Retinoblastoma: Achieving new standards with methods of chemotherapy

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The management of retinoblastoma (RB) has dramatically changed over the past two decades from previous radiotherapy methods to current chemotherapy strategies. RB is a remarkably chemotherapy-sensitive tumor. Chemotherapy is currently used as a first-line approach for children with this malignancy and can be delivered by intravenous, intra-arterial, periocular, and intravitreal routes. The choice of route for chemotherapy administration depends upon the tumor laterality and tumor staging. Intravenous chemotherapy (IVC) is used most often in bilateral cases, orbital RB, and as an adjuvant treatment in high-risk RB. Intra-arterial chemotherapy (IAC) is used in cases with group C or D RB and selected cases of group E tumor. Periocular chemotherapy is used as an adjunct treatment in eyes with group D and E RB and those with persistent/recurrent vitreous seeds. Intravitreal chemotherapy is reserved for eyes with persistent/recurrent vitreous seeds. In this review, we describe the various forms of chemotherapy used in the management of RB. A database search was performed on PubMed, using the terms "RB," and "treatment," "chemotherapy," "systemic chemotherapy," "IVC," "IAC," "periocular chemotherapy," or "intravitreal chemotherapy." Relevant English language articles were extracted, reviewed, and referenced appropriately.

Retinoblastoma (RB) has emerged as a malignancy with one of the highest survival rates among all pediatric cancers, owing to improving treatment methods over the years.[1-3] There is a major shift from globe-sacrificing methods to globe-saving alternatives in the treatment of most cases, using novel techniques of chemotherapy. Chemotherapy can be delivered by intravenous, intra-arterial, periocular, and intravitreal routes. The choice of route of chemotherapy administration depends upon the tumor laterality and tumor staging. In this review, we will discuss the methods of chemotherapy.

A database search was performed on PubMed, using the terms "RB," and "treatment," "chemotherapy," "systemic chemotherapy," "intravenous chemotherapy (IVC)," "intra-arterial chemotherapy (IAC)," "periocular chemotherapy," or "intravitreal chemotherapy." Relevant English language articles were extracted, reviewed, and referenced appropriately.

Intravenous Chemotherapy

Intravenous chemotherapy is used for chemoreduction along with focal therapy for intraocular RB to facilitate globe and vision salvage, In addition, IVC is employed for orbital RB to control the malignancy prior to enucleation, for chemoprophylaxis in eyes with high-risk RB to prevent systemic metastasis, and for treatment of metastatic RB[4-10] [Table 1]. The advantages of IVC include:[9,11-16]

- Control of intraocular tumor
- Resolution of retinal detachment (RD)
- Globe salvage
- Vision salvage
- Prevention of pinealoblastoma
- Prevention of systemic metastasis in high-risk RB, and
- Reduction of long-term second nonocular cancers.

Chemoreduction of intraocular retinoblastoma

In 1953, Carl Kupfer first introduced IVC for the treatment of RB.[17] Kupfer used nitrogen mustard along with X-ray treatment, with an aim to decrease the dose of radiation.[17] Similar technique was adopted by Reese *et al*. but ultimately the technique was abandoned owing to side-effects.[18] However, the use of IVC for chemoreduction of intraocular RB gained popularity only in 1996 following reports of successful treatment of RB from four major oncology centers.[4-7] Since then, the use of chemotherapeutic regimen vincristine sulfate, etoposide phosphate, and carboplatin (VEC) for 6 cycles every 3-4 weeks has become widely acceptable.[19]

Intravenous chemotherapy causes a mean decrease of 35-48% in tumor base and 49-58% in tumor thickness [Fig. 1].[4,20] Increased penetration of carboplatin greater than 15 fold is achieved with single freeze-thaw cryotherapy delivered 24 hours before IVC.[21] Standard dose VEC is used in most cases, while high-dose VEC with intensified dose of carboplatin and etoposide combined with standard dose of vincristine is preferred in patients with bilateral groups D and E RB[3,4,16,19,22] [Table 2]. The International Classification of RB (ICoR) can predict the success of chemoreduction in cases with intraocular RB.[11] In an analysis of 249 eyes with RB based on ICoR by Shields *et al*., tumor control (avoidance of external beam radiotherapy (EBRT) and enucleation) with standard dose VEC was recorded in 100% of group A, 93% of group B, 90% of group C, and 47% of group D eyes.[11] Subtenon's carboplatin with systemic high dose VEC achieves tumor

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Table 1: Indications of chemotherapy for RB

| Chemotherapy	Indications
Intravenous	Intraocular RB especially bilateral cases
	Orbital RB
	High-risk RB
	Metastatic RB
Intra-arterial	Intraocular RB as primary treatment
	Refractory intraocular RB as secondary treatment
Periocular	Recurrent or residual vitreous seeds
	Bilateral RB with poor prognosis at diagnosis
	In cases with contraindication of systemic chemotherapy
Intravitreal	Recurrent or residual vitreous seeds

RB: Retinoblastoma

Table 2: Routes and dosages of chemotherapy for RB

Route of administration	Drug	Dose
Intravenous chemotherapy	Vincristine	1.5 mg/m^2 or 0.05 mg/kg¶ standard dose 0.025 mg/kg high-dose
	Etoposide	150 mg/m^2 or 5 mg/kg¶ standard dose 12 mg/kg high-dose
	Carboplatin	560 mg/m^2 or 18.6 mg/kg¶ standard dose 28 mg/kg high-dose
Intra-arterial chemotherapy	Melphalan	3-7.5 mg/30 cc normal saline
	Carboplatin	15-50 mg/30 cc normal saline
	Topotecan	0.15-1.5 mg/30 cc normal saline
	Methotrexate	6-12 mg/30 cc normal saline
Periocular chemotherapy	Carboplatin	20 mg/2 cc
	Topotecan	0.09-0.27 mg/kg or 2.01-4.62 mg/m^2
Intravitreal chemotherapy	Melphalan	20-30 ug/0.1 cc
	Methotrexate	400 ug/0.1 cc
	Carboplatin	3-6 ug/0.05 cc

¶For patients <36 months of age. RB: Retinoblastoma

control with the globe salvage in 60% group D eyes.[22] Group E eyes are the most difficult to treat as the tumor burden is often extreme and recurrence is problematic, but investigators found that combination of VEC followed by prophylactic low-dose EBRT achieves tumor control with globe salvage in 83% group E eyes.[23] Despite encouraging results with VEC for group E eyes, enucleation is still preferred for unilateral group E eyes since preenucleation chemotherapy can downstage the disease and increase the risk of metastatic death.[24]

Intravenous chemotherapy can cause dramatic resolution of subretinal fluid associated with RB.[12] In an analysis of 17 eyes with total RD from RB, complete resolution of RD occurred in 76% eyes and partial resolution in 24%.[12] Visual outcome in RB cases following IVC depends on tumor location and presence or absence of RD. Good visual outcome is achieved with extramacular tumors not associated with RD. Visual acuity of
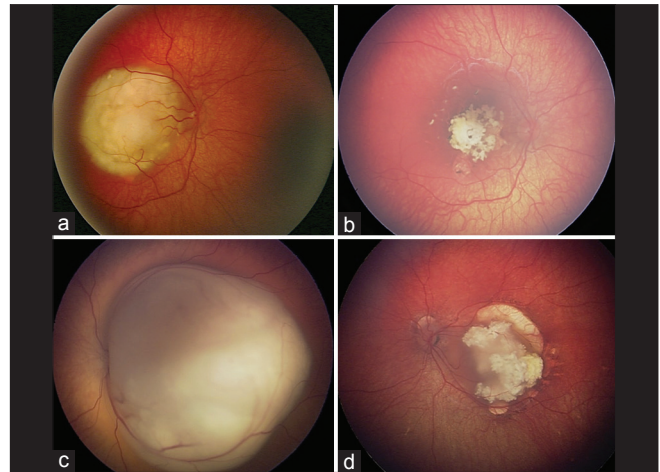
Figure 1: Treatment of intraocular retinoblastoma with intravenous chemotherapy (a) group B retinoblastoma of the right eye showed (b) complete tumor control with 6 cycles of intravenous chemotherapy (IVC). (c) Group C retinoblastoma of the left eye showed (d) complete tumor control with 6 cycles of IVC

20/200 or better is achieved in 67-71% eyes and 20/40 or better in 37-50% eyes.[13,20]

Intravenous chemotherapy is the treatment of choice in bilateral cases of RB. In these cases with germline mutation, in addition to intraocular tumor control, IVC also prevents the occurrence of pinealoblastoma and reduces the incidence of long-term second nonocular cancers to 4% at 11 years.[14,15,19] These additional benefits could be a direct effect of IVC or indirect benefit by avoidance of EBRT.
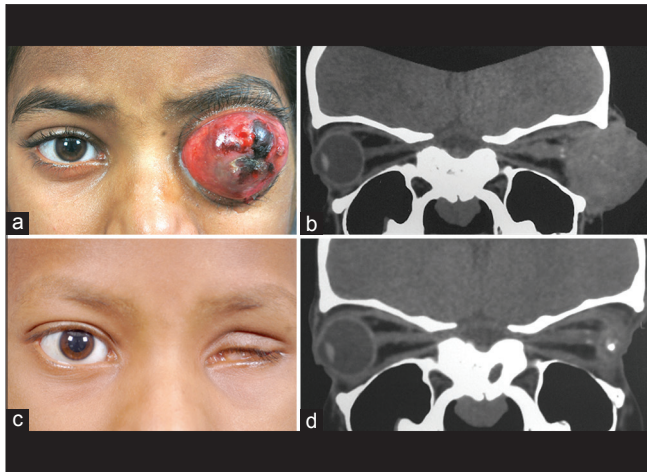
Chemoreduction of the orbital retinoblastoma

The incidence of orbital RB varies from 6% to 8% in developed countries and 5-44% in developing countries.[25-28] The presence of orbital invasion increases the risk of systemic metastasis by 10-27 fold and is associated with poor prognosis.[29]

The purpose of IVC in orbital RB is to facilitate enucleation/extended enucleation/exenteration as appropriate [Fig. 2]. Multimodal treatment protocol by combination of IVC, EBRT, and surgery is recommended.[8,27,30,31] IVC using 3 to 9 cycles of high-dose VEC allows resolution of orbital component and facilitates enucleation/extended enucleation/exenteration. This is followed by 40-50 Gy EBRT over 20-25 fractions and extended high dose chemotherapy for a total of 12 cycles.[8,27] Using this treatment protocol, Honavar and Singh studied 16 cases with unilateral orbital RB without intracranial extension and systemic metastasis, and reported good clinical outcome.[8,27] All affected eyes became phthisical after 3-6 cycles of high-dose VEC facilitating enucleation, and 88% were free of local recurrence or systemic metastasis at 3-year follow-up.[8,27]

Chemoprophylaxis in high-risk retinoblastoma

High-risk RB identified from histopathologic factors from enucleated eyes predicts the development of metastatic disease and related mortality.[32-35] Patients demonstrating such risk factors are given postenucleation adjuvant IVC as chemoprophylaxis for protection from presumed systemic micrometastases and related death.

Figure 2: Treatment of the orbital retinoblastoma with intravenous chemotherapy (a) Orbital retinoblastoma of the left eye confirmed on (b) computed tomography scan of the orbit. (c and d) Nine cycles of high-dose chemotherapy resulted in phthisis bulbi facilitating enucleation. No residual tumor was noted on histopathology. The patient subsequently underwent left orbit external beam radiotherapy and further three cycles of high-dose chemotherapy

Four to six cycles of adjuvant IVC is administered in cases with high-risk RB.[9,36] In cases with extrascleral extension and/or tumor extension to optic nerve transection additional orbital EBRT (40-50 Gy) is recommended.[9,36] In a study of 80 patients with high-risk RB by Honavar et al. a significant difference was found in the incidence of metastasis between the group that had received adjuvant therapy (4%) and the group that had not (24%), indicating the importance of postenucleation adjuvant IVC.[36] In a recent study of 52 patients with high-risk RB, Kaliki et al. found that the use of VEC as postenucleation adjuvant IVC further reduced the incidence of systemic metastasis. In that series, no child with high-risk RB developed metastatic disease, signifying the importance of IVC as chemo-prevention.[9]

Metastatic retinoblastoma

Metastatic RB is more common in developing countries (9-11%) than developed countries (5-6%).[10,37-39] The higher incidence of metastatic disease in developing countries is due to late referral and delayed diagnosis. Metastatic RB is associated with poor prognosis.[10,37-39]

High-dose chemotherapy with autologous stem cell rescue (ASCR) may be beneficial for some cases of metastatic RB.[40,41] In a study of 13 patients with trilateral RB by Dunkel et al. induction chemotherapy with VEC and cyclophosphamide in addition to high-dose chemotherapy with thiotepa-based or melphalan and cyclophosphamide with ASCR resulted in prevention of death in 38% cases without the need of EBRT at 6 years follow-up.[40] Beneficial effects were seen in cases with central nervous system (CNS) metastatic disease with high-dose chemotherapy and ASCR with survival in 40% cases (2 of 5 cases) at a mean follow-up period of 6 years.[40] Similar encouraging results were noted with high-dose chemotherapy and ASCR in cases with extra-CNS metastatic disease with survival in 67% (10 of 15 cases) cases at 9 years follow-up.[42] The use of EBRT to the metastatic sites is controversial.[40-43]

Complications of intravenous chemotherapy

The predictable complications of IVC include febrile episodes, temporary alopecia, and bone marrow suppression.[19] Cytopenias requiring platelet and/or packed red cells is common with high-dose chemotherapy and uncommon with standard-dose chemotherapy. Vincristine and etoposide can cause peripheral neuropathy, and allergic reactions to etoposide and carboplatin can occur.[19]

Cisplatin-induced ototoxicity is reported in 0-17% cases.[44,45] Properly dosed carboplatin in children with RB result in rare occurrences of hearing deficit.[44] Etoposide-induced secondary acute myelogenous leukemia has been reported in the literature; however, the incidence of IVC induced secondary acute myeloid leukemia is very low.[46,47] Though IVC-induced infertility has been speculated, there is no evidence supporting this with our protocol of VEC. Our personal experience using proper dosing of IVC reveals excellent tumor control with minimal toxicities and no fertility issues.

Intra-arterial Chemotherapy

Over the past few years, there has been increasing enthusiasm regarding IAC in the treatment of RB. Reese et al. were the first to investigate IAC for RB by intracarotid administration of triethylene melamine in 1958.[48] Subsequently in 1990's, Kaneko described the selective ophthalmic arterial injection of melphalan by distal occlusion of internal carotid artery with a balloon catheter.[49] This technique was further modified by Abramson et al. by supraselective IAC involving injection of melphalan directly into the proximal portion of the ophthalmic artery.[50] Shields et al. independently studied IAC and found excellent tumor control with low ophthalmic risks.[51] Various studies have shown that IAC can be used as primary treatment or secondary treatment in eyes with recurrent/residual RB.[50-58] [Table 1]. The various agents used for IAC in RB include melphalan, carboplatin, topotecan, and methotrexate[50-58] [Table 2]. The advantages of IAC include: [50-57]
- Control of intraocular tumor
- Resolution of RD
- Globe salvage
- Minimal systemic side-effects.

In a study of selective IAC with melphalan in 408 eyes of 343 patients by Suzuki et al. globe salvage was achieved in 100% group A, 88% group B, 65% group C, 45% group D, and 30% group E eyes.[52] Visual acuity of 20/40 or better was achieved in 51% eyes.[52] Gobin et al. reported their experience in 95 eyes with supraselective IAC, with 82% globe salvage when used as primary treatment and 58% globe salvage when used as secondary treatment.[53] Shields et al. reported their experience in 70 consecutive patients treated with supraselective IAC, with 72% globe salvage when used as primary treatment and 62% globe salvage when used as secondary treatment [Fig. 3].[55] Based on ICoR, globe salvage was achieved in 100% group B, 100% group C, 94% group D, and 36% group E eyes.[55] Based on various studies, IAC allows the globe salvage in 58-100% cases when used as primary treatment, and 50-75% cases as secondary treatment.[51-57] Globe salvage can be achieved in 100% group B, 100% group C, 75-100% group D, and 30-36% group E eyes.[51-57] However, IAC for group E RB should be used with caution due to the increased prevalence of high-risk RB in these eyes, necessitating enucleation and adjuvant IVC rather than IAC.[59,60]

Similar to IVC, IAC causes resolution of subretinal fluid associated with RB.[61] In a study of 15 patients with RB-induced RD, resolution of RD was noted in 43% cases with complete RD and 100% cases with partial RD.[61]

Complications of Intra-arterial Chemotherapy

Intra-arterial chemotherapy causes minimal systemic side-effects. Transient neutropenia develops in 11% patients after IAC that does not require transfusion.[53,55] Owing to minimal systemic absorption of drugs, IAC offers no protection against systemic metastasis, pinealoblastoma, and second cancers. Of 78 patients treated with IAC, two children developed systemic metastasis.[53] Local side-effects at the injection site and carotid spasm can also occur.

Ocular complications with IAC are well-documented.[50,52-56,62-67] Less severe, temporary side-effects include periorbital edema, periocular hyperemia, madarosis, and ocular dysmotility. More severe complications include vitreous hemorrhage in 13-27%, RD in 15 to 27%, retinal pigment epithelial changes occur in 5-53%, retinal ischemia in 4-24%, and chorioretinal atrophy in <1 to 29% cases.[50,52-56,62-67] These changes occur either secondary to drug toxicity or competency of ophthalmic artery catheterization resulting in structural and vascular damage of the retina causing visual loss.[67]

Periocular chemotherapy

Periocular administration of chemotherapy allows delivery of higher concentrations of chemotherapy drugs to the posterior segments of the eye. In 1996, Harbour et al. explored the use of periocular carboplatin in the treatment of RB in animal models.[68] Subsequent study by Mendelsohn et al. demonstrated that administration of periocular carboplatin is safe and results in higher vitreous concentration of carboplatin by 8-10-fold compared to intravenous administration.[69] Similarly, Mao et al. showed that the concentrations in the aqueous and vitreous humor after subconjunctival administration of etoposide were 2-4 times higher than those obtained after intravenous administration.[70] A study by Carcabaso et al. revealed that comparable vitreous concentrations of topotecan were achieved when administered through periocular or systemic routes.[71]

The available data does not support the use of periocular chemotherapy as monotherapy. Periocular carboplatin is used as an adjunct treatment for eyes with persistent vitreous seeding despite other forms of treatment, in patients with bilateral RB with poor prognosis at diagnosis, or in those in whom IVC is contraindicated[72] [Tables 1 and 2, Fig. 4] Periocular carboplatin is effective for noncalcified vitreous seeds, and not effective against solid tumor or subretinal seeds.[73] Periocular topotecan is effective against group A and B tumors.[74] The various delivery systems of periocular chemotherapy being investigated include episcleral implants, fibrin sealants, and nanomolecular composition.[72]

Complications of periocular chemotherapy

Periocular chemotherapy is devoid of systemic side-effects. The most common side-effect is periorbital edema and erythema. The other side-effects include ocular motility changes, orbital fibrosis, optic atrophy, pseudo-preseptal cellulitis, and rarely ophthalmic arterial alterations.[72]
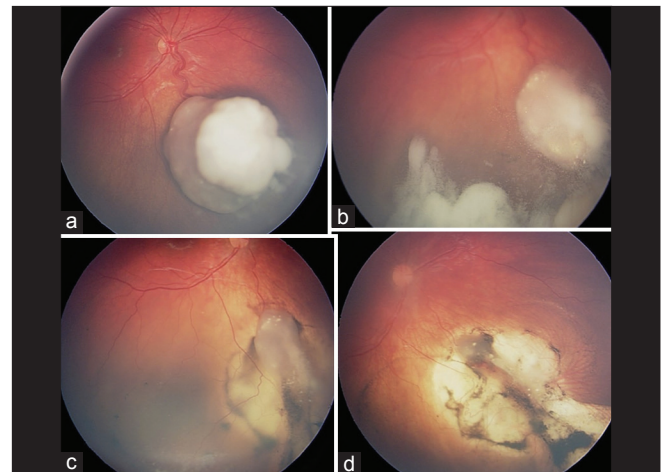
Intravitreal chemotherapy

Ericson and Rosengren first investigated the use of intravitreal chemotherapy for RB in 1960's.[75] However, this technique did not gain popularity due to the risk of tumor seeding after any intraocular intervention in RB. In 1995, Seregard et al. demonstrated the absence of local recurrence and metastatic disease following administration of intravitreal thiotepa.[76]

Inomata and Kaneko found melphalan to be the most sensitive chemotherapeutic agent against RB based on in vitro testing of 12 agents, and a dose of 4 ug/ml achieved complete tumor suppression [Fig. 5].[77] In the rabbit model, the concentration of 5.9 µg/ml showed no retinal toxicity, and this correlates to human vitreous doses of 20-30 ug.[16] These findings have prompted 20-30 ug melphalan as the drug of choice for intravitreal chemotherapy, with minimal ocular
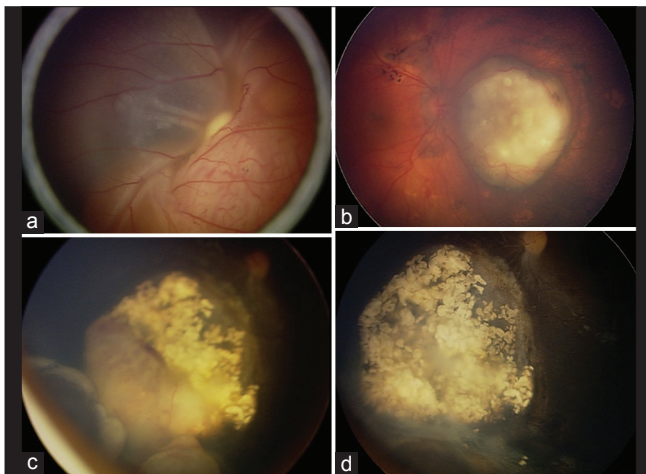
Figure 3: Treatment of intraocular retinoblastoma with intra-arterial chemotherapy (a) group E retinoblastoma of the left eye showed (b) complete tumor control with primary intra-arterial chemotherapy (IAC). Surrounding retinal pigment epithelial changes is also noted. (c) Tumor recurrence following intravenous chemotherapy showed (d) complete tumor control with secondary IAC

Figure 4: Treatment of vitreous seeds with periocular chemotherapy (a) group C retinoblastoma of the right eye showed (b) dispersion of vitreous seeds during intravenous chemotherapy. (c) Reduction in vitreous seeds following one dose of 20 mg/2 cc periocular carboplatin and (d) complete tumor control following the second dose of periocular carboplatin
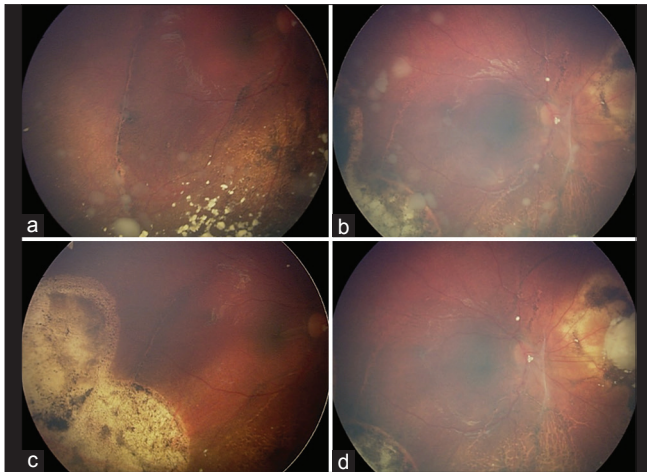
Figure 5: Treatment of vitreous seeds with intravitreal chemotherapy (a and b). Recurrent vitreous seeds in the right eye following 3 cycles of intra-arterial chemotherapy (c and d). Complete tumor control was achieved with 6 monthly doses of 20 ug melphalan

complications and no significant electroretinogram changes at this dose.[78,79] Dose greater than 50 ug is associated with severe ocular complications.[79] Satisfactory results have also been reported with an intravitreal methotrexate, carboplatin and topotecan[80-82] [Table 2]. In the recent times, the use of intravitreal chemotherapy through pars plana route for recurrent/residual vitreous seeds has shown promising results[78-88] [Table 1].

Kaneko and Suzuki treated 41 eyes with 8ug intravitreal melphalan and reported the globe salvage in 51% cases.[88] In a study of 23 eyes with active vitreous seeds, Munier *et al*. reported the globe salvage in 87% eyes with complete remission of vitreous seeds over a mean follow-up period of 2 years.[85] Intravitreal melphalan 20-30 ug was injected every 7-10 days via the parsplana approach.[85] Shields *et al*. studied 11 eyes treated with intravitreal melphalan and reported the globe salvage in 100% eyes at a mean follow-up of 9 months.[83] Intravitreal melphalan 20-30 ug was injected every month via the pars plana approach with concomitant triple freeze-thaw cryotherapy to the injection site.[83] Kivelä *et al*. adapted the intraocular lymphoma protocol to inject intravitreal methotrexate and reported complete remission of vitreous seeds in 100% cases (2 of 2 eyes), subretinal seeds in 67% (2 of 3 eyes), and small retinal foci in 50% (2 of 4 eyes).[80]

Omplications of intravitreal chemotherapy

The most concerning side-effect of intravitreal chemotherapy is extraocular tumor spread. Extraocular tumor spread from intravitreal chemotherapy can occur per-operatively due to spilling of tumor cells from surgical instruments while removing from the eye or reflux of contaminated vitreous at the injection site; or postoperatively due to tumor growth along the needle tract.[87] Extraocular tumor spread can be prevented by ultrasound biomicroscopic guided selection of injection site to avoid injection directly into the contaminated posterior chamber and subsequent tumor growth along the needle tract; anterior chamber paracentesis to create a transient hypotony and avoid reflux of contaminated vitreous at the injection site secondary to variations in intraocular pressure; triple freeze-thaw cryotherapy at the injection site; and injecting a bleb of subconjunctival chemotherapy (carboplatin) prior to intravitreal chemotherapy.[81,83,85,87]

The other serious side-effects include iris atrophy, vitreous hemorrhage, RD, and chorioretinal atrophy. Minor side-effects include transient conjunctivitis, transient keratitis, corneal edema, cataract, ocular inflammation, vitreous condensation and banding, and retinal pigment epithelial changes.[89]

Conclusion

The management of RB has evolved over the years with improving methods of treatment. The combination of various treatment modalities is likely to increase the rate of tumor control and globe salvage. The treatment of intraocular RB is likely heading in the direction of a combination of IVC and IAC along with focal treatments such as cryotherapy and transpupillary thermotherapy. Periocular chemotherapy and intravitreal chemotherapy are promising adjunct therapies in refractory cases.

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