

Chemotherapy for Retinoblastoma

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Abstract

Retinoblastoma is the most common primary malignant intraocular tumor of childhood. It has a mortality close to 60% in the developing world. With early diagnosis and treatment, survival rates could be high as 95%. Management of Retinoblastoma has undergone a paradigm change in the past two decades with globe salvage becoming the goal of treatment. Safety and efficacy of chemotherapeutic agents combined with their targeted delivery has increased the success rates of tumor control. This article reviews the treatment strategies using different routes of drug delivery to contain ocular and extraocular retinoblastoma, the risks and benefits and future of chemotherapy.

Keywords: Retinoblastoma, Chemotherapy, Intra-arterial melphalan, IAC, Intravitreal melphalan, Periocular cisplatin, VEC regimen

Chemotherapy for Retinoblastoma

Retinoblastoma is the most common primary intraocular malignancy in children. It accounts for 4.3–31% of all childhood cancers in India with an incidence of 6–12 per million children.^(1,2) The incidence is 12 per million children aged 0–4 years in USA and 4.1 per million children aged 0–14 in Europe.^(3,4) It is a potentially fatal cancer.⁽⁵⁾ Survival of the patients is poor in the underdeveloped countries varying from mean survival rate ranging from 40% (23–70%) in lower-income countries to 79% (54–93%) in upper-middle-income countries and 95–97% in developed nations.^(6,7)

Management plan is individualized for each patient based on multiple factors including laterality of the eye involved, size and location of the tumor(s), visual prognosis, extraocular extension, high risk clinical features like vitreous hemorrhage, orbital cellulitis-like-presentation, neovascular glaucoma, and tumor in ciliary body/ anterior segment, and the presence of metastasis.⁽⁹⁾ Management involves a multidisciplinary team consisting of ophthalmologists, pediatric oncologists, radiation oncologists and interventional neuroradiologists, depending on their availability. Treatment options include enucleation, radiation (brachytherapy, external beam radiation), chemotherapy and focal therapies such as cryotherapy, laser photocoagulation, transpupillary thermotherapy (TTT).⁽⁸⁾

Since the first use of intravenous nitrogen mustard in the treatment of retinoblastoma by Kupffer in 1953,⁽¹⁰⁾ chemotherapy has been used via various routes such as intravenous, periocular, intra-arterial, and intravitreal. Systemic or intravenous chemotherapy has been used for chemoreduction in the primary treatment, or as prophylaxis to prevent the development of metastasis in cases with high risk clinical and histopathological features, and in the management of metastatic disease.^(11,12) It also prevents the development of

pinealoblastoma or trilateral retinoblastoma.⁽¹³⁾ Periocular chemotherapy was introduced to increase the intraocular concentration in the primary treatment of advanced cases in combination with systemic chemotherapy. Intra-arterial chemotherapy is a relatively new administration method that provides localized delivery of high-dose chemotherapy to the eye while sparing systemic side effects. It has dramatically increased the globe salvage for the advanced unilateral and bilateral cases. Recently, intravitreal chemotherapy injection was used for the management of vitreous seeds, which is a main reason of failure of globe salvage therapy in most cases.⁽¹⁴⁾

Intravenous Chemotherapy(IVC)

Intravenous Chemotherapy is the first line treatment for inherited, bilateral retinoblastomas with germ-line mutations.⁽¹¹⁾

The International Classification of Retinoblastoma is used to guide therapy and it has been found to be predictive of treatment success following intravenous chemotherapy.⁽¹⁵⁾

The standard regimen for intravenous systemic chemotherapy is the VEC protocol - vincristine 0.05 mg/kg, etoposide 5 mg/kg, and carboplatin 25 mg/kg. It is administered in six cycles at 4-week intervals. There is an almost >50% decrease in tumor volume after 3 cycles.⁽¹⁴⁾ It is used in combination with focal therapies such as cryotherapy, transpupillary thermotherapy or laser photocoagulation. In a review of 249 eyes with retinoblastoma, it was reported that primary chemoreduction along with focal treatment was successful in achieving globe salvage in 100% in group A, 93% in group B, 90% in group C and 47% in group D tumors.⁽¹⁵⁾ Tumor unresponsiveness (i.e. persistence of retinal tumors, vitreous seeds, or subretinal seeds after the second treatment cycle, with no appreciable sign of regression) occurred in 17.5% and tumor recurrence in

25.7% of IVC-treated RB.⁽¹⁶⁾ In a similar study by Shields et al⁽¹⁷⁾, after a combined 6-cycle chemotherapy and focal treatment, recurrence rates were 26%, 53% and 37% for vitreous seeds, subretinal seeds and retinal tumor respectively at 1-year follow-up. Retinal tumor and subretinal seed recurrences increased to 51% and 62% respectively in the first 3 years after chemotherapy and remained stable thereafter. At 5-year follow-up, the recurrence rate for vitreous seeds increased to 50%.⁽¹⁷⁾ Presence of subretinal seeds around the base of the tumor at diagnosis was predictive of tumor and vitreous seed recurrences. Tumor base > 15 mm and age <1year were predictive of recurrence of subretinal seeds.⁽¹⁷⁾ The mean interval from last cycle of chemotherapy to the first recurrence of retinal tumor, vitreous seeds and subretinal seeds was 4 months, 2 months, and 2 months respectively. Therefore, frequent follow-up of the eye is important during chemotherapy for prompt management of recurrences with focal treatment.⁽¹⁷⁾ Suboptimal concentration of chemotherapeutic agents in the vitreous could have been the underlying reason for such recurrences.

Side effects related to systemic chemotherapy include prolonged bone marrow suppression(7%; 100% require packed cell transfusions and 50% develop febrile neutropenia), alopecia, ototoxicity (5-33%), systemic infection(3%), secondary acute myelocytic anemia (2-12%). In a case series by Gombos, 15 patients who received systemic chemotherapy developed secondary acute myelogenous leukemia which was fatal.⁽¹⁸⁾

Adjuvant systemic chemotherapy is used after enucleation in patients with high-risk histopathological features for prophylaxis to prevent the systemic metastasis. In a review of 80 retinoblastoma patients with high risk histopathological features.⁽¹⁹⁾

Periocular Chemotherapy

Periocular/ subconjunctival carboplatin is used to increase the intraocular concentration of the chemotherapeutic agent in eyes with advanced stages of retinoblastoma. Periocular delivery of carboplatin delivers 10 times the concentration to the eye but one tenth the systemic dose in humans with retinoblastoma.⁽²⁰⁾ It is delivered at a dose of 10-20 mg as three injections at monthly intervals. It is effective in managing advanced RB with vitreous seeds. In a study by Honavar et al, 72% eyes were salvaged when deep posterior sub-Tenon carboplatin as adjunct to systemic chemotherapy showed favorable clinical response in comparison to a 30% eye salvage in the control group in whom only intravenous chemotherapy was used.⁽²²⁾ Periocular/ subconjunctival carboplatin has no short-term or long-term systemic toxicity and most of the ocular complications are acute not delayed as determined by a 12-year long follow-up.⁽²¹⁾ Acute complications include periorbital edema, preseptal cellulitis, orbital adipose tissue atrophy, fibrosis of extraocular muscles

and Tenon's capsule limiting ocular motility, optic nerve atrophy.⁽²³⁾

Intra-arterial Chemotherapy(IAC)

Intra-arterial chemotherapy, an innovative way of delivering chemotherapy to the intraocular tumor, was first attempted as early as in 1958, by Reese et al.⁽²⁴⁾ They achieved successful regression of RB by employing X-ray together with triethylenemelamine into the carotid artery. In 1966, Kiribuchi from Japan injected 5-fluorouracil into the frontal or supraorbital artery to treat intraocular retinoblastoma. Kaneko et al⁽²⁵⁾ treated 6 patients with recurrent Retinoblastoma using 40 mg of melphalan injected through using 40 mg of internal carotid artery melphalan plus hyperthermia and cured 2 patients of the malignancy but with high systemic toxicity. They later devised a low-dose and more focal delivery method comprising of melphalan dose of 5-10 mg/m² with balloon occlusion of the distal internal carotid artery.⁽²⁶⁾ The technical success rate was 97.51%. In 2008, Abramson et al used a similar but slightly more direct technique, super-selective IAC, to cannulate and infuse specifically into the ophthalmic artery without the need for distal balloon occlusion of the internal carotid artery.⁽²⁷⁾ A microcatheter was fed via the femoral artery into the carotid artery on the side of the eye to be treated. The catheter was extended into the ophthalmic artery under direct fluoroscopic control. Chemotherapy was then delivered in a pulsatile manner injecting 1/30th of the diluted volume of drug each minute over a 30-minute period. When two or more drugs were given, melphalan was first infused and then the others were infused successively.

After one application, mean reduction of 33% in tumor base circumference and 46% in tumor thickness were noted, and subretinal fluid resolved at a rate of 76%. In their review of 95 eyes treated with supra-selective intra-arterial melphalan, topotecan, carboplatin or methotrexate, they reported globe conservation at rates of 81.7% and 58.4% with primary and secondary treatment, respectively.⁽²⁸⁾ Standard administration is once a month, with a total of three cycles. A standard dose of 5 mg of melphalan is used.⁽²⁸⁾ Topotecan (1 mg) and carboplatin (30-50 mg) are alternative drugs. Topotecan and melphalan can be used in combination, especially in the presence of dense vitreous seeds.

In a review of 70 eyes with retinoblastoma, by Shields et al,⁽²⁹⁾ intra-arterial chemotherapy resulted in globe salvage in 72% of primary treated eyes - 100% of group B, 100% of group C, and 94% of group D and 36% of group E eyes. The globe salvage was 62% when it was employed as secondary treatment after failure of previous intravenous chemotherapy.⁽²⁹⁾ In another study by Peterson et al, intra-arterial melphalan was employed as second therapy following failure with systemic chemotherapy and adjunct focal treatment. It dramatically reduced the rate of enucleation from 100% to 23.5% in these group D tumors.⁽³⁰⁾ IAC was shown to

be effective in retinoblastomas with retinal detachment. Partial retinal detachment showed complete resolution in 100%, and complete resolution was noted in 43% cases of full retinal detachment.⁽³¹⁾

Despite its safety profile and decreased need for hospitalization, IAC has its side effects. There is concern about the potential risk due to ionizing radiation owing to recurrent exposure with every cycle. Local side effects (per catheterization) include lid edema (5%), blepharoptosis (5%), forehead hyperemia (2%), vitreous hemorrhage (2%), branch retinal artery obstruction (1%), ophthalmic artery spasm with reperfusion (2%), ophthalmic artery obstruction (2%), partial choroidal ischemia (2%), and optic neuropathy (<1%).²⁹ Having obviated the need for enucleation, metastatic potential cannot be predicted. Additionally, the assessment of risk of development of pinealoblastoma, second malignancies, and metastasis following intra-arterial chemotherapy needs longer follow-up to be understood. The high learning curve and cost are prohibitory in terms of its widespread use in developing countries.

Intravitreal Chemotherapy

Persistent or recurrent vitreal seeding is the primary indication for intravitreal chemotherapy.⁽¹¹⁾ Melphalan is the most commonly used drug for intravitreal injection. Intravitreal melphalan is combined with intra-arterial/intravenous chemotherapy to reduce the chance of failure due to vitreous/retinal seeds. In a review of 8 cases, combined intravitreal chemotherapy and inter-arterial/intravenous chemotherapy for advanced group D and E eyes led to 100% regression of vitreous seeds and 87.5% globe salvage.^(33,34) In cases of extensive vitreous seeds, topotecan is used intravitreally in combination with melphalan. When it was combined with topotecan, control of vitreous seeding increased to 100%.⁽⁴⁶⁾

Intravitreal melphalan (20-30µg/0.1ml) injections are given weekly (minimum of 6 injections) using 30-G needle via the pars plana 1-2 clock hours from the site of vitreous seeds.⁽³⁵⁾ As soon as the needle is removed, the injection site is treated with cryotherapy to prevent tumor seeding. Injected eye is irrigated with sterile distilled water for atleast three minutes to further reduce the risk of extraocular spread due to tumor spillage. 99% of RB cells became non-viable due to hypotonicity-induced lysis when submerged in distilled water.^(36,37) Vitreous seed regression occurs after a median of four injections. Mild retinal pigment epithelial changes at the site of injection and non-axial cataract are the complications.⁽³⁸⁾

Chemotherapy in extraocular retinoblastoma

The leading cause of death in RB patients is extraocular spread – orbital spread, central nervous system involvement and distant metastases.⁽³⁹⁾ At the underdeveloped countries, the incidence of orbital RB is more than 50% due to the delayed presentation at diagnosis.⁽⁴⁰⁾ Orbital RB is managed by tumor shrinkage by 3 to 6 cycles of neoadjuvant therapy followed by

enucleation and 9 cycles of adjuvant chemotherapy + radiotherapy at a dose of 40Gy.⁽⁴¹⁾

Hematogenous metastasis is managed by induction systemic chemotherapy (vincristine, cyclophosphamide, cisplatin, etoposide) followed by autologous hematopoietic stem cell therapy and high-dose chemotherapy (carboplatin, thiotepa, etoposide, topotecan) +/- local radiotherapy. This approach was reported to achieve 67% survival at 5 years.⁽⁴²⁾

For central nervous system involvement, high-dose chemotherapy is employed with autologous hematopoietic stem cell rescue therapy and intrathecal thiotepa administration and cranio-spinal radiotherapy.⁽⁴³⁾ With this approach, the survival was extended despite the 100% mortality.

Way Forward

There has been a paradigm shift in the goal of treatment from life salvage to globe salvage. However, the visual outcome after chemotherapy is not well evaluated. The relevant question is whether sparing the globe translates to visual success.

Long-term visual acuity outcome studied in eyes treated with systemic chemotherapy showed that the mean 5-year visual outcome was 20/20–20/40 in 50% of patients and 20/200 or better in 67%. Foveal involvement by the original tumor and subretinal fluid predicted poor visual potential. There was no evidence of visual loss due to drug toxicity.⁽⁴⁴⁾ In eyes treated with intra-arterial chemotherapy, 31% of patients retained vision of 20/50 or better.⁽⁴⁵⁾

We hope that with further innovations in the management of retinoblastoma, the goal of treatment would be streamlined to vision salvage and retention of good visual acuity.

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