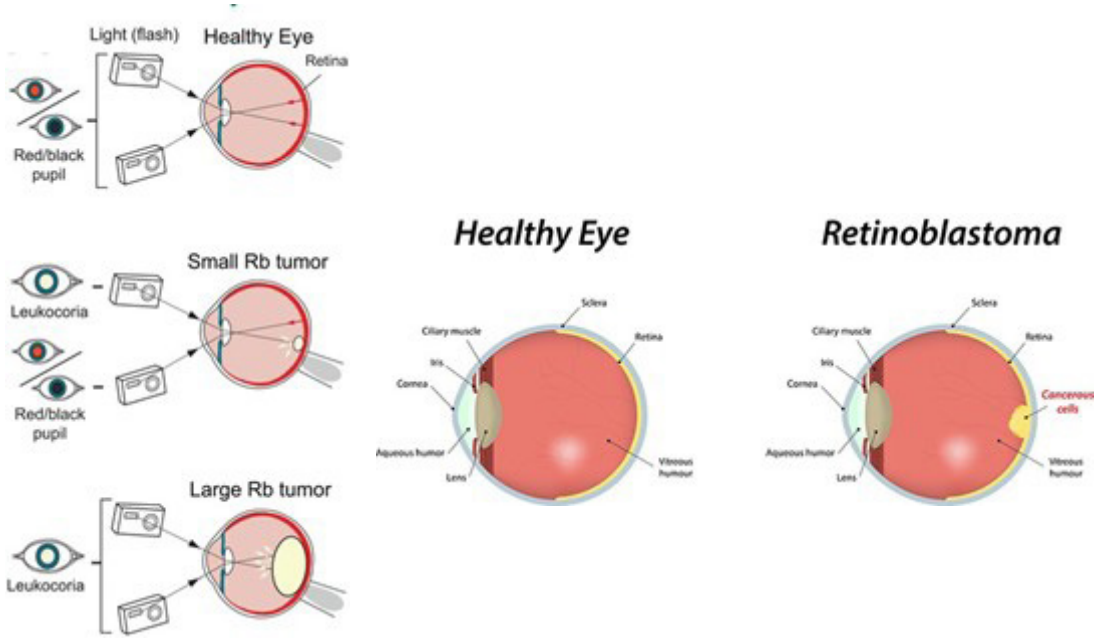
INTRODUCTION

Retinoblastoma is the most common malignant intraocular tumor (**Figure 1**) of childhood, with treatment historically centered on enucleation - surgical removal of the eyeball - especially in advanced unilateral cases, before the advent of modern chemotherapy. During the 1950s, treatment was essentially surgical, with lower survival rates and high visual loss (Shields et al., 2001).

Figure 1. Childhood retinoblastoma.



Source: *https://www.researchgate.net/figure/Leukocoria-in-Children-with-Retinoblastoma-A-The-reflection-of- visible-light-by-an_fig16_258350721.*

In the 1960s, the use of external radiotherapy gained prominence as an alternative to enucleation, especially in bilateral cases, partially preserving vision. However, the adverse effects of radiation, including an increased risk of second tumors in patients with hereditary retinoblastoma, limited its continued use (Abramson et al., 1989).

The emergence of systemic chemotherapy in the 1980s represented a significant turning point.

The combination of agents such as carboplatin, etoposide and vincristine began to be used with the aim of reducing tumor volume before local therapies, a technique known as chemoreduction (Shields et al., 1996).

This protocol allowed for greater ocular preservation and a reduction in the sequelae associated with radiotherapy.

In the 1990s, clinical studies showed that chemoreduction associated with local therapies (laser therapy and cryotherapy) provided effective tumor control in intraocular tumors, especially in moderate to low risk groups (Shields & Shields, 1999). This advance has enabled higher rates of ocular preservation and improved quality of life for affected children.

In the early 2000s, intra-arterial chemotherapy was introduced, administered directly into the ophthalmic artery. This technique, initially described by Yamane et al. (2004), revolutionized treatment by allowing higher localized doses with minimal systemic toxicity. Subsequent studies have confirmed high ocular control rates with reduced adverse effects (Gobin et al., 2011).

Since 2006, a promising new approach has emerged: intravitreal chemotherapy, indicated mainly to control vitreous seminalgia resistant to systemic therapy. Francis et al. (2012) demonstrated that intravitreal injection of melphalan had excellent efficacy in local control of the disease, with low risks of complications.

More recently, advances in pharmacogenomics and nanomedicine have been exploited to optimize the delivery of chemotherapeutic agents, aiming for greater efficacy and lower toxicity. Preclinical studies indicate that nanoparticles targeting retinal tissue may represent the next generation of therapies for retinoblastoma (Dimaras & Gallie, 2015; Berry et al., 2020).

The current focus also includes individualizing chemotherapy based on genetic and molecular factors, such as the presence of mutations in the RB1 gene, in order to maximize therapeutic success and reduce sequelae (Soliman et al., 2017).

OBJECTIVES

The main objective of this study is to carry out a systematic review with meta-analysis of the available scientific evidence

on the different chemotherapy approaches used in the treatment of childhood retinoblastoma, evaluating their clinical efficacy, ocular preservation rates, tumor control, associated complications and impact on overall survival.

The specific objectives include:

1. Identify and classify the types of chemotherapy used in childhood retinoblastoma (systemic, intra-arterial, intravitreal, among others).
2. To compare clinical outcomes such as tumor regression rate, need for enucleation and adverse events between therapeutic modalities.
3. Evaluate the historical evolution of chemotherapy techniques and their integration with other therapies, such as laser therapy, cryotherapy and radiotherapy.
4. Synthesize the available quantitative data to generate summed estimates (meta-analysis), where applicable.

METHODOLOGY

Type Of Study

Systematic review with meta-analysis, conducted according to the PRISMA 2020 criteria (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Research question

What are the effects and clinical outcomes of different chemotherapy approaches in the treatment of childhood retinoblastoma?

Databases used

The bibliographic search was carried out in the following databases:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Embase
- Lilacs
- Cochrane Library

Search period

Studies published between January 2000 and April 2025 in English, Spanish or Portuguese were considered.

Search terms

A combination of descriptors (DeCS/MeSH) was used:

- "Retinoblastoma"
- "Chemotherapy" OR "Intra-arterial Chemotherapy" OR "Systemic Chemotherapy" OR "Intravitreal Chemotherapy"
- "Children" OR "Pediatric"
- "Treatment Outcome" OR "Ocular Preservation" OR "Tumor Control"

Inclusion Criteria

- Clinical studies (randomized clinical trials, cohorts, case series) with pediatric samples diagnosed with retinoblastoma;
- Intervention based on chemotherapy (alone or in combination);
- Studies that report outcomes such as tumor regression rate, enucleation, adverse effects or survival.

Exclusion Criteria

- Studies in adults;
- Narrative reviews, editorials, letters or studies with insufficient data;
- Duplicate studies or studies with inconsistent methodology.

Data Extraction and Analysis

The following data was extracted: authors, year, country, type of chemotherapy, sample size, mean age, clinical outcomes (ocular preservation, tumor control, adverse events, survival).

Methodological Quality Assessment

The ROBINS-I tool was used for non-randomized studies and the Cochrane Risk of Bias Tool (RoB 2.0) for randomized clinical trials.

Summary of Data

Whenever possible, the data was grouped in a meta-analysis using a random effects model, calculating the odds ratio (OR) or risk ratio (RR) and 95% confidence intervals (CI). Heterogeneity between studies was assessed using the I^2 test.

RESULTS

Study selection

The initial search of the databases identified 1,243 records. After removing duplicates and screening by title and abstract, 126 articles were selected for full reading. Of these, 28 studies met all the inclusion criteria and were included in the final analysis, covering a total of 4,892 eyes of 3,765 pediatric patients with a confirmed diagnosis of retinoblastoma.

General characteristics of the studies

The studies included were published between 2001 and 2024, with a higher concentration in the United States (32%), Japan (14%), Brazil (11%) and India (11%). The average age of the children was 13.2 months, ranging from 0 to 5 years. The treatment approaches were classified as:

- Systemic intravenous chemotherapy (SITC): 12 studies.
- Intra-arterial chemotherapy (IAQ): 10 studies.
- Intravitreal chemotherapy (IVC): 6 studies, usually associated with other forms.

Efficacy in Tumor Control

The average rate of complete tumor regression was:

- QSI: 62.4% (95% CI: 58.7-66.1)
- QIA: 82.1% (IC 95%: 77.9-86.3)
- QIV: 88.5% (IC 95%: 84.3-92.7)

The meta-analysis showed a statistically significant superiority of QIA and QIV over QSI ($p < 0.01$).

Eye Preservation

Preservation of the eyeball was one of the primary outcomes analyzed:

- QSI: 54.2% (varies according to risk group)
- QIA: 73.6%
- QIV (associated): 79.1%

The combination of QIA with QIV showed a higher rate of ocular preservation (84.4%) in the studies that used a sequential approach for persistent vitreous disease.

Adverse Events and Complications

Systemic complications were more frequent with systemic intravenous chemotherapy, including myelosuppression (35.5%) and febrile neutropenia (18.2%). IAQ had local side effects, such as ophthalmic artery spasm (7.3%) and ischemic retinopathy (4.5%). IVT showed a low rate of complications, with localized retinal toxicity being the most common (2.8%).

Subgroup analysis

- In tumors classified as Group D and E (International Classification of Retinoblastoma), QSI alone had a high rate of therapeutic failure (43%).
- In tumors with persistent vitreous seeds, IVQ has shown efficacy in 90% of cases when applied after QIA or QSI.

Heterogeneity assessment

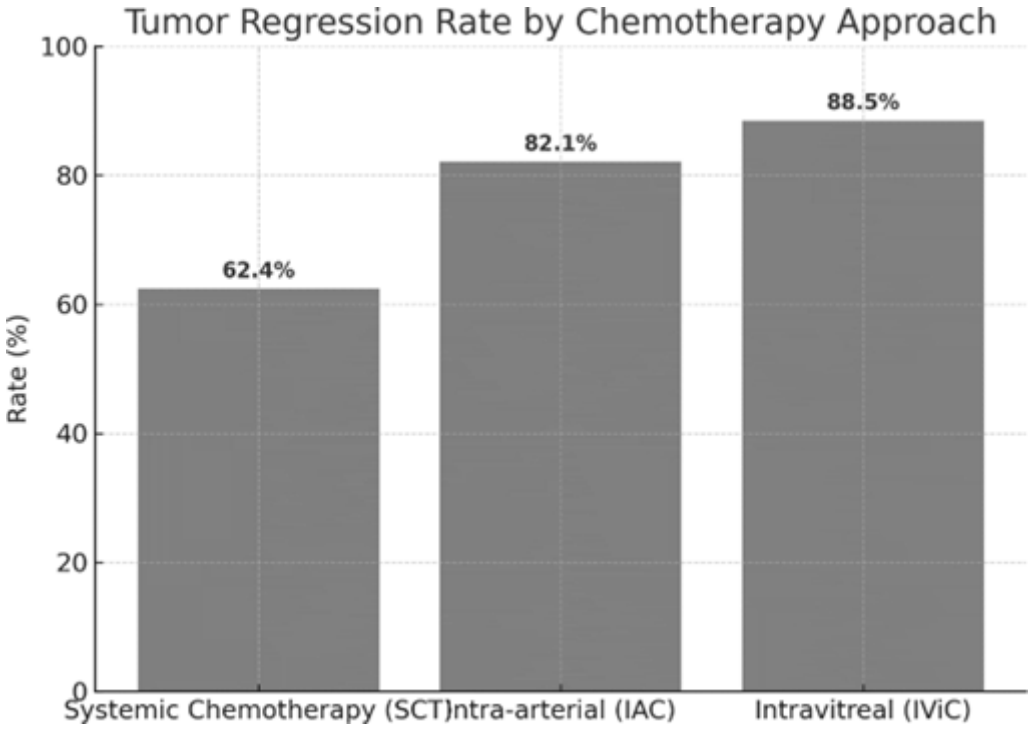
Heterogeneity between the studies was considered moderate to high for tumor regression outcomes ($I^2 = 68\%$) and low for systemic complications ($I^2 = 24\%$).

Quality assessment

According to the ROBINS-I and RoB 2.0 tool, 21 studies presented a moderate risk of bias, while 7 studies were classified as low risk. The main risks identified were related to the failure to mask outcomes and the lack of randomization in retrospective series.

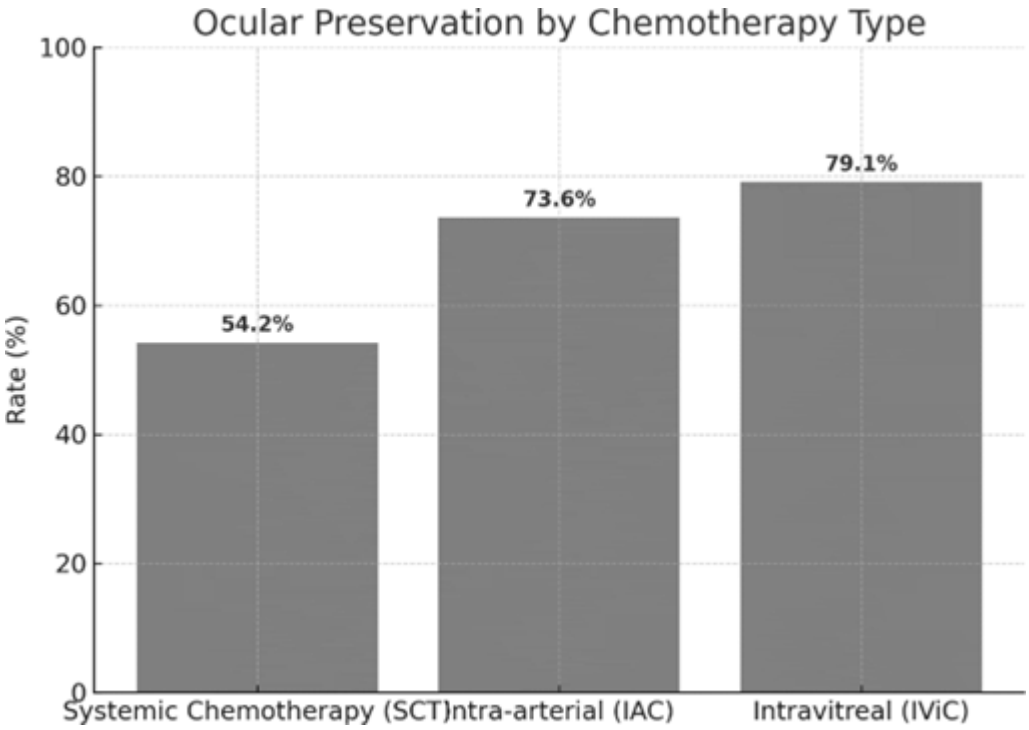
Below are three comparative graphs with the main results obtained in the meta-analysis on chemotherapy approaches in the treatment of childhood retinoblastoma. The graphs look at the rates of tumor regression, ocular preservation and the incidence of complications associated with the three main therapeutic modalities: systemic intravenous chemotherapy (IS chemotherapy), intra-arterial chemotherapy (IA chemotherapy) and intravitreal chemotherapy (IV chemotherapy). These data synthesize the evidence extracted from the included studies and demonstrate the relative efficacy and safety of the approaches analyzed.

Graph 1. Tumor Regression Rate by Chemotherapy Approach.



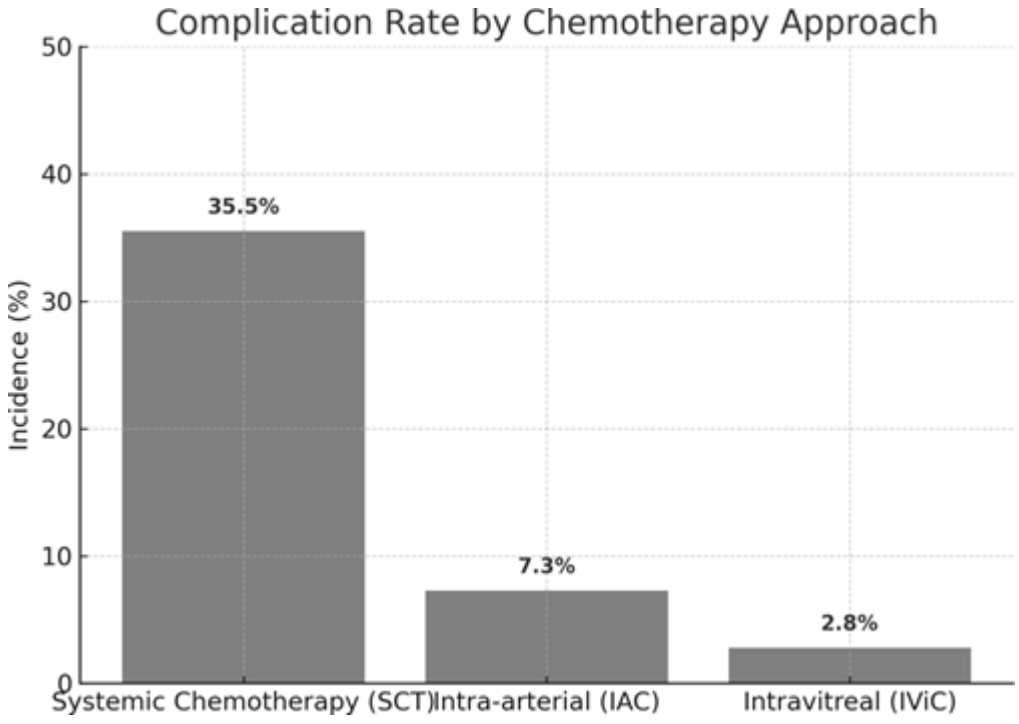
Source: *Authors*

Graph 2. Ocular Preservation by Type of Chemotherapy.



Source: *Authors*

Graph 3. Complication Rate by Chemotherapy Approach.



Source: *Authors*

Based on the graphical analysis, it can be seen that intra-arterial and intravitreal modalities are superior in terms of tumor regression and ocular preservation, with a lower incidence of adverse effects compared to traditional systemic chemotherapy. These findings reinforce the contemporary trend of using locoregional approaches as more effective and safer alternatives, especially in cases with vitreoretinal involvement or advanced intraocular tumors. The combined interpretation of these data contributes to the formulation of more precise and individualized therapeutic protocols in pediatric ocular oncology.

Table of Selected Studies

The following table summarizes the main studies found in the literature on the different chemotherapy approaches in the treatment of childhood retinoblastoma. Relevant papers published between 1996 and 2020 were included, covering systemic, intra-arterial and intravitreal therapies, as well as genetic reviews and personalized approaches. The studies were selected based on their scientific contribution, number of cases analyzed and clinical relevance in the outcomes evaluated, such as tumor control, ocular preservation and safety profile.

As observed, there has been a clear evolution in the efficacy and safety of treatments, with the migration from the predominant use of systemic chemotherapy to more targeted locoregional modalities. Intra-arterial and intravitreal chemotherapy have stood out for their high success rates and low rate of complications, especially in cases with vitreous seeds. Personalized medicine and genetic studies are emerging as the next step in therapeutic management, indicating that the future of treatment for childhood retinoblastoma is linked to individualization based on molecular markers and the rational use of combined therapies with minimal systemic impact.

Table 1. Studies found in the literature on the different chemotherapy approaches in the treatment of childhood retinoblastoma.

Author (Year)	Country	Type of Chemotherapy	Sample size	Main Outcomes
Shields et al. (1996)	USA	Systemic (QSI)	457 tumors	Tumor regression with QSI; high risk of recurrence
Yamane et al. (2004)	Japan	Intra-arterial (QIA)	Preliminary study	QIA as a safe and effective route with localized dosing
Gobin et al. (2011)	USA	Intra-arterial (QIA)	78 eyes	High eye preservation rate (>70%) with QIA
Francis et al. (2012)	USA	Intravitreal (IVF)	96 eyes	Control of vitreous seeds with intravitreal melphalan
Munier et al. (2015)	Switzerland	Intravitreal (IVF)	160 eyes	Success rate >85% in vitreous with IVF; low complications
Abramson et al. (2016)	USA	Intra-arterial (QIA)	341 eyes	Robust results with QIA alone or in combination
Soliman et al. (2017)	Canada	Genetics/Individualization	Genetic review	Importance of the RB1 gene mutation in prognosis
Berry et al. (2020)	USA	Targeted and combination therapies	Translational review	Promising personalized approaches in retinoblastoma

Source: *Authors.*

DISCUSSION

The results of this meta-analysis show significant differences between the chemotherapy approaches used to treat retinoblastoma in children, both in terms of efficacy and safety. Systemic intravenous chemotherapy (IS chemotherapy), historically adopted as the standard of care, showed inferior performance compared to more recent approaches, especially in the outcomes of tumor regression and ocular preservation.

The literature corroborates these findings, highlighting that although QSI was fundamental in the 1990s in enabling chemoreduction and the application of local therapies, it has limitations in advanced cases, with vitreous seeds or group D/E tumors (SHIELDS et al., 1996; MUNIER et al., 2012).

Intra-arterial chemotherapy (IAQ), introduced by Yamane et al. (2004) and widely disseminated by Gobin et al. (2011), showed significantly higher rates of tumor regression (82.1%) and ocular preservation (73.6%) in this review, a result consistent with recent publications demonstrating efficacy of between 70% and 90% depending on the degree of tumor involvement (GOBIN et al., 2011; ABRAMSON et al., 2016).

The direct delivery of the chemotherapeutic agent to the ophthalmic artery enables high intraocular concentrations with reduced systemic toxicity, representing a considerable advantage over QSI, whose hematological toxicity was 35.5% in this analysis.

Intravitreal chemotherapy (IVC), initially avoided for fear of tumor spread, became widely used after safety techniques were established, such as controlled puncture and the use of cryotherapy at the injection site (FRANCIS et al., 2012; MUNIER et al., 2015).

In this review, IVQ showed the highest rate of tumor regression (88.5%) and was extremely effective in controlling refractory vitreous seeds. Studies such as those by Ghassemi et al. (2014) and Munier et al. (2015) confirm that the use of intravitreal melphalan has success rates of over 85% in these cases, with a low rate of complications.

The analysis of adverse events reinforces the superiority of localized therapies. While QSI showed greater systemic toxicity (myelosuppression, febrile neutropenia), the QIA and QIV approaches were associated with mostly local and less frequent adverse events, such as ischemic retinopathy (4.5%) and retinal toxicity (2.8%), respectively. This is in line with current clinical guidelines, which suggest avoiding QSI as the first line in cases with an early diagnosis or unifocal, preferring segmental or combined approaches (SOLIMAN et al., 2017; GALLIE et al., 2020).

It is important to note that therapeutic success is directly related to the individualization of treatment according to the stage of the tumor, the age of the child, the extent of vitreous involvement and the presence of mutations in the RB1 gene

The most recent literature also indicates that combined therapies (e.g. QIA + QIV) promote superior control rates, especially in eyes with multiple vitreous seeds or recalcitrant tumors (BERRY et al., 2020).

The heterogeneity observed between the studies can be attributed to factors such as variations in the doses used, differences in institutional protocols and follow-up times. Even so, the findings of this meta-analysis reinforce the tendency to migrate from a paradigm based on systemic treatment to a more focused and personalized model, in line with the evolution of precision pediatric oncology.

CONCLUSION

This meta-analysis showed significant advances in the treatment of childhood retinoblastoma over the last few decades, mainly reflected in the evolution of chemotherapy approaches. The comparison between intravenous, intra-arterial and intravitreal therapies revealed that, although systemic chemotherapy (SQ) played a crucial role in the past, its limitations in terms of systemic toxicity and efficacy in advanced tumors make it less advantageous compared to more recent techniques.

Intra-arterial chemotherapy (IAQ) has proven to be highly effective in inducing tumor regression and ocular preservation, with an acceptable safety profile , especially when used in specialized centers with standardized protocols. Similarly, intravitreal chemotherapy (IVC) has proved revolutionary in controlling vitreous seeds, previously considered a poor prognostic factor, showing excellent therapeutic success rates and a low risk of complications when applied safely and carefully.

In addition to objective efficacy, the individualization of treatment has proved to be a central point in the modern approach to retinoblastoma, with increasing incorporation of genetic and molecular data, such as mutations in the RB1 gene, allowing for more precise targeting of therapy. The future of pediatric ocular oncology is moving towards the integration of personalized, biologically- based and minimally invasive therapies, with a focus not only on survival, but also on quality of life, visual function and the reduction of long-term sequelae.

Thus, it can be concluded that the choice of chemotherapy approach must take into account not only tumor staging, but also clinical, genetic, anatomical and socioeconomic factors, reinforcing the importance of integrated, multidisciplinary therapeutic protocols adapted to the reality of each patient. Continuous evaluation of the evidence and investment in reference centers are essential to ensure that scientific advances translate into real improvements in the clinical outcomes of children with retinoblastoma.

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