World Journal of Pharmacology

Online Submissions: http://www.wjgnet.com/esps/
wjpharmaco@wjgnet.com
doi:10.5497/wjp.v2.i3.65

World J Pharmacol 2013 September 9; 2(3): 65-72
ISSN 2220-3192 (online)

TOPIC HIGHLIGHT

Ashim K Mitra, Professor, *Series Editor*

Retinoblastoma and treatment: A current evaluation of advanced therapy

Nisha V Shah, Samuel K Houston, Timothy G Murray

Nisha V Shah, Samuel K Houston, Timothy G Murray, Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL 33136, United States

Author contributions: Shah NV, Houston SK and Murray TG solely contributed to this paper.

Correspondence to: Timothy G Murray, MD, MBA, Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 900 N.W., 17th Street, Miami, FL 33136, United States. tmurray@murraymd.com
Telephone: +1-305-3266166 Fax: +1-305-3266417
Received: February 4, 2012 Revised: May 31, 2013
Accepted: June 18, 2013
Published online: September 9, 2013

Abstract

Retinoblastoma is the most common primary childhood ocular tumor, affecting nearly 3.5 per million children worldwide. A mutation in the *RB1* gene, which presents as either germline or sporadic, along with additional mutational events, promote neoplastic growth in the retina. Fortunately, current treatment protocols result in success rates approaching 99% at specialized centers, with many children maintaining useful vision. Overall, treatment is guided by aggressiveness and size, and is classified by systems such as the Reese-Ellsworth System and the International Classification of Retinoblastoma. Due to advances in chemotherapy protocols combined with use of focal laser consolidation, treatment paradigms have shifted from enucleation to external beam radiation therapy to chemotherapy as globe-salvaging therapies. Smaller, less complex tumors may be controlled by plaque radiotherapy or focal laser ablative therapy. However, larger and more complex tumors, such as those that have vitreous or subretinal seeding, require methods of chemoreduction combined with focal consolidation to yield better outcomes. Standard chemotherapy protocols utilize vincristine, etoposide, and carboplatin with or without cyclophosphamide. Finally, there has been a recent push in local treatments for retinoblastoma to minimize systemic toxicities. These modalities include intravitreal or subconjunctival injections and more recently, direct chemotherapy administration into the ophthalmic artery. As a result, enucleation is used less often, but remains an important treatment for the most aggressive, refractory cases. The advancement of retinoblastoma treatment looks promising; however, worldwide access to these treatments and the lack of long-term follow-up of new local treatment modalities constitute current and future challenges.

Key words: Retinoblastoma; Treatment

Core tip: Retinoblastoma is the most common primary childhood ocular tumor, affecting nearly 3.5 per million children worldwide. Due to advances in chemotherapy protocols combined with use of focal laser consolidation, treatment paradigms have shifted from enucleation to external beam radiation therapy to chemotherapy as globe-salvaging therapies. The advancement of retinoblastoma treatment looks promising; however, worldwide access to these treatments and the lack of long-term follow-up of new local treatment modalities constitute current and future challenges.

Shah NV, Houston SK, Murray TG. Retinoblastoma and treatment: A current evaluation of advanced therapy. *World J Pharmacol* 2013; 2(3): 65-72 Available from: URL: http://www.wjgnet.com/2220-3192/full/v2/i3/65.htm DOI: http://dx.doi.org/10.5497/wjp.v2.i3.65

INTRODUCTION

With nearly 3.5 per million children affected worldwide[1],

retinoblastoma remains the most common primary childhood ocular cancer, accounting for nearly 3% of childhood tumors[2,3]. Heritable or familiar retinoblastoma occurs from a germline mutation in the *RB1* gene, and typically presents within the first year of life with bilateral disease, often with multifocal tumors. The more common sporadic (non-heritable) form typically presents later with unilateral disease with a single tumor focus. The *RB1* mutation, with additional proposed mutational events, promotes neoplastic growth in the retina, leading to clinical retinoblastoma tumors with risk of vision loss, extraocular extension, optic nerve invasion, metastasis, and death.

The worldwide incidence of retinoblastoma ranges between 7000-8000 cases a year. The worldwide mortality rate of 3000-3376 ranges among nations: from 3%-5% in North America and Europe to 20% in Latin America, 39% in Asia, and up to 70% in Africa. Fortunately, due to advances in treatment and early detection, the survival rate for retinoblastoma in the United States and other countries has approached 99% at specialized centers[3,4].

Treatment of retinoblastoma is complex and involves participation from various medical specialties including ocular oncology, pediatric oncology, pediatrics, interventional radiology, and ocular pathology. Factors affecting management include size and location of the tumor, metastatic risk, location, and laterality[5,6]. Due to advances in the past decade, systemic chemotherapy combined with focal laser treatment has gained popularity, particularly since it preserves the globe with hopes of maintaining some vision[5,6]. Treatment ranges from chemotherapy, to plaque radiation, to enucleation for the more severe and refractory cases. Recently, local treatments such as intra-arterial chemotherapy offer a novel alternative by demonstrating promise as a primary and salvage treatment, while minimizing systemic toxicities. The current review discusses the evolution of retinoblastoma treatment, highlighting recent advances with the aim of saving the life, eye, and vision of children with retinoblastoma.

Classification

Various classification guidelines have been created to classify the severity of retinoblastoma. The Reese-Ellsworth (R-E) classification (Table 1) was developed when the primary mode of treatment consisted of external beam radiotherapy (EBRT) and enucleation. This classification system is based on tumor size and location, with vitreous and subretinal seeding reserved for stage Vb tumors. The R-E classification system offered information regarding globe salvage with EBRT. More recently, in the era of chemoreduction with focal consolidation, a new system to predict response to this treatment was developed. In 2003, the International Classification of Retinoblastoma (ICRB) (Table 2) was introduced to stage retinoblastoma and accounted for the advances in chemotherapy. Previous methods such as the R-E classification system can be used to predict the success rates of chemoreduction, but does so in a non-incremental fashion[7]. Newer methods of classification, such as the "Practical Grouping system of RB" have also been effective tools. The Practical System also accounts for the distance of the seeds from the tumor, and the presence of glaucoma, hemorrhages, and optic nerve invasion[8]. Overall, the newer classification systems are based on clinical features involving the presence of subretinal fluid, subretinal seeds, and vitreous seeds, key factors that determine treatment success.

TREATMENTS

Children with unilateral, sporadic retinoblastoma have several management options, which include enucleation, plaque radiotherapy, laser therapy, systemic chemotherapy, and intra-arterial chemotherapy. If the tumor is small to medium size and there is little subretinal fluid, plaque radiotherapy can generally achieve tumor control. Small tumors may also be amenable to focal laser ablative therapy. Larger tumors or those with vitreous or subretinal seeding or subretinal fluid usually require methods of chemoreduction combined with focal consolidation utilizing laser ablation. The largest size retinoblastoma, with no potential for functional vision, often requires enucleation[5,9]. Most children with trilateral retinoblastoma, which is defined as bilateral retinoblastoma with pineal gland involvement, are treated with intravenous chemoreduction[10,11]. Novel therapies have been investigated for local delivery of chemotherapeutics, including focal, periocular injection of carboplatin, as well as superselective intra-arterial delivery of chemotherapeutics.

Radiation

EBRT previously served as primary globe-salvaging treatment, but is now rarely used due to risk of recurrence and to radiation-induced side effects. Such ocular side effects include cataract, radiation maculopathy, and radiation optic neuropathy, as well as effects on bony development leading to facial malformations. Additionally, EBRT toxicity may lead to secondary cancers in the radiation field involving the orbital soft tissue as well as osteosarcomas[11-13].

Radioactive plaques with various isotopes, but more commonly iodine-125 in the United States, are temporarily placed onto the scleral surface of the eye under ultrasound guidance, to deliver 40-45 Gy of radiation to the tumor apex[14]. They are most effective in small tumors < 15 mm in diameter or < 10 mm thickness. Other factors involve location of tumor in relation to optic nerve and fovea, plaque placement feasibility, and refractory nature of the tumor[14]. A study on 208 tumors undergoing plaque brachytherapy for RB showed that plaque therapy is most effective in tumors refractory to chemoreduction, laser, thermotherapy, and cryotherapy. These patients displayed tumor control of 83% at 1 year and 79% at 5 years. The study found the most common 5-year side effects were cataract, papillopathy, maculopathy, and glaucoma. Evidence suggests that prognostic factors for successful radiation treatment include tumors that lack subretinal or vitreous seeding[14,15]. Although radiation is a reliable

Table 1 Reese-Ellsworth classification

Group	Globe salvage likelihood	Features
I	Very favorable	< 4 disc diameters at or behind equator (1) solitary (2) multiple
II	Favorable	4-10 disc diameters, at or behind equator (1) solitary (2) multiple
III	Doubtful	(1) anterior to equator (2) solitary, > 10 disc diameter behind equator
IV	Unfavorable	(1) multiple tumors, some > 10 disc diameters (2) lesion extends anteriorly to ora serrata
V	Very unfavorable	(1) tumors occupying over 50% of retina (2) vitreous seeding

Source: Adapted from[56].

method, it may not outweigh the risk of radiation retinopathy[15], and with the development of novel delivery techniques such as periocular and intra-arterial chemotherapy, plaque brachytherapy is used less often in salvage or primary therapy.

Laser therapy

Laser therapy consists of using a diode laser *via* indirect ophthalmoscopy to apply precise burns to the entirety of the tumor. Laser therapy is performed during exam under anesthesia (EUA), and is used as monotherapy, combined with systemic or intraarterial chemotherapy, or for focal tumor recurrences. For small, unilateral tumors, local laser ablative therapy may spare a child systemic or local chemotherapy and can be used as monotherapy. However, children must continue to have frequent EUAs, as new tumors can occur at sites away from the solitary lesion. Studies have shown that systemic chemotherapy combined with focal laser consolidation is more efficacious than systemic chemotherapy alone, with in-depth discussion in the next section. Finally, laser therapy does not prove efficacious for vitreous or subretinal seeds, but is often used for focal, marginal recurrences following primary tumor treatment. Overall, laser ablative therapy plays an important role in the primary management of retinoblastoma.

Chemotherapy

To maintain globe-salvage while eliminating the risk of radiation complications, systemic chemotherapy has become a popular treatment modality in the management of retinoblastoma[16]. Due to carboplatin's success among treatment of other pediatric tumors, it remains a widely used choice to treat RB[16] and is combined with other agents such as etoposide, vincristine, and occasionally cyclophosphamide[17,18]. Evidence suggests that such multi-agent chemotherapy may have better outcomes when given in combination with focal laser ablation. For instance, of 36 eyes with R-E Group I -V that were given carboplatin and vincristine at 3-wk intervals over a 6 mo period, nearly half (52%) of eyes showed tumor growth and 42% had vitreous seeding, indicating that multi-agent chemotherapy alone may not be sufficient[19]. Shields *et al*[9] showed that of 83 eyes in R-E Groups I -IV, chemoreduction with 6 cycles of Fluorouracil (5FU), epirubicin and cyclophosphamide combined with cryotherapy, thermotherapy, or plaque radiotherapy showed treatment failure of 10% by 5 years, causing the need for additional EBRT; for eyes in R-E Group V, combination failure was 47% at 5 years. The study also showed that by 5 years, 35% of eyes required enucleation. The eyes requiring enucleation included 15% of R-E Group I -IV eyes and 53% of R-E Group V eyes. Although there was no long-term follow-up, no child developed metastasis or died in the series[9].

When treatment involves both 4-9 cycles of chemotherapy and a diode laser ablation to all tumor areas including macular and foveal components, tumor control rates for R-E Group I -IV have been reported to be 100% at 3 years[20]. Further evidence suggests that recurrence rates of more aggressive (R-E Group Vb and Group D) tumors may decrease when treated with systemic chemotherapy and local consolidation. Shields *et al*[21] demonstrated that ICRB Group D tumors (or RB with diffuse seeds) had a 47% success rate with chemoreduction combined with focal consolidation. Schefler *et al*[20] has also shown success rates as high as 83% in aggressive Group V tumors that were treated with the diode laser therapy to the macular and foveal components of the tumor in combination with 4-9 cycles of systemic chemotherapy. Of note, 57% of these patients retained a 20/80 or better vision outcome, despite direct ablation to the fovea[20].

Lastly, the most aggressive ICRB Group E tumors benefit most from enucleation and histological analysis. High-risk features on histopathologic analysis may be considered for adjuvant chemotherapy. These factors include deep choroidal invasion, or involvement of the anterior chamber, iris, ciliary body, or optic nerve. Successful prognostic factors for systemic chemoreduction include tumor margins at least 3 mm from fovea/optic disk and lack of subretinal fluid[22]. Poor prognostic features include anterior chamber seeding, iris infiltration, ciliary body infiltration, involvement of optic nerve, choroidal involvement, and infiltrates into the sclera[23].

Standard chemotherapy protocols utilize vincristine, etoposide, and carboplatin with or without cyclophosphamide. Other medications that have been the subject of more recent studies involving systemic treatment and local delivery include melphalan, paclitaxel, topotecan, and cisplatin.

Paclitaxel, an antineoplastic agent that stabilizes microtubules, and topotecan, a topoisomerase I inhibitor, have shown early promise. At the cellular level, paclitaxel used in combination with β-lapachone has been shown to induce apoptosis in human RBY79 cells[24]. In animal models, local delivery of paclitaxel *via* subconjunctival injections resulted in reduced tumor size in a dose-dependent manner. Toxicities observed were conjunctival and corneal toxicity and lens opacification[25]. Another antineoplastic agent that shows potential therapeutic effects for retinoblastoma treatment is topotecan, which

Table 2 International classification of retinoblastoma

Group	Subgroup	Quick reference	Features
A	A	Small tumor	size ≤ 3 mm
B	B	Larger tumor	Size > 3 mm
		Macula	≤ 3 mm to foveola
		Juxtapapillary	≤ 1.5 mm to disc
		Subretinal fluid	Clear subretinal fluid ≤ 3 mm from margin
C	C1	Focal seeds	Subretinal seeds ≤ 3 mm from tumor
	C2		Vitreous seeds ≤ 3 mm from tumor
	C3		Both subretinal and vitreous seeds ≤ 3 mm from tumor
D	D1	Diffuse seeds	Subretinal seeds > 3 mm from tumor
	D2		Vitreous seeds > 3 mm from tumor
	D3		Both subretinal and vitreous seeds > 3 mm from tumor
E	E	Extensive retinoblastoma	> 50% globe involvement or Neovascular glaucoma hemorrhage in anterior chamber, vitreous, or subretinal space Invasion to postlaminar optic nerve, choroid (> 2 mm), sclera, orbit, anterior chamber

Source: Adapted from[7].

traps the cell cycle in S-phase[26]. Studies showed similar topotecan vitreous drug levels in rabbit eyes that were administered *via* the periocular or systemic route[27] although murine retinoblastoma models suggest prolonged drug levels when delivered intravitreously[28]. Chantada *et al*[29] administered various periocular doses in a pilot study on 5 children with retinoblastoma, which showed dose-dependent systemic absorption with no toxicities. Another study on children showed tumor reduction with a median dose of 3.72 mg/m^2 when periocular topotecan was combined with fibrin, causing reduced tumor volume and lowering rates of enucleation or additional systemic chemotherapy[30].

Although chemotherapy has been shown to be efficacious in the treatment of RB, it is not without risks, especially when toxic chemotherapeutics are administered to children and infants. Systemic chemotherapy has been associated with systemic toxicities, including pancytopenias requiring hospitalizations and transfusions[31]. In addition, there is concern for nephrotoxicity, as well as ototoxicity in platinum-based chemotherapy agents. Carboplatin related ototoxicity has been reported in up to 5% of patients undergoing treatment for retinoblastoma, the risk increasing when carboplatin is administered with cisplatin[32]. However, there is controversy regarding the actual incidence of ototoxicity in children treated with chemotherapy for RB with recent reports by the Childrens' Oncology Group indicating a very low incidence and recommendation that these agents not be withheld for these concerns. Nonetheless, focus has shifted on adjuvant agents that avoid or decrease systemic doses of chemotherapy, as well as local delivery of chemotherapeutics to avoid systemic administration.

In the pre-clinical setting, vascular targeting agents, such as anecortave acetate, have proven efficacious in the LHBETATAG mouse model for retinoblastoma, demonstrating a decrease in the vascularity of tumors while enhancing tumor control when combined with chemotherapy or other agents[33]. Glycolytic inhibitors, such as 2-deoxy-D-glucose, have also been investigated in the LHBETATAG model and shown to target hypoxic regions of tumors. Retinoblastoma tumors have been shown to have up to 21% hypoxia, areas that consist of slow-growing tumor cells unlike other hyperproliferation areas[34]. These hypoxic cells are resistant to chemotherapy and radiation therapy which target hyperproliferation cells. Advanced retinoblastoma tumors universally fail due to persistent vitreous seeding, tumor foci without an established blood supply and proposed regions of hypoxia[35]. Further studies and human trials are needed to determine the utility of glycolytic inhibitors, anti-angiogenic agents, as well as other novel agents. Of note, the use of adjuvant agents must be optimally timed and used in combination to maximize the efficacy and synergistic effect[36].

Local treatments

Local treatment forms include subconjunctival (sub-Tenons') injections, intravitreal injections[37,38] and intra-arterial administration. The advantage of administering chemotherapeutic agents locally includes the ability to administer higher concentrations of medication that would otherwise cause considerable toxicity if administered systemically. Local chemotherapy in the form of intravitreal or subconjunctival/sub-Tenon's injections has been shown to have benefits in murine/animal models, where subconjunctival carboplatin injections had a dose dependent effect on tumor control[37,38]. The rational for this treatment is to provide a deeper chemotherapy administration that bathes the sclera. Leng *et al*[39] demonstrated that periocular carboplatin injection may especially be an effective adjunct in the treatment of resistant, advanced retinoblastoma. A case report of retinoblastoma refractory to diode laser ablation showed tumor regression with chorioretinal scarring after receiving periocular injections of carboplatin. In a phase I / II trial, Abramson *et al*[40] investigated the efficacy and toxicity of up to 2 mL and 20 mg/injection of peri-ocular carboplatin injection for treating intraocular retinoblastoma. Three of five eyes

with vitreous disease showed a response to treatment while the eye with subretinal seeding did not display a response. Although 54% of eyes had vitreous seeding, major tumor response was observed. Toxicities included transient periorbital edema, optic atrophy, muscle fibrosis, and vascular alteration. Such vascular sclerosis may lead to subsequent delay in transit through the vessels, a factor that must be considered when administering other future treatments, including systemic chemotherapy or local intra-arterial delivery. Thus, there seems to be promise of periocular carboplatin injections for treating resistant retinoblastoma with vitreous seeding, but vascular alterations need to be considered when planning intra-arterial delivery in patients that have received periocular carboplatin in the past.

To avoid systemic chemotherapy and to deliver concentrated doses to local tissue, local delivery of chemotherapeutics is currently being investigated *via* intra-arterial delivery. A group in Japan[41,42] pioneered the technique of selective ophthalmic arterial infusion (SOAI). A catheter is passed into the carotid artery and advanced past the ostium of the ophthalmic artery. A balloon is then used to occlude distal flow, followed by infusion of chemotherapeutics, thus minimizing exposure to the brain. In a study involving 187 patients (610 eyes) treated with intraocular retinoblastoma, technical success rates of the procedure were as high as 97.51%[41]. The study found no complication of brain infarction from catheterization. Side effects included bradycardia, facial redness, and mild eye-lid swelling. This study concluded that for patients with intraocular retinoblastoma, SOAI using balloon occlusion may provide a safe and effective form of drug delivery. Of note, this initial study failed to report on tumor control rates or visual outcomes, but provided proof of principle for this novel delivery technique.

Following these initial studies, other groups investigated techniques for intra-arterial delivery, including direct cannulation of the ophthalmic artery, termed superselective intra-arterial chemotherapy[43]. Initial phase I / II studies showed promise as salvage therapy as 6 of 8 eyes were spared from enucleation[43]. Abramson *et al*[43] showed that intra-arterial chemotherapy could also be used as a primary therapy. Effective drug combinations showing promise in R-E Group V classification patients include melphalan alone, melphalan with topotecan, and melphalan with topetecan and carboplatin. A 4-year prospective study on 95 eyes undergoing intra-arterial chemotherapy *via* selective catheterization of the ophthalmic artery further showed promising results. Chemotherapy injections included melphalan with or without topotecan. Two-year survival rates free of ocular events were as high as 81.75% for eyes that received this treatment as primary therapy. In addition, no eyes in R-E Group I -IV were enucleated. Enucleation was performed, however in 19 of 83 (23%) of Group V eyes due to vitreous seeding[44]. One of the largest studies on SOAI involved 1452 procedures on 408 eyes with Group A-E retinoblastoma that received melphalan[42]. The patients were followed from 1988-2007, and showed a technical success rate of 98.8%. In terms of therapeutic response, secondary neoplasms occurred in only 11 patients, the 15-year cumulative incident rate being 5.8%. Hundred percent of ICRB Group A eyes were salvaged, 88% of Group B, 65% of Group C, 45% of Group D, and 30% of Group E. For patients with non-macular tumors, over half (51%) of eyes had a visual acuity greater than 0.5 and 36% of eyes had a visual acuity > 1.0 at the last follow up visit. Side effects noted were severe orbital inflammation in 0.5% of cases, diffuse chorioretinal atrophy in another 0.5%, and transient periocular swelling in some cases. No patients showed systemic toxicities[42].

A study by Vajzovic *et al*[45] at Bascom Palmer Eye Institute studied the complication and safety profile of intra-arterial melphalan chemotherapy in 12 eyes of 10 children with advanced RB (R-E stage Vb or International Classification Group D). The study of 12 eyes receiving ophthalmic artery melphalan for 9 mo showed no tumor progression at the 6-mo follow up visit. The study suggested that melphalan holds promise as a globe-conserving treatment option in advanced RB cases[46]. Further study showed that in the most severe cases requiring enucleation, infusing melphalan directly in the ophthalmic artery has proven to significantly decrease the enucleation rate from 100% to 23.5%[37]. Additional patients from Bascom Palmer were included in a study by Peterson *et al*[46] showing that of 17 tumors of 15 patients, 76% of the tumors were spared enucleation due to its response to melphalan. Of note, the study demonstrated that doses below 5 mg had a higher rate of failure and vitreous hemorrhage compared to those eyes treated with 5 mg or higher. These findings suggest further studies are needed determine ideal dosing strategies. Finally, Shields *et al*[47] published a series of reports on children with Rb undergoing intra-arterial chemotherapy. They showed that Group C or D eyes showed 100% and 33% globe salvage, respectively. The treatment showed promise for patients with subretinal seeds where 9/11 (82%) demonstrated complete response, and 6/9 (67%) of eyes with vitreous seeds showed complete response.

For cases presenting with vitreous seeding, studies have shown promise in melphalan administered *via* intravitreal injections, showing long term success rates of eye preservation up to 60%[15,41]. However, penetrating an eye harboring retinoblastoma presents the risk of extraocular extension. Recent techniques have been described combining elimination of vitreous reflux and application of cryotherapy to the sight of injection to minimize the risk of extraocular extension. Nonetheless, in cultures where enucleation is not acceptable, risks *vs* benefits of these treatments must be weighed and discussed thoroughly with the family.

For cases with bilateral retinoblastoma, melphalan administration with focal ablative treatment may also avoid enucleation[12,45]. Evidence suggests that subsequent, bilateral administration of chemotherapy through the ophthalmic artery may be safe and effective, termed tandem therapy. A case series on 4 patients by Abramson *et al*[43] showed no metastasis, and a 100% salvage rate, although 1 patient did develop neutropenia.

Intra-arterial melphalan has been shown to cause several local side effects and warrants some discussion. The study by Vajzovic *et al*[45] on 12 children showed local side effects such as retinal and choroidal microemboli in 9% of cases, vitreous hemorrhage in 25% of cases, and myositis in 8% of cases. Other side effects reported with melphalan include lid edema, forehead hyperemia, eyelash loss[12], as well as neutropenia, intraretinal hemorrhages, peripapillary cotton wool spots, vitreous hemorrhages, and periocular edema from myositis[45]. Other vascular side effects include ophthalmic artery stenosis, and potentially blinding vascular obstruction from thrombotic events[47-49]. A report by Shields *et al*[47] showed that of 16 cases, eyelid edema, blepharoptosis, and orbital congestion with temporary loss of motility were seen, but resolved within 6 mo. Permanent and potentially blinding complications included 3 cases of ophthalmic artery stenosis, 2 cases with retinal artery occlusion[47], and other reports of ciliary thrombosis in enucleated eyes receiving IAC have been reported[47,49].

Failure rates of intra-arterial melphalan therapy are higher for tumors refractory to other treatment modalities. A histopathologic case series of the enucleated eyes of 3 patients showed the presence of viable tumor, even after super-selective intra-arterial melphalan treatment. Two of the three eyes were high grade tumors, based on TNM staging, with optic nerve invasion[50]. A recent study by Graeber *et al*[51] also showed presence of non-necrotic, non-calcified tumor cells in 5/9 enucleated eyes that underwent chemosurgery.

PROGNOSIS

Children who do not develop tumor recurrence for at least 5 years are considered cured[52]. Lifetime follow up is still required due to risks of metastatic spread and death from secondary malignancies, which can be as high as 40% within 50 years of diagnosis for bilateral/hereditary RB[53]. Trilateral retinoblastoma, which involves both eyes and the pineal gland, is highly fatal, with a median survival of 9 mo[54]. Long-term survivors should also be followed for the development of second malignancies with periodic physical examination, laboratory screening, and radiology testing, depending upon specific risk factors.

CONCLUSION

Overall, the characteristics of retinoblastoma in terms of classification, size, location, and presence of seeding, guide the ocular oncologist to determine potential treatment modalities. However, it is of utmost importance to include the family in the decision-making process. Treatment paradigms have shifted from enucleation and EBRT as primary therapy to chemoreduction with focal laser consolidation. Current treatment protocols result in success rates approaching 99% in specialized centers, with many children maintaining useful vision. The next era of retinoblastoma treatment is shifting to local delivery of agents to avoid systemic chemotherapy. However, much remains unknown regarding the long-term efficacy of these local treatments, as well as the side effect profile. Despite these advancements in developed countries, one of the challenges in treating retinoblastoma worldwide remains access to care: if every patient with RB could be referred to tertiary care centers, mortality would drop by 62% to reach 1200/year[55]. The advancement of retinoblastoma treatments look promising, but future studies looking at long-term outcomes of various treatment modalities, toxicities, and the effect on genetic manipulation is warranted.

REFERENCES

1 **MacCarthy A**, Birch JM, Draper GJ, Hungerford JL, Kingston JE, Kroll ME, Onadim Z, Stiller CA, Vincent TJ, Murphy MF. Retinoblastoma in Great Britain 1963-2002. *Br J Ophthalmol* 2009; **93**: 33-37 [PMID: 18838413]

2 Retinoblastoma-Childhood. Available from: URL: http://www.cancer.net. July 11, 2011

3 **Gombos DS**, Chevez-Barrios AP. Current treatment and management of retinoblastoma. *Curr Oncol Rep* 2007; **9**: 453-458 [PMID: 17991352 DOI: 10.1007/s11912-007-0063-7]

4 **Desjardins L**, Levy C, Lumbroso L, Doz F, Schlienger P, Validire P, Asselain B, Bours D, Zucker JM. [Current treatment of retinoblastoma. 153 children treated between 1995 and 1998]. *J Fr Ophtalmol* 2000; **23**: 475-481 [PMID: 10844307]

5 **Shields CL**, Shields JA. Retinoblastoma management: advances in enucleation, intravenous chemoreduction, and intra-arterial chemotherapy. *Curr Opin Ophthalmol* 2010; **21**: 203-212 [PMID: 20224400 DOI: 10.1097/ICU.0b013e328338676a]

6 **Gombos DS**, Kelly A, Coen PG, Kingston JE, Hungerford JL. Retinoblastoma treated with primary chemotherapy alone: the significance of tumour size, location, and age. *Br J Ophthalmol* 2002; **86**: 80-83 [PMID: 11801509 DOI: 10.1136/bjo.86.1.80]

7 **Linn Murphree A**. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmol Clin North Am* 2005; **18**: 41-53, viii [PMID: 15763190 DOI: 10.1016/j.ohc.2004.11.003]

8 **Shields CL**, Mashayekhi A, Demirci H, Meadows AT, Shields JA. Practical approach to management of retinoblastoma. *Arch Ophthalmol* 2004; **122**: 729-735 [PMID: 15136321 DOI: 10.1001/archopht.122.5.729]

9 **Shields CL**, Honavar SG, Meadows AT, Shields JA, Demirci H, Singh A, Friedman DL, Naduvilath TJ. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. *Am J Ophthalmol* 2002; **133**: 657-664 [PMID: 11992863 DOI: 10.1016/S0002-9394(02)01348-X]

10 **Shields CL**, Meadows AT, Shields JA, Carvalho C, Smith AF. Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral retinoblastoma). *Arch Ophthalmol* 2001; **119**: 1269-1272 [PMID: 11545631 DOI: 10.1001/archopht.119.9.1269]

11 **Abramson DH**, Ellsworth RM, Kitchin FD, Tung G. Second nonocular tumors in retinoblastoma survivors. Are they radiation-induced? *Ophthalmology* 1984; **91**: 1351-1355 [PMID: 6595610]

12 **Abramson DH**, Frank CM. Second nonocular tumors in survivors of bilateral retinoblastoma: a possible age effect on radiation-related risk. *Ophthalmology* 1998; **105**: 573-579; discussion 579-580 [PMID: 9544627 DOI: 10.1016/S0161-6420(98)94006-4]

13 **Wong FL**, Boice JD, Abramson DH, Tarone RE, Kleinerman RA, Stovall M, Goldman MB, Seddon JM, Tarbell N, Fraumeni JF, Li FP. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *JAMA* 1997; **278**: 1262-1267 [PMID: 9333268 DOI: 10.1001/jama.1997.03550150066037]

14 **Shields CL**, Shields JA, Cater J, Othmane I, Singh AD, Micaily B. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. *Ophthalmology* 2001; **108**: 2116-2121 [PMID: 11713089 DOI: 10.1016/S0161-6420(01)00797-7]

15 **Kaneko A**, Suzuki S. Eye-preservation treatment of retinoblastoma with vitreous seeding. *Jpn J Clin Oncol* 2003; **33**: 601-607 [PMID: 14769836 DOI: 10.1093/jjco/hyg113]

16 **Gallie BL**, Bunding AS, Chan H. New chemotherapy and focal therapy for intraocular retinoblastoma. *Ophthalmology* 1995; **102** Suppl: 109

17 **Shields CL**, Honavar SG, Meadows AT, Shields JA, Demirci H, Naduvilath TJ. Chemoreduction for unilateral retinoblastoma. *Arch Ophthalmol* 2002; **120**: 1653-1658 [PMID: 12470138 DOI: 10.1001/archopht.120.12.1653]

18 **Advani SH**, Rao SR, Iyer RS, Pai SK, Kurkure PA, Nair CN. Pilot study of sequential combination chemotherapy in advanced and recurrent retinoblastoma. *Med Pediatr Oncol* 1994; **22**: 125-128 [PMID: 8259098 DOI: 10.1002/mpo.2950220212]

19 **Wilson MW**, Rodriguez-Galindo C, Haik BG, Moshfeghi DM, Merchant TE, Pratt CB. Multiagent chemotherapy as neoadjuvant treatment for multifocal intraocular retinoblastoma. *Ophthalmology* 2001; **108**: 2106-2114; discussion 2114-2115 [PMID: 11713087 DOI: 10.1016/S0161-6420(01)00805-3]

20 **Schefler AC**, Cicciarelli N, Feuer W, Toledano S, Murray TG. Macular retinoblastoma: evaluation of tumor control, local complications, and visual outcomes for eyes treated with chemotherapy and repetitive foveal laser ablation. *Ophthalmology* 2007; **114**: 162-169 [PMID: 17070578 DOI: 10.1016/j.ophtha.2006.06.042]

21 **Shields CL**, Shields JA. Basic understanding of current classification and management of retinoblastoma. *Curr Opin Ophthalmol* 2006; **17**: 228-234 [PMID: 16794434 DOI: 10.1097/01.icu.0000193079.55240.18]

22 **Rodriguez-Galindo C**, Wilson MW, Haik BG, Merchant TE, Billups CA, Shah N, Cain A, Langston J, Lipson M, Kun LE, Pratt CB. Treatment of intraocular retinoblastoma with vincristine and carboplatin. *J Clin Oncol* 2003; **21**: 2019-2025 [PMID: 12743157 DOI: 10.1200/JCO.2003.09.103]

23 **Honavar SG**, Singh AD. Management of advanced retinoblastoma. *Ophthalmol Clin North Am* 2005; **18**: 65-73, viii [PMID: 15763192 DOI: 10.1016/j.ohc.2004.09.001]

24 **D'Anneo A**, Augello G, Santulli A, Giuliano M, di Fiore R, Messina C, Tesoriere G, Vento R. Paclitaxel and betalapachone synergistically induce apoptosis in human retinoblastoma Y79 cells by downregulating the levels of phospho-Akt. *J Cell Physiol* 2010; **222**: 433-443 [PMID: 19918798 DOI: 10.1002/jcp.21983]

25 **Suárez F**, Jockovich ME, Hernandez E, Feuer W, Parel JM, Murray TG. Paclitaxel in the treatment of retinal tumors of LH beta-Tag murine transgenic model of retinoblastoma. *Invest Ophthalmol Vis Sci* 2007; **48**: 3437-3440 [PMID: 17652710 DOI: 10.1167/iovs.06-0796]

26 **Dennis MJ**, Beijnen JH, Grochow LB, van Warmerdam LJ. An overview of the clinical pharmacology of topotecan. *Semin Oncol* 1997; **24**: S5-12-S5-S5-12-18 [PMID: 9122737]

27 **Carcaboso AM**, Bramuglia GF, Chantada GL, Fandiño AC, Chiappetta DA, de Davila MT, Rubio MC, Abramson DH. Topotecan vitreous levels after periocular or intravenous delivery in rabbits: an alternative for retinoblastoma chemotherapy. *Invest Ophthalmol Vis Sci* 2007; **48**: 3761-3767 [PMID: 17652749 DOI: 10.1167/iovs.06-1152]

28 **Tsui JY**, Dalgard C, Van Quill KR, Lee L, Grossniklaus HE, Edelhauser HF, O'Brien JM. Subconjunctival topotecan in fibrin sealant in the treatment of transgenic murine retinoblastoma. *Invest Ophthalmol Vis Sci* 2008; **49**: 490-496 [PMID: 18234990 DOI: 10.1167/iovs.07-0653]

29 **Chantada GL**, Fandino AC, Carcaboso AM, Lagomarsino E, de Davila MT, Guitter MR, Rose AB, Manzitti J, Bramuglia GF, Abramson DH. A phase I study of periocular topotecan in children with intraocular retinoblastoma. *Invest Ophthalmol Vis Sci* 2009; **50**: 1492-1496 [PMID: 18978345 DOI: 10.1167/iovs.08-2737]

30 **Mallipatna AC**, Dimaras H, Chan HS, Héon E, Gallie BL. Periocular topotecan for intraocular retinoblastoma. *Arch Ophthalmol* 2011; **129**: 738-745 [PMID: 21670340 DOI: 10.1001/archophthalmol.2011.130]

31 **Wood PA**, Hrushesky WJ. Cisplatin-associated anemia: an erythropoietin deficiency syndrome. *J Clin Invest* 1995; **95**: 1650-1659 [PMID: 7706473 DOI: 10.1172/JCI117840]

32 **Jehanne M**, Lumbroso-Le Rouic L, Savignoni A, Aerts I, Mercier G, Bours D, Desjardins L, Doz F. Analysis of ototoxicity in young children receiving carboplatin in the context of conservative management of unilateral or bilateral retinoblastoma. *Pediatr Blood Cancer* 2009; **52**: 637-643 [PMID: 19148943 DOI: 10.1002/pbc.21898]

33 **Boutrid H**, Piña Y, Cebulla CM, Feuer WJ, Lampidis TJ, Jockovich ME, Murray TG. Increased hypoxia following vessel targeting in a murine model of retinoblastoma. *Invest Ophthalmol Vis Sci* 2009; **50**: 5537-5543 [PMID: 19578014 DOI: 10.1167/iovs.09-3702]

34 **Boutrid H**, Jockovich ME, Murray TG, Piña Y, Feuer WJ, Lampidis TJ, Cebulla CM. Targeting hypoxia, a novel treatment for advanced retinoblastoma. *Invest Ophthalmol Vis Sci* 2008; **49**: 2799-2805 [PMID: 18326690 DOI: 10.1167/iovs.08-1751]

35 **Dewhirst MW**, Cao Y, Moeller B. Cycling hypoxia and free radicals regulate angiogenesis and radiotherapy response. *Nat Rev Cancer* 2008; **8**: 425-437 [PMID: 18500244 DOI: 10.1038/nrc2397]

36 **Piña Y**, Houston SK, Murray TG, Koru-Sengul T, Decatur C, Scott WK, Nathanson L, Clarke J, Lampidis TJ. Retinoblastoma treatment: impact of the glycolytic inhibitor 2-deoxy-d-glucose on molecular genomics expression in LH(BETA)T(AG) retinal tumors. *Clin Ophthalmol* 2012; **6**: 817-830 [PMID: 22701083]

37 **Harbour JW**, Murray TG, Hamasaki D, Cicciarelli N, Hernández E, Smith B, Windle J, O'Brien JM. Local carboplatin therapy in transgenic murine retinoblastoma. *Invest Ophthalmol Vis Sci* 1996; **37**: 1892-1898 [PMID: 8759359]

38 **Hayden BH**, Murray TG, Scott IU, Cicciarelli N, Hernandez E, Feuer W, Fulton L, O'Brien JM. Subconjunctival carboplatin in retinoblastoma: impact of tumor burden and dose schedule. *Arch Ophthalmol* 2000; **118**: 1549-1554 [PMID: 11074812 DOI: 10.1001/archopht.118.11.1549]

39 **Leng T**, Cebulla CM, Schefler AC, Murray TG. Focal periocular carboplatin chemotherapy avoids systemic chemotherapy for unilateral, progressive retinoblastoma. *Retina* 2010; **30**: S66-S68 [PMID: 20419851]

40 **Abramson DH**, Frank CM, Dunkel IJ. A phase I/II study of subconjunctival carboplatin for intraocular retinoblastoma. *Ophthalmology* 1999; **106**: 1947-1950 [PMID: 10519590 DOI: 10.1016/S0161-6420(99)90406-2]

41 **Yamane T**, Kaneko A, Mohri M. The technique of ophthalmic arterial infusion therapy for patients with intraocular retinoblastoma. *Int J Clin Oncol* 2004; **9**: 69-73 [PMID: 15108036 DOI: 10.1007/s10147-004-0392-6]

42 **Suzuki S**, Yamane T, Mohri M, Kaneko A. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. *Ophthalmology* 2011; **118**: 2081-2087 [PMID: 21715012 DOI: 10.1016/j.ophtha.2011.03.013]

43 **Abramson DH**, Dunkel IJ, Brodie SE, Marr B, Gobin YP. Bilateral superselective ophthalmic artery chemotherapy for bilateral retinoblastoma: tandem therapy. *Arch Ophthalmol* 2010; **128**: 370-372 [PMID: 20212212 DOI: 10.1001/archophthalmol.2010.7]

44 **Gobin YP**, Dunkel IJ, Marr BP, Brodie SE, Abramson DH. Intra-arterial chemotherapy for the management of retinoblastoma: four-year experience. *Arch Ophthalmol* 2011; **129**: 732-737 [PMID: 21320950 DOI: 10.1001/archophthalmol.2011.5]

45 **Vajzovic LM**, Murray TG, Aziz-Sultan MA, Schefler AC,

Wolfe SQ, Hess D, Fernandes CE, Dubovy SR. Supraselective intra-arterial chemotherapy: evaluation of treatment-related complications in advanced retinoblastoma. *Clin Ophthalmol* 2011; **5**: 171-176 [PMID: 21383945]

46 **Peterson EC**, Elhammady MS, Quintero-Wolfe S, Murray TG, Aziz-Sultan MA. Selective ophthalmic artery infusion of chemotherapy for advanced intraocular retinoblastoma: initial experience with 17 tumors. *J Neurosurg* 2011; **114**: 1603-1608 [PMID: 21294621 DOI: 10.3171/2011.1.JNS10466]

47 **Shields CL**, Bianciotto CG, Jabbour P, Ramasubramanian A, Lally SE, Griffin GC, Rosenwasser R, Shields JA. Intra-arterial chemotherapy for retinoblastoma: report No. 1, control of retinal tumors, subretinal seeds, and vitreous seeds. *Arch Ophthalmol* 2011; **129**: 1399-1406 [PMID: 21670328]

48 **Shields CL**, Shields JA. Intra-arterial chemotherapy for retinoblastoma: the beginning of a long journey. *Clin Experiment Ophthalmol* 2010; **38**: 638-643 [PMID: 20584015 DOI: 10.1111/j.1442-9071.2010.02297.x]

49 **Eagle RC**, Shields CL, Bianciotto C, Jabbour P, Shields JA. Histopathologic observations after intra-arterial chemotherapy for retinoblastoma. *Arch Ophthalmol* 2011; **129**: 1416-1421 [PMID: 21746972 DOI: 10.1001/archophthalmol.2011.223]

50 **Vajzovic LM**, Murray TG, Aziz-Sultan MA, Schefler AC, Fernandes CE, Wolfe SC, Hess DJ, Dubovy SR. Clinicopathologic review of enucleated eyes after intra-arterial chemotherapy with melphalan for advanced retinoblastoma. *Arch Ophthalmol* 2010; **128**: 1619-1623 [PMID: 21149791 DOI: 10.1001/archophthalmol.2010.296]

51 **Graeber CP**, Gobin YP, Marr BP, Dunkel IJ, Brodie SE, Bornfeld N, Char DH, Folberg R, Imhof SM, Lin AY, Berry JL, Al Mesfer S, Moll AC, Abramson DH. Histopathologic findings of eyes enucleated after treatment with chemosurgery for retinoblastoma. *Open Ophthalmol J* 2011; **5**: 1-5 [PMID: 21399766 DOI: 10.2174/1874364101105010001]

52 **Kopelman JE**, McLean IW, Rosenberg SH. Multivariate analysis of risk factors for metastasis in retinoblastoma treated by enucleation. *Ophthalmology* 1987; **94**: 371-377 [PMID: 3587919]

53 **Marees T**, Moll AC, Imhof SM, de Boer MR, Ringens PJ, van Leeuwen FE. Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. *J Natl Cancer Inst* 2008; **100**: 1771-1779 [PMID: 19066271 DOI: 10.1093/jnci/djn394]

54 **Kivelä T**. Trilateral retinoblastoma: a meta-analysis of hereditary retinoblastoma associated with primary ectopic intracranial retinoblastoma. *J Clin Oncol* 1999; **17**: 1829-1837 [PMID: 10561222]

55 **Kivelä T**. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol* 2009; **93**: 1129-1131 [PMID: 19704035 DOI: 10.1136/bjo.2008.150292]

56 **Reese AB**. Retinoblastoma. In: Reese AB, editor. Tumors of the eye. 1st ed. New York: Harper and Row, 1963: 155-156

P- Reviewer Cervia D **S- Editor** Song XX **L- Editor** A **E- Editor** Zheng XM

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com