Retinoblastoma

Paulo Henrique dos Santos Klinger[1*], Cláudio Galvão de Castro Junior[2,3], Antonella Adriana Zanette[4], Neviçolino Pereira de Carvalho[1], Adriana Seber[5,6]

1. Hospital Santa Marcelina – Associação para Criança e Adolescente com Câncer – São Paulo (SP), Brazil.
2. Hemacore – São José dos Campos (SP), Brazil.
3. Certho – Guaratinguetá (SP), Brazil.
4. Hospital Erastinho – Curitiba (PR), Brazil.
5. Universidade Federal de São Paulo – Instituto de Oncologia Pediátrica – São Paulo (SP), Brazil.
6. Hospital Samaritano de São Paulo – São Paulo (SP), Brazil.

***Corresponding author:** phsklinger@gmail.com

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ABSTRACT

Retinoblastoma is the most common form of ocular cancer in children, with an estimated prevalence of one in every 15,000 to 20,000 births. Although it accounts for only 3% of pediatric neoplasms, its impact is significant in children under 5 years of age. It is a malignant neoplasm of the retina, of embryonic origin, with an oncogenic basis in the mutation of the tumor suppressor gene *RB1* (somatic or germline). The disease can be broadly classified as intraocular or extraocular. Extraocular disease, especially in stages IVa (metastatic disease with hematogenous spread, single or multiple foci, to bone marrow, bones, liver, lymph nodes) and IVb (extension to the central nervous system, pre-chiasmatic lesions, or leptomeningeal disease), poses significant challenges to treatment, requiring specialized centers for referral and early diagnosis. This article reviews recent therapeutic approaches, including the use of thiotepa in high-dose chemotherapy with stem cell rescue in a single transplant, or in double schemes for patients with stage IVa and IVb at diagnosis or relapsed.

Keywords: Hematopoietic Stem Cell Transplantation. Retinoblastoma. Neoplasm Metastasis.

INTRODUCTION

Retinoblastoma is the most common ocular cancer in children, accounting for approximately 3% of all pediatric malignancies, and most cases are diagnosed in children under the age of 5[1]. Retinoblastoma is a malignant neoplasm of the retina, primarily initiated by the biallelic inactivation of the *RB1* tumor suppressor gene (either somatic or germline). Additional genetic alterations contribute to malignant transformation. In a small subset of patients, retinoblastoma develops independently of *RB1* mutations, being driven instead by *MYCN*[1]. Since a significant proportion of cases are hereditary, it is exceedingly important to teach retinoblastoma survivors to have their children examined at birth to make an early diagnosis, which is crucial for improving clinical outcomes and preventing both vision loss and mortality.

The first warning sign for pediatricians is a whitish pupil or leukocoria, which appears instead of the normal red reflex when a light is directed into the child's eye. This sign is often noticeable in photographs and should be emphasized in medical education for general practitioners, pediatricians, and ophthalmologists.

Unlike most cancers, diagnosis does NOT rely on biopsy but rather on specialized ophthalmologic examination using indirect ophthalmoscopy under anesthesia. Small tumors can be treated with laser therapy and cryotherapy, while intra-arterial chemotherapy, alone or in combination with intravitreal chemotherapy, has significantly improved the control of more advanced intraocular stages, increasing eye preservation rates and reducing the need for enucleation.

Extraocular disease in stages IVa (metastatic disease to the bone marrow, bones, liver, lymph nodes) and IVb (extension to the central nervous system, pre-chiasmatic lesions, or leptomeningeal disease) presents significant treatment challenges[2]. Management typically involves a combination of systemic chemotherapy, specific ophthalmologic procedures, neurosurgical evaluation, and autologous hematopoietic cell transplantation (HCT). Intrathecal chemotherapy is sometimes employed, although its role remains a subject of debate[3]. In very rare cases, radiotherapy may also be considered[3]. When HCT is performed, thiotepa should be used due to the excellent central nervous system penetration. Patients with stage IVa have up to 81% survival with this strategy[4]. However, in stage IVb diseases, even with the use of thiotepa, single transplants result in a survival rate of 28%[4] in the United States of America and 50% of the 24 children treated at a single Brazilian institution[5]. Tandem HCT, that involves three sequential high-dose thiotepa-carboplatin cycles[6], have been used to treat brain tumors and is currently also being used in Brazil to treat stage IVb retinoblastoma, but results are not available yet.

Trilateral retinoblastoma is a rare and aggressive presentation characterized by the presence of bilateral or multifocal unilateral retinoblastoma and an associated intracranial neuroblastic tumor, most commonly found in the pineal or suprasellar region. It occurs exclusively in patients with germline *RB1* mutations. The disease carries a poor prognosis due to its high metastatic potential and challenges in early detection[7]. Aggressive therapy, including HCT, is currently used and can rescue most of these children[5]. Research is ongoing focusing on the role of GD2-targeted monoclonal antibodies[8] (*e.g.*, dinutuximab), checkpoint inhibitors, small molecule inhibitors targeting *RB1*-deficient tumors oncolytic virotherapy, epigenetic modulators, and CAR T-cell therapy[9].

Similar to the treatment of the disease at diagnosis, intra-ocular relapsed retinoblastoma must be treated with the appropriate local therapies (*e.g.*, cryotherapy, thermotherapy, laser photocoagulation), intra-arterial and intravitreal chemotherapy, brachytherapy, external beam radiation therapy, and enucleation, as well as systemic and, in selected cases, intrathecal chemotherapy for extra-ocular diseases. Early diagnosis and appropriate ophthalmologic management have the greatest impact on vision preservation and survival. Vigilant follow-up is crucial due to the risk of recurrence and secondary malignancies, especially in hereditary cases[10] (Tables 1 and 2).

Table 1. Conditioning regimens options for retinoblastoma.

Carboplatin etoposide and thiotepa[4,5]				
Days	**Drug**	**Route**	**Dose**	
			Patients < 12 kg	Patients ≥ 12 kg
D-9 to D-7	Carboplatin	IV in 4 hours (once a day)	AUC = 7/day OR maximum 16.7 mg/kg (*whichever is lower*)	AUC = 7/day OR maximum 500 mg/m² (*whichever is lower*)
D-6 to D-4	Thiotepa Etoposide	IV in 3 hours (once a day) IV in 3 hours immediately after thiotepa (once a day)	10 mg/kg/day 8.3 mg/kg/day	300 mg/m²/day 250 mg/m²/day
D-3 to D-1		rest		
D0		PBSC infusion (48–72 h after the last dose of etoposide)		
		Tandem with thiotepa and carboplatin[5,6]		
D-4 to D-3	Carboplatin Thiotepa	IV in 4 hours (once a day) IV in 3 hours (once a day)	AUC = 7/day* OR maximum 16.7 mg/kg (*whichever is lower*) 10 mg/kg/day	AUC = 7/day* OR maximum 500 mg/m² (*whichever is lower*) 300 mg/m²/day
D-2 to D-1		rest		
D 0		PBSC infusion (48–72 h after the last dose of thiotepa)		

PBSC: peripheral blood stem cells. Source: Elaborated by the authors.

Table 2. Indications for autologous transplantation in retinoblastoma.

Disease	Autologous	Allogeneic	Comments
Extraocular retinoblastoma stages IVa and IVb Trilateral retinoblastoma Extra-ocular relapse of retinoblastoma	Clinically indicated	Generally not recommended	The spinal fluid must be treated with intratecal chemotherapy and must be in remission prior to the hematopoietic cell transplantation. Irradiation must be avoided due to the high rate of secondary tumors.

Source: Elaborated by the authors.

CONCLUSION AND PERSPECTIVES

Improvements in treatment involve several strategies, including early diagnosis, specialized referral centers capable of doing fundoscopic examination under anesthesia, treating with appropriate ophthalmologic armamentarium, inclusion of multimodal approaches that include HCT to treat stage IV, trilateral diseases and close specialized surveillance. This set of measures not only increases survival but also reduces morbidity with unique and individualized approaches.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data sets were generated or analyzed in the current study.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Carvalho NP, Klinger PHS, Castro Junior CG, Zanette AA and Seber A. **Conception and design:** Carvalho NP, Klinger PHS, Castro Junior CG, Zanette AA and Seber A. **Manuscript writing:** Carvalho NP, Klinger PHS, Castro Junior CG, Zanette AA and Seber A. **Final approval:** Seber A and Klinger PHS.

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