Pearls and Forget-Me-Nots in the Management of Retinoblastoma

Retinoblastoma represents approximately 4% of all pediatric malignancies and is the most common intraocular malignancy in children.

BY CAROL L. SHIELDS, MD

The management of retinoblastoma has gradually evolved over the years from enucleation to radiotherapy to current techniques of chemotherapy. Eyes with massive retinoblastoma filling the globe are still managed with enucleation, whereas those with small, medium, or even large tumors can be managed with chemoreduction followed by tumor consolidation with thermotherapy or cryotherapy. Despite multiple or large tumors, visual acuity can reach ≥20/40 in many cases, particularly in eyes with extrafoveal retinopathy, and facial deformities that have been found following external beam radiotherapy are not anticipated following chemoreduction. Recurrence from subretinal and vitreous seeds can be problematic. Long-term follow-up for second cancers is advised.

Most of us can only remember a few interesting points from a lecture, even if was delivered by an outstanding, colorful speaker. Likewise, we generally retain only a small percentage of the information that we read, even if written by the most descriptive or lucent author. We usually remember the "three pearls" that are emphasized or the "five forget-me-nots" that are listed. In this article, the important items on systemic care are highlighted as pearls and critical information on ocular care will be listed as forget-me-nots.

What is the origin of the name *forget-me-not*? There are numerous tales associated with this beautiful dusky blue flower. A tragic legend states that a knight and his lady were walking near a river and, upon picking the flower, he tripped into the river with his armour and chanted "Forget me not." So forget not the legend. Now let's learn and remember the unforgettables about retinoblastoma.

Retinoblastoma represents approximately 4% of all pediatric malignancies and is the most common intraocular malignancy in children.[1-3] It is estimated that 250 to 300 new cases of retinoblastoma are diagnosed in the United States each year, and 5,000 cases are found world-

TABLE 1. INTERNATIONAL CLASSIFICATION OF RETINOBLASTOMA (ICRB)

Group	Quick Reference	Specific Features
A	Small tumor	Rb <3 mm*
B	Larger tumor	Rb >3 mm* or
	Macula	Macular Rb location (<3 mm to foveola)
	Juxtapapillary	Juxtapapillary Rb location (<1.5 mm to disc)
	Subretinal fluid	Rb with subretinal fluid
C	Focal seeds	Rb with:
		Subretinal seeds <3 mm from Rb and/or
		Vitreous seeds <3 mm from Rb
D	Diffuse seeds	Rb with:
		Subretinal seeds >3 mm from Rb and/or
		Vitreous seeds >3 mm from Rb
E	Extensive Rb	Extensive Rb nearly filling globe or
		Neovascular glaucoma
		Opaque media from intraocular hemorrhage
		Invasion into optic nerve, choroid, sclera, orbit, anterior chamber

Rb = retinoblastoma.
** Refers to 3 mm in basal dimension or thickness.*

wide. Large countries such as India and China individually estimate approximately 1,000 new cases of retinoblastoma per year. Most children (>95%) with retinoblastoma in the United States and other developed nations survive their malignancy, whereas approximately 50% survive worldwide. The reason for the poor survival rates in undeveloped nations relates to late detection of advanced retinoblastoma, and the patients often present with orbital invasion or metastatic disease. In Brazil, for example, the mean age at presentation for retinoblastoma is approximately 25 months, compared with ≤18 months in the United States.[4] The average Brazilian family delays seeking medical care for a mean of 6 months. The delay is longer if the only symptom is strabismus in an eye with retinoblastoma (lag time is 9 months) compared with children with symptoms of leukocoria (lag time is 6 months) or tumor mass (lag time is 2 months).[4]

SYSTEMIC CONCERNS WITH RETINOBLASTOMA

Pearl No. 1. Patients with germline mutation retinoblastoma are at risk for pinealoblastoma and second cancers.

Retinoblastoma can be classified in four different ways: sporadic or familial, unilateral or bilateral, nonheritable or heritable, and somatic or germline mutation. About two thirds of all cases are unilateral and one third of cases are bilateral. Genetically, it is simpler to discuss retinoblastoma with the classification of somatic or germline mutation. Germline mutation implies that the mutation is present in all cells of the body, whereas somatic mutation means that only the tissue of concern, the retinoblastoma, has the mutation. All patients are offered genetic testing for retinoblastoma. The testing is performed on the tumor specimen (when available) and a blood sample. The tumor specimen is carefully harvested following enucleation on a separate tray and then snap frozen to protect the integrity of the DNA. After tissue harvesting, the surgeon must reglove before returning to the surgical case to avoid seeding tumor into the patient socket. Both specimens are tested using various methods to evaluate for known mutations as well as new mutations for retinoblastoma, predominantly on chromosome 13 long arm.[5]

Patients with germline mutation have mutation in both the tumor and the peripheral blood, whereas those with somatic mutation show only mutation in the tumor and not the blood. This implies that all cells might be affected with the mutation in germline cases so that these patients could be at risk for other cancers (second cancers and pinealoblastoma). Patients with bilateral and familial retinoblastoma have presumed germline mutation because they have multifocal or heritable disease. Patients with unilateral sporadic retinoblastoma usually carry somatic mutation, but approximately 7% to 15% of these patients will show a germline mutation. Nichols et al performed sensitive multistep clinical molecular screening of 180 unrelated individuals with retinoblastoma and found germline RB1 mutations in 77 out of 85 bilateral retinoblastoma patients (91%), seven out of 10 familial unilateral patients (70%), and six out of 85 unilateral sporadic patients (7%). Mutations included 36 novel alterations spanning the entire RB1 gene.[5] Thus, it is most important to have children with unilateral sporadic retinoblastoma genetically tested for possible germline mutation.[5] Our team generally performs this evaluation within the first 6 months after initial therapy.

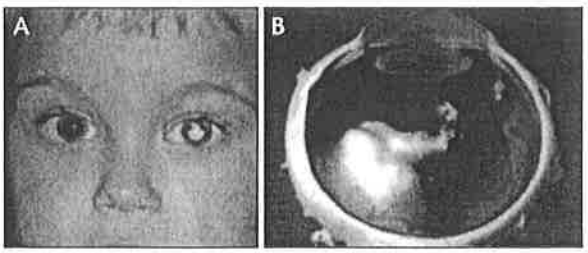

Figure 1. Leukocoria in an eye with retinoblastoma: Clinical photograph (A); and pathology confirming endophytic retinoblastoma (B).

Pearl No. 2. Patients with retinoblastoma are at risk for death from metastatic retinoblastoma, related brain tumor (pinealoblastoma), or long-term second cancer.

Children with retinoblastoma are at risk for three important, life-threatening problems including metastasis from retinoblastoma, intracranial neuroblastic malignancy (trilateral retinoblastoma/pinealoblastoma), and second primary cancers.

Retinoblastoma metastasis typically develops within 1 year of diagnosis of the intraocular tumor. Those at greatest risk for metastasis show histopathologic features of retinoblastoma invasion beyond the lamina cribrosa in the optic nerve, in the choroid, sclera, orbit, or anterior chamber.[6-8] It is critical that a qualified ophthalmic pathologist examine the eye for high-risk features. Optic nerve invasion has been found in approximately 30% of eyes that come to enucleation, and choroidal invasion in slightly more than 30% of eyes.[6-8] This feature is not uncommon and could be life-threatening to the patient. Patients with postlaminar optic nerve invasion or gross (>2 mm) choroidal invasion or a combination of any optic nerve or choroidal invasion should be treated with chemotherapy. The chemotherapy generally involves vincristine, etoposide, and carbo-

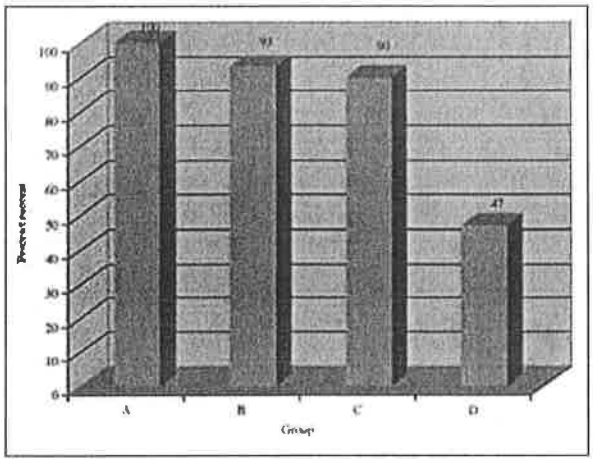

Figure 2. The International Classification of Retinoblastoma predicts chemoreduction success. Groups A, B, and C eyes achieve successful complete tumor regression in at least 90% of cases without the need for external beam radiotherapy or enucleation. Group D eyes are successful with chemoreduction in nearly 50% of cases. Group E eyes are not included as they are typically treated with enucleation.

platin for 4 to 6 months to prevent metastastic disease.[8]

Pinealoblastoma or related brain tumors typically occur in the first 5 years of life, most often within 1 year of diagnosis of the retinoblastoma.[9,10] This has been termed *trilateral retinoblastoma* and overall is found in about 3% of all children with retinoblastoma, but those with germline mutation manifest this tumor in up to 10% of cases.[10] Unfortunately, pinealoblastoma is usually fatal. Systemic chemotherapy, particularly the chemoreduction protocol currently used for retinoblastoma, might prevent trilateral retinoblastoma.[11] A recent publication from our institution found that none of the 142 patients treated with chemoreduction for retinoblastoma developed pinealoblastoma.[11] It was anticipated that about five to 15 of these patients should have manifested pinealoblastoma, but the chemotherapy may have prevented the development of the condition. This remarkable observation indicates that neoadjuvant chemotherapy could be beneficial. Longer follow-up in our series of >300 children with retinoblastoma treated with chemoreduction continues to show the same trend with very few cases of pinealoblastoma.

It should be noted that benign pineal cysts can simulate pinealoblastoma and can best be differentiated using high-resolution magnetic resonance imaging (MRI).[12] Pineal cysts are not uncommon in the pediatric population and are most often coincidentally found on MRI. With MRI, the cyst shows gadolineum enhancement of the wall but not the center cavity, whereas pinealoblastoma are typically larger than cysts and show full enhancement. Pineal cysts require no treatment.

Pearl No. 3. Patients who survive a second cancer are at risk for a third, fourth, and even fifth nonocular cancer, so lifelong systemic care is important.

Second cancers occur in survivors of bilateral or heritable (germline mutation) retinoblastoma.[13-15] Patients with hereditary retinoblastoma have approximately a 4% chance of developing a second cancer during the first 10 years of follow-up, 18% during the first 20 years, and 26% within 30 years.[13] Second cancers most often include osteogenic sarcoma, spindle-cell sarcoma, chondrosarcoma, rhabdomyosarcoma, neuroblastoma, glioma, leukemia, sebaceous cell carcinoma, squamous cell carcinoma, and malignant melanoma. Therapeutic radiotherapy previously delivered for the retinoblastoma can further increase the rate of second cancers. Hereditary retinoblastoma patients who received ocular radiation carried a 29% chance for periocular second cancer compared with only a 6% chance in hereditary retinoblastoma patients treated without radiotherapy.[13] Abramson and colleagues have shown that <50% of patients survive their second cancer, and they are at risk to develop a third nonocular cancer (22% by 10 years) at a mean interval of 6 years.[15] Survivors continue to be at risk for fourth and fifth nonocular cancers.[15] There is some concern that patients treated with chemoreduction, particularly etoposide, might be at risk for secondary acute myelogenous leukemia.[16]

OPHTHALMIC DIAGNOSIS AND MANAGEMENT OF RETINOBLASTOMA

Forget-me-not No. 1. Retinoblastoma classically appears as a nodular gray translucent retinal mass to a white opaque mass, often with subretinal fluid.

The clinical manifestations of retinoblastoma vary with the stage of the disease.[1-3] A small retinoblastoma <2 mm in diameter appears transparent or slightly translucent in the sensory retina. Larger tumors stimulate dilated retinal blood vessels feeding the tumor, foci of intrinsic calcification, and can produce subretinal fluid (exophytic pattern), subretinal seeding, and vitreous seeding (endophytic pattern). Retinoblastoma of any size can produce leukocoria, but this is most often seen with large tumors (Figure 1).

Forget-me-not No. 2. The new International Classification of Retinoblastoma (ICRB) involves groups A through E in increasing severity of disease.

Several classifications of retinoblastoma have been developed including the Reese Ellsworth classification and the more recent ICRB (Table 1).[17,18] The ICRB is sim-

ple to remember and is useful for prediction of chemoreduction success.[18] Based on the ICRB, chemoreduction success is achieved in 100% of group A, 93% of group B, 90% of group C, and 47% of group D eyes (Figure 2).[18]

Management of retinoblastoma is tailored to each individual case and based on the overall situation, including the threat of metastatic disease, risks for second cancers, systemic status, laterality of the disease, size and location of the tumor(s), and estimated visual prognosis. The currently available treatment methods include intravenous chemoreduction (carboplatin, etoposide, and vincristine), subconjunctival carboplatin boost, thermotherapy, cryotherapy, laser photocoagulation, plaque radiotherapy, external beam radiotherapy, and enucleation (Table 2).[19,20]

For unilateral retinoblastoma, enucleation is necessary in approximately 75% of cases, and conservative treatment (nonenucleation methods) is possible in 25%.[19] The reason for the high rate of enucleation is that unilateral sporadic retinoblastoma is typically detected when the eye is in an advanced disease state. For children with less advanced unilateral disease, chemoreduction plus focal consolidation of each tumor with thermotherapy or cryotherapy, or the use of plaque radiotherapy are beneficial. For bilateral retinoblastoma, chemoreduction plus thermotherapy or cryotherapy is necessary in most cases, and about 60% of patients require enucleation of one eye for a dangerously advanced tumor.[21-23] Enucleation of both eyes is necessary only in 1% of cases.[19]

TABLE 2. TREATMENT STRATEGY BASED ON LATERALITY AND RETINOBLASTOMA GROUPING

ICRB	Unilateral	Bilateral*
A	Laser or cryotherapy	Laser or cryotherapy
B	VC or plaque	VC
C	VEC or plaque	VEC
D	Enucleation or VEC	VEC+SCC
E	Enucleation	Enucleation, but if both eyes equally advanced, then VEC+SCC+planned low-dose EBRT

**Treatment in bilateral cases is usually based on the most advanced eye.*
Laser = laser photocoagulation;
VC = vincristine, carboplatin plus thermotherapy or cryotherapy;
plaque = plaque radiotherapy;
VEC = vincristine, etoposide, carboplatin plus thermotherapy or cryotherapy;
SCC = subconjunctival carboplatin;
EBRT = external beam radiotherapy.

Forget-me-not No. 3. The most common cause of chemoreduction failure is the recurrence of vitreous and/or subretinal seeds.

We now have nearly 15 years' experience with chemoreduction for retinoblastoma. Many observations on the successes and limitations of this technique have been published. We have learned that chemoreduction will reduce retinoblastoma by approximately 35% in tumor base and nearly 50% in tumor thickness. We have also learned that subretinal fluid will completely resolve in approximately 75% of eyes that present with total retinal detachment. Subsequently, several reports elaborated on the response of vitreous and subretinal seeds to chemoreduction. Despite these successes, vitreous and subretinal seeds pose the greatest problem with potential for recurrence, often remote from the main tumor. In a report on 158 eyes with retinoblastoma treated using vincristine, etoposide, and carboplatin for six cycles, all retinoblastomas, subretinal seeds, and vitreous seeds showed initial regression.[21] Approximately 50% of the eyes with vitreous seeds, however, showed at least one vitreous seed recurrence at 5 years, and 62% of the eyes with subretinal seeds showed at least one subretinal seed recurrence at 5 years. Of the 158 eyes, recurrence of at least one retinal tumor per eye was found in 51% eyes by 5 years. A more recent analysis of 457 consecutive retinoblastomas focused on individual tumor control with chemoreduction and focal tumor consolidation.[23] Tumors treated with chemoreduction alone showed recurrence in 45% by 7-year follow-up, whereas those treated with chemoreduction plus thermotherapy, cryotherapy, or both showed recurrence in 18% of patients by 7 years.

Following chemoreduction, tumor consolidation with thermotherapy or cryotherapy is important for tumor control. Macular retinoblastoma represents a specifically difficult situation regarding therapy (Figure 3). Consolidation with thermotherapy in the foveal region could lead to immediate visual loss, so controversy exists regarding the need or benefit of adjuvant focal thermotherapy following chemoreduction. In an analysis of 68 patients with macular retinoblastoma, it was found that 35% of those treated with chemoreduction alone showed recurrence by 4 years compared with 17% of those treated with chemoreduction plus extrafoveal thermotherapy.[24] Surprisingly, small retinoblastomas were most likely to show tumor recurrence. This is believed to be related to the reduced chemotherapy dose from small feeder vessels or to the more well-differentiated features

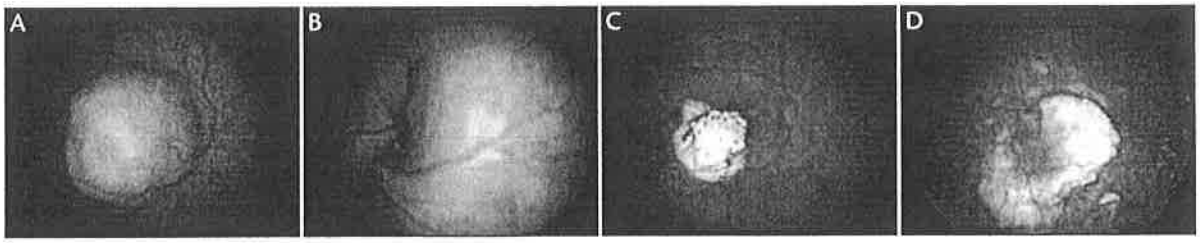

Figure 3. Regression of macular retinoblastoma after chemoreduction. (A) Right eye before treatment; group B retinoblastoma. (B) Left eye before treatment; group D retinoblastoma. (C) Right eye after treatment; tumor regression with partial foveal sparing. (D) Left eye after treatment; tumor regression with calcified scar through the macula.

of small retinoblastomas with less responsiveness to chemotherapy.

Plaque radiotherapy is a method of brachytherapy in which a radioactive implant is placed on the sclera over the base of a retinoblastoma to irradiate the tumor transclerally. Its use is limited to tumors <16 mm in base and 8 mm in thickness, and complete treatment can be achieved in approximately 4 days. Plaque radiotherapy provides long-term tumor control in 90% of eyes when used as a primary treatment.[1-3] In eyes that need plaque radiotherapy for tumor recurrence after chemoreduction, complete control of the tumor is achieved in 96% of cases.[25] Plaque radiotherapy can be used for extensive recurrent subretinal seeds or vitreous seeds, but there is a higher failure rate. All eyes treated with plaque radiotherapy should be monitored for radiation maculopathy and papillopathy.

Forget-me-not No. 4. Avoid vitrectomy in eyes with retinoblastoma.

A number of ocular disorders in infants and children can resemble retinoblastoma. The most common pseudoretinoblastomas includes Coats' disease, persistent hyperplastic primary vitreous (PHPV) (also known as persistent fetal vasculature [PFV]), and ocular inflammation such as toxocariasis.[1-3] Think of retinoblastoma in any child with retinal detachment, vitreous hemorrhage or intraocular mass.

The diagnosis of retinoblastoma should be confidently excluded before treatment of a pseudoretinoblastoma. Vitrectomy or retinal detachment repair should be withheld in a child until the diagnosis of retinoblastoma is reliably excluded.[26] Any child with unexplained, atraumatic hyphema or vitreous hemorrhage should be evaluated for retinoblastoma using clinical examination, ultrasonography, and possibly even computed tomography (CT) or MRI. Consultation with an ocular oncologist experienced with retinoblastoma could be helpful in confirming the clinical diagnosis and directing therapy.

Forget-me-not No. 5. Enucleation is an acceptable treatment for advanced retinoblastoma.

Enucleation is an important and powerful method for managing retinoblastoma.[1-3] Enucleation is employed for advanced tumors with no hope for useful vision in the affected eye or if there is a concern for invasion of the tumor into the optic nerve, choroid, or orbit. Eyes with unilateral groups D or E are usually managed with primary enucleation. Eyes with bilateral groups D or E generally have one eye eventually needing secondary enucleation following chemoreduction.

The technique of enucleation is to gently remove the eye intact without seeding the malignancy into the orbit. The globe should be handled cautiously and the muscles hooked with care to avoid excess pressure on the particularly thin sclera under the muscle insertions. After the globe is removed, fresh tissue is harvested on a separate tray in the operating room for DNA analysis, using a specific technique. The surgeon performing the tissue harvest should be careful to minimize seeding the tumor on the outside of the globe, as this could cause diagnostic confusion for the pathologist interpreting tumor invasion. The surgeon harvesting fresh tissue must remove the used gloves and reglove after this step to avoid the risk of tumor contamination into the child's orbit. If spillage onto the surgeon's gown occurs, then complete regowning and regloving is necessary. Following enucleation, an orbital implant is placed to provide a more natural cosmetic appearance of the patient's artificial eye and to enable motility of the prosthesis.[27] There are several available orbital implants including polymethylmethacrylate sphere, coralline hydroxyapatite, coated coralline hydroxyapatite, polyethylene, and others.

ONGOING NATIONAL CLINICAL TRIALS

The Children's Oncology Group has approved of four collaborative retinoblastoma studies for the evaluation of chemoreduction for intraocular disease as well as chemotherapy for high-risk retinoblastoma and chemotherapy for metastatic disease. There are currently four main trials:

• Chemoreduction for Group B. A single-arm prospective trial evaluating vincristine and carboplatin (plus adjuvant thermotherapy/cryotherapy) for retinoblastoma.

• Chemoreduction for groups C and D. A single-arm prospective trial evaluating vincristine, etoposide, and carboplatin (plus adjuvant thermotherapy/cryotherapy) plus subconjunctival carboplatin for retinoblastoma.

• Chemotherapy for high-risk retinoblastoma. A single-arm prospective trial evaluating vincristine, etoposide, and carboplatin for eyes with histopathologic high-risk features including invasion of the optic nerve, choroid, or sclera.

• Chemotherapy for metastatic disease. A single-arm prospective trial evaluating treatment of advanced retinoblastoma and primarily conducted in regions where metastatic disease is more prevalent.

SUMMARY

Retinoblastoma continues to be a challenge both diagnostically and therapeutically. It is important to first clearly establish the correct diagnosis before embarking on therapy. Retinoblastoma is classified into groups A, B, C, D, and E, based on the tumor size, location, and related subretinal or vitreous seeds. Many factors enter into the decision regarding management such as patient age, tumor laterality, size, location, and extent, and especially anticipated visual prognosis. Chemoreduction is an important conservative method for most children with bilateral retinoblastoma and for only a minority of children with unilateral retinoblastoma. Enucleation still proves to be useful for advanced tumors.

Remember the legend of the beautiful, five-petaled spring flower, the forget-me-not. Like the forget-me-not, retinoblastoma can grow in dark shady areas and remain hidden for weeks or months. Like the forget-me-not, retinoblastoma easily germinates and spreads its seed pods. The five forget-me-nots of retinoblastoma include:

1. Retinoblastoma classically appears as a nodular gray translucent- to white-opaque mass, often with subretinal fluid.

2. The new ICRB involves group A through E in increasing severity of disease.

3. The most common cause of chemoreduction failure is the recurrence of vitreous and/or subretinal seeds.

4. Avoid vitrectomy in eyes with retinoblastoma.

5. Enucleation is an acceptable treatment for advanced retinoblastoma. ■

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