Research Article

Conservative treatment modalities in retinoblastoma

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Retinoblastoma is the most common primary intraocular malignancy of childhood. A potentially curable cancer, its treatment has improved significantly over the last few decades. The purpose of this article is to review the literature on various conservative treatment modalities available for the treatment of retinoblastoma and their effectiveness, when used alone or in combination. PubMed, Medline, Embase, and the Cochrane library were searched through 2012 for published peer reviewed data on conservative treatment modalities for retinoblastoma. Various studies show that while enucleation remains the standard of care for advanced intraocular tumors, conservative modalities that can result in globe salvage and preservation of useful vision are being increasingly employed. Such modalities include systemic chemotherapy, focal consolidation with transpupillary thermotherapy, laser photocoagulation and cryotherapy, plaque brachytherapy, and delivery of local chemotherapy using subconjunctival, sub-tenon, or intra-arterial routes. When used alone or in combination, these treatment modalities can help in avoidance of external beam radiotherapy or enucleation, thus reducing the potential for long-term side effects, while salvaging useful vision. Radioactive plaque brachytherapy has an established role in selected patients with intraocular retinoblastoma. Local injections of chemotherapeutic agents via the sub-tenon or sub-conjunctival route have been used with varying degrees of success, usually as an adjunct to systemic chemotherapy. Intra-arterial ophthalmic artery delivery of melphalan has shown promising results. It is important to recognize that today, several treatment options are available that can obviate the need for enucleation, and cure the cancer with preservation of functional vision. A thorough knowledge and understanding of these conservative treatment modalities is essential for appropriate management.

**Key words:** Chemotherapy, focal treatment, retinoblastoma

Retinoblastoma is the most common primary intraocular malignancy of childhood.\(^1\) The majority of cases are seen in children aged \(<5\) years. The incidence of retinoblastoma is approximately 1 in 18,000 live births worldwide.\(^2\) Unfortunately, more than 3000 children die of retinoblastoma every year, with mortality rates being significantly higher in Asia and Africa.\(^3\) However, the brighter side is that retinoblastoma is a potentially curable cancer, and its treatment has improved significantly over the last few decades.\(^4\) While enucleation remains the standard of care for advanced intraocular tumors, conservative modalities that can result in globe salvage, and preservation of functional vision are being successfully employed in a significant number of patients. Saving vision and preserving the eyeball in a child with retinoblastoma is challenging. Several treatment options that may be used to achieve this include systemic chemotherapy, focal treatment with thermotherapy, laser photocoagulation or cryotherapy, plaque brachytherapy, and local chemotherapy.

**Methodology**

The purpose of this article is to review the literature on various conservative modalities for the treatment of retinoblastoma and their effectiveness when used alone or in combination. PubMed, Medline, Embase, and the Cochrane library were searched through 2012 for published peer-reviewed data on conservative treatment modalities for retinoblastoma. A detailed search was conducted in all document types using the mesh terms: Conservative treatment in retinoblastoma, classification of retinoblastoma, macular retinoblastoma, transpupillary thermotherapy, systemic chemoreduction, focal consolidation, laser photocoagulation, cryotherapy, plaque brachytherapy, local chemotherapy, subconjunctival/sub-tenon carboplatin, intra-arterial chemotherapy, and regression pattern in retinoblastoma. It is hoped that this discussion provides relevant information and guidance regarding the conservative management of retinoblastoma.

**Classification System for Retinoblastoma**

The diagnosis of retinoblastoma is made on the basis of clinical findings at presentation and the use of imaging modalities. Staging of tumor at the time of diagnosis is critical for appropriate management. In order to do so, a thorough knowledge of the currently used Classification System of Retinoblastoma is of paramount importance. The *Reese Ellsworth Classification* [Table 1] developed in the 1960s by Dr. Algernon Reese and Dr. Robert Ellsworth was the most widely accepted classification system for intraocular tumors and was based on the location, multi-focality, and the size of the tumor.\(^5\)

The *Reese Ellsworth* classification system was essentially designed to predict the outcome of treatment with external beam radiotherapy (EBRT), which was used internationally as the primary eye salvage treatment until the introduction of chemotherapy in the 1990’s. Some drawbacks of this classification system were as follows:

**Table 1: Reese Ellsworth Classification**

| Classification | Description |
|----------------|-------------|
| 1               | Bilateral, multifocal tumors |
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Peripheral, multi-focal, and large tumors were assumed to be more aggressive in the EBRT era and earned a higher ranking in the Reese Ellsworth classification, implying a worse ocular prognosis. With the introduction of chemotherapy, this classification system was found to be a poor predictor of chemoreduction success.[9]

The Reese Ellsworth classification system did not address the problem of sub-retinal seeding and did not differentiate between focal and diffuse vitreous seeding.[9]

Hence, it was the need of the hour to propose a new classification that could predict treatment results with chemotherapy more accurately. Multiple centres participated and agreed upon a single classification designed by Murphree and associates. Thus, the International Classification for Intraocular Retinoblastoma [Table 2] was introduced which has subsequently been validated.[10-12]

### Treatment Modalities: Which, When, How?

Conservative treatment modalities for retinoblastoma include systemic chemoreduction, focal consolidation with laser photocoagulation, cryotherapy or thermotherapy, plaque brachytherapy, and local chemotherapy via the subconjunctival, sub-tenon, or intra-arterial routes. Depending on tumor characteristics at the time of initial diagnosis, the treatment protocol is determined. Table 3 gives a broad outline of the treatment protocol that is being currently followed for management of intraocular retinoblastoma.[13] In the following sections, each of these treatment modalities will be discussed in detail.

#### Transpupillary thermotherapy

Thermotherapy involves the application of heat directly to the tumor, usually in the form of infrared radiation. A temperature between 45°C and 60°C is the goal of this therapeutic approach, which is below the coagulative threshold and therefore spares the retinal vessels from coagulation.[14,15] Various proposed mechanisms of action for transpupillary thermotherapy (TTT) include a direct cytotoxic effect of heat on tumor cells and heat-induced alteration of tumor microenvironment, expression of heat shock protein, induction and regulation of apoptosis, action on signal transduction, modulation of drug resistance of tumor cells and increased uptake of carboplatin into tumor cells at temperatures above 44°C.[16,17] The procedure is done under general anesthesia with wide pupillary dilatation using an infrared diode laser (810 nm) mounted on an indirect ophthalmoscope. A spot size of 1.2 mm and a mean power of 300-600 mW is used to cover 100% of tumor area. The end point is a gentle, light gray colour change (“take”) within the tumor during a 1-5 min period, without causing vascular spasm or rapid tumor whitening. In general, the power is started at 200 mW and is increased or decreased at 50-mW increments until an adequate, slow-onset take is observed in the mass.[14,15]

Several studies have been published on the role of TTT in retinoblastoma. In one such study, Abramson et al.[14] reported that retinoblastoma tumors <1.5 DD in base diameter could be successfully treated with TTT alone. In another study, Shields et al.[15] demonstrated the role of TTT in 188 tumors (80 eyes/58 patients) with complete regression in 161 tumors (85.6%) and recurrence in 27 tumors (14.4%). Focal iris atrophy (36%) and peripheral focal lens opacity (24%) were the most common complications. The authors concluded that thermotherapy alone is effective for relatively small retinoblastomas (<3 mm), without associated vitreous or subretinal seeds.[15]

#### Laser photocoagulation

Photocoagulation is done with an argon (532 nm) laser with the purpose of coagulating all the blood supply to the tumor. A mean power of around 350 mW for continuous duration lasting a few seconds is used to obtain satisfactory obliteration of feeding blood vessels. Effective therapy usually requires 2-3 sessions at monthly intervals. Laser photocoagulation alone
is recommended only for small posterior tumors lying away from the fovea and the optic disc, as it can damage these vital areas and can cause visual loss and other complications.[18-20] Complications of this treatment include retinal detachment, vascular occlusions, retinal traction, and pre-retinal fibrosis.[18-20] The advantage of TTT over laser photocoagulation is that tumors adjacent to the fovea or the optic nerve can be treated with TTT, whereas laser can irreversibly damage these important areas. Also, the lower rise in temperature and higher wavelength in TTT (810 nm) helps it to act directly on the retina so that the blood vessels are not damaged. During laser therapy (532 nm), the blood vessels are coagulated, which may lead to retinal ischaemia.[14,21,22]

Cryotherapy

Cryotherapy alone may be used as primary therapy for small peripheral tumors located anterior to the equator. Cryotherapy induces the tumor tissue to freeze rapidly, and a temperature up to −90°C causes intracellular ice crystal formation, protein denaturation, pH changes and cell rupture, resulting in damage to the vascular endothelium with secondary thrombosis and infarction of the tumor tissue.[23,24] Tumors are typically treated three times (triple freeze and thaw technique) per session transconjunctivally, with repeat sessions at monthly intervals.[23,24] Ninety percent of tumors that are less than 3 mm in diameter are cured permanently. The complications are few and rarely serious, and include lid edema, transient conjunctival edema, and transient localized serous retinal detachments.[23,24] Vitreous hemorrhage can be observed in large or previously irradiated tumors.[24]

Plaque brachytherapy

Radioactive plaque brachytherapy has an established role for selected patients of retinoblastoma. The indications include solitary tumors located anterior to the equator until the ora serrata, primary unilateral retinoblastoma of size <16 mm in base, and <8 mm in thickness, and recurrent or residual tumors after primary chemotherapy or failed EBRT.[25-28] Relative contraindications include larger tumors and those involving the macula. Radioisotopes such as Iodine (I125) and Ruthenium (Ru106) are the most commonly used isotopes.[29-31] Iodine (I125) seeds are inserted into a gold carrier to protect normal surrounding tissue from radiation. The radiation dose required is calculated by dosimetry planning to provide upto 40 Gy to the tumor apex. The plaque is kept in situ until the desired radiation dose has been delivered, usually over a period of 2-4 days. Special plaques with a notch are used to treat tumors adjacent to the optic disc. Side effects of radiation therapy include dryness of the eye, irritation, madarosis, cataract, scleral necrosis, or surgical complications.[25-28] Second malignancies do not appear to be associated with this type of local therapy. In one study on the role of plaque brachytherapy in retinoblastoma, Shields et al. reported that plaque radiotherapy provided tumor control in 79% of cases at 5-year follow-up.[28] It was found to be particularly useful for those tumors that failed treatment with other conservative modalities. Tumors in young patients without vitreous or subretinal seeding showed the best long-term control.[28]

Recently, newer non-invasive radiotherapy techniques such as stereotactic conformal radiotherapy (SCR) that use highly accurate positioning to deliver treatment with small beams have been shown to provide an interesting alternative to brachytherapy. A recent study has shown that SCR provides more homogeneous dose within the target volume and similar or lower doses to the surrounding normal tissues.[32] However, additional studies with long-term results are needed to prove its efficacy over plaque therapy.

Systemic chemotherapy

Systemic chemotherapy has been used to treat intraocular retinoblastoma since the early 1990s. This treatment modality gained momentum after observations of increased tumor control and ocular salvage rates of 30-70% when systemic chemotherapy was given prior to EBRT.[33] The recognition of increased risk of second non-ocular cancers with external beam radiation also contributed to the growing popularity of chemotherapy.

The common indications of chemotherapy for retinoblastoma include tumors that are large and cannot be treated with local therapies alone [Fig. 1], recurrent and relapsed tumors, and as an adjuvant therapy to enucleation in cases of high-risk histopathologic characteristics.[34-36] The most commonly used chemotherapeutic agents include carboplatin vincristine and etoposide.[35] Table 4 shows the standard dosage and schedule

| Group | Treatment options |
|-------|-------------------|
| A     | Focal therapy     |
|       | (TTT/Cryotherapy/Laser Photocoagulation) |
| B     | 1) Systemic chemotherapy (VEC)* |
|       | 2) Focal therapy along with chemotherapy cycles |
|       | 3) Plaque radiotherapy |
| C     | 1) Systemic chemotherapy (VEC)* |
|       | 2) Focal therapy |
|       | 3) Sub-tenon Carboplatin |
| D     | 1) Systemic chemotherapy (VEC)* |
|       | 2) Focal therapy |
|       | 3) Sub-tenon Carboplatin |
|       | 4) External beam radiotherapy |

*VEC: Vincristine, Etoposide, Carboplatin, 6 cycles, given every 28 days

Figure 1: Fundus photograph of a 2-year-old girl showing multiple tumors in the left eye
of drugs that are recommended for use.\[^{37}\] Cyclosporine has also been used by some centres to overcome drug resistance.\[^{38}\] Other drug combinations have been reported such as two-drug therapy of Vincristine and Carboplatin in order to decrease the side effects of Etoposide.\[^{39}\]

Chemotherapy is used to reduce the size of the tumor to allow local therapies such as cryotherapy, laser photoagulation or thermotherapy to eradicate the remaining disease. This combination therapy is effective in avoiding EBRT and enucleation, thereby decreasing the potential long-term side effects, while salvaging some useful vision. Combined treatment has been proven to be more efficacious for tumor control than chemotherapy alone. Studies have shown that chemotherapy alone resulted in tumor control rates of 51-65% as compared to 62-100% with combined treatment in patients with retinoblastoma (R-E Groups I–IV).\[^{9,40-43}\] For more advanced tumors (R-E group V), chemotherapy alone resulted in tumor recurrence in 63-75% of tumors, as compared to 17-57% of tumors treated with chemoreduction combined with local consolidation.\[^{9,40-43}\] Shields et al., reported success rates of 100% in group A, 93% in group B, 90% in group C, and 47% in group D eyes, when tumors were treated with a combination of systemic chemotherapy and focal therapy.\[^{44}\] In another study on macular retinoblastoma, treatment with chemoreduction plus adjuvant foveal-sparing thermotherapy was found to be more favourable (83%) than chemoreduction alone (65%).\[^{44}\]

Close monitoring of the child by a pediatric oncologist is required during and after chemotherapy, with regular assessment of blood counts to look for any signs of toxicity. The standard chemotherapy regimen is usually well tolerated by patients. Side effects include myelosuppression, neutropenia, invasive bacterial infection, hepatotoxicity and increased risk of second malignancies.\[^{34-36,45,46}\] Ototoxicity and renal toxicities are rare.

**Local chemotherapy**

**Sub-conjunctival/sub-tenon route**

Local injections of chemotherapeutic agents via the sub-tenon or sub-conjunctival route have been used as an adjunct to systemic chemotherapy, in order to avoid enucleation and EBRT in cases of group C and group D retinoblastoma with vitreous/subretinal seeds. This is because systemic chemotherapy alone is not very effective in avoiding EBRT/enucleation in patients with advanced intraocular retinoblastoma, especially those with vitreous seeds. In one study, Friedman et al.,\[^{36}\] reported that only 53% of RE Group V eyes (C, D, or E in the International classification) could be controlled with chemotherapy alone. Chan et al.,\[^{47}\] and Villablanca et al.,\[^{48}\] reported that approximately 40% of group C and 70% of group D eyes failed systemic chemotherapy alone. Based on these observations, the trial proposed by the Children's Oncology Group (COG) involved use of systemic chemotherapy with carboplatin, vincristine and etoposide, along with subtenon carboplatin for group C and D eyes.\[^{49,50}\] Sub-tenon carboplatin, although slightly more invasive than the subconjunctival route, is associated with rapid diffusion of the drug and a decreased incidence of lid swelling. Side effects reported include optic nerve ischemic necrosis and atrophy, reduced ocular motility due to fibrosis, orbital fat necrosis, moderate loss of orbital volume, and pseudopseudopterpeal cellulitis.\[^{34-33}\] The Children's Oncology Group recommends the use of 20 mg sub-tenon carboplatin along with systemic chemoreduction and focal consolidation for Group C and D tumors.\[^{54}\] Leng et al., reported that cases with early retinoblastoma tumors that progressed despite laser ablative therapy could be effectively controlled with adjuvant treatment using sub-conjunctival carboplatin.\[^{55}\] While short-term results are favorable for tumor control, the long-term risk profile needs to be determined.

**Superselective intra-arterial chemotherapy**

Concern about the side effects of systemic chemotherapy in young children has stimulated the development of novel approaches for delivering chemotherapy to the globe. There have been reports suggesting that intra-arterial infusion of chemotherapy is effective for intraocular retinoblastoma. Over the last two decades, Japanese investigators have reported their experience with an interventional radiology technique of infusing melphalan into the carotid artery in cases with retinoblastoma.\[^{56-58}\] Melphalan is a powerful alkylating agent, but its applications have been limited with systemic administration because of severe bone marrow toxicity. The technique of intra-arterial infusion involved the use of a femoral artery puncture and a balloon catheter that was passed into the internal carotid artery and inflated to occlude the internal carotid artery beyond the orifice of the ophthalmic artery, allowing chemotherapy infused into the cervical internal carotid artery to perfuse the eye selectively, without perfusing the brain. Utilizing this technique, Suzuki and Kaneko reported their experience in 187 patients with promising results.\[^{59}\] The disadvantage with this technique was that the infusions were not truly selective, because intracranial vascular territories also received high concentrations of chemotherapy through the cavernous branches of the internal carotid.\[^{59}\] Moreover, all eyes received concomitant treatment with hyperthermia, external beam radiation, and/or intraocular injection of melphalan, making it difficult to ascertain the contribution of the carotid artery infusion in achieving excellent clinical outcomes.\[^{59}\] In a Phase I/II clinical trial, Abramson et al.,\[^{59}\] reported their initial experience with direct intra-arterial (ophthalmic artery) chemotherapy using melphalan in 10 children with advanced retinoblastoma who were indicated for enucleation. They developed a technique that would permit repeated cannulation of the ophthalmic artery.\[^{59}\] Under general anaesthesia, the femoral artery was punctured and an arterial sheath was placed.\[^{59}\] Anticoagulation was obtained with intravenous heparin.\[^{59}\] The catheter was guided into the ipsilateral internal carotid artery.\[^{59}\] An arteriogram was performed to visualize the eye and the cerebral vasculature and to determine the take-off of the ophthalmic artery from the internal carotid.\[^{59}\] Using fluoroscopy and roadmapping, the ophthalmic artery

| Drug         | Dosage and schedule                                                                                   |
|--------------|--------------------------------------------------------------------------------------------------------|
| Carboplatin  | 560 mg/m² in 120 ml/m² D5 ¼ NS IV infusion over 60 min with adequate hydration, day 0 of each cycle (18.6 mg/kg for patients<36 months of age) |
| Etoposide    | 150 mg/m² in 150 ml/m² D5 ¼ NS IV infusion over 60 min, days 0 and 1 of each course (5 mg/kg for patients <36 months of age) |
| Vincristine  | 1.5 mg/m² IV push day 0 of each cycle. Maximum dose not to exceed 2 mg (0.05 mg/kg for patients <36 months of age) |
was selectively catheterized using a microcatheter. Once the microcatheter was in stable position at the ostium of the ophthalmic artery, a selective angiogram was performed to verify that the artery vascularized the entire vascular crescent. The drug was prepared as 5 mg/ml and then diluted in 30 cc of saline. After the chemotherapy infusion, the catheters were withdrawn, and hemostasis of the femoral artery was obtained by manual compression.

In their study, Abramson et al., reported a dramatic regression of tumors, vitreous seeds, and subretinal seeds in each case. No severe systemic side effects such as sepsis, anemia, neutropenia or death occurred. There was no toxicity to the cornea, anterior segment, pupil or motility. Vision stabilized or improved after treatment and 7 eyes that were destined to undergo enucleation were salvaged. Recently, Gobin et al., reported on their 4 year experience of selective ophthalmic artery cannulation on 95 eyes of 78 patients with unilateral or bilateral advanced intraocular retinoblastoma. The Kaplan-Meier estimates of ocular event-free survival rates at 2 years were 70.0% for all eyes, 81.7% for eyes that received intra-arterial chemotherapy as the primary treatment, and 58.4% for eyes that had previous treatment failure with intravenous chemotherapy and/or EBRT. There were no permanent extra-ocular complications, thus suggesting that intra-arterial chemotherapy is safe and effective for the treatment of advanced intraocular retinoblastoma.

Based on these encouraging results, intra-arterial chemotherapy has also been used as a primary treatment modality for less advanced cases of intraocular retinoblastoma (RE I, II, III, and ICRB B and C). In a study by Abramson et al., a high rate of success was achieved with retention of 100% of treatable eyes and results equaled or exceeded conventional therapy with less toxicity. Other studies have also shown the safety and efficacy of intra-arterial chemoablation for retinoblastoma, including the use of alternative sites. While initial results are promising, long-term results are needed to establish the role of intra-arterial chemotherapy in retinoblastoma.

### Regression Patterns

Familiarity with tumor regression patterns is essential in order to be able to differentiate tumor regression from an incomplete response or tumor recurrence. Upon regression, the retinoblastoma assumes a smaller size with stable margins and frequently attains some degree of calcification. Judgment of regression is challenging, as some tumors become completely calcified, whereas others have minimal or no calcification [Figs. 2 and 3]. Regression patterns were initially reported in retinoblastoma tumors that were treated with EBRT. Recently, regression patterns following systemic chemoreduction have been described. Table 5 summarizes the regression patterns noted after chemotherapy.

To conclude, saving the globe and preserving functional vision in a child with retinoblastoma is challenging. Several treatment options are available in the armamentarium of an ocular oncology practice that can obviate the need for enucleation, and cure the cancer with preservation of functional vision. A thorough knowledge and understanding of all these conservative treatment modalities is essential for appropriate management.

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