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Chapter

Retinoblastoma Management: Advances in Chemotherapy

Amani Al Kofide and Eman Al-Sharif

Abstract

The treatment of children with retinoblastoma (RB) has evolved from primarily enucleation of the eye(s) to highly selective methods of chemotherapy administration and approach. Indulgent and comprehensive understanding of the multitude of factors including accurate classification and grading of disease, timing and response to therapy, when to consolidate with local methods of therapy, combination regimens to control systemic disease and prevent relapse while minimizing risk of secondary cancers are crucial factors in the management of children with retinoblastoma. Chemotherapy was introduced in the 1950s and has become an integral component in management of RB. Methods of administration range from systemic to locally directed therapy including; intravitreal, periocular and intra-arterial chemotherapy. This chapter is intended to discuss the evolution and current chemotherapeutic agents with various routes of administration. The indications, adverse occurrences, short- and long-term complications of both local and systemic treatments will be elucidated.

Keywords: chemotherapy, retinoblastoma, metastasis, intravenous, intra-arterial, intravitreal, periocular, vitreous seeds

1. Introduction

The treatment of retinoblastoma is challenging, as the governing objectives are preserving life, protecting from pineoblastoma, decreasing the lifetime incidence of secondary tumors and salvaging useful vision without exposing the patient to significant and serious side effects that may endanger the patient's survival and quality of life. The treatment of retinoblastoma evolved steadily during the past decades, and multiple modalities of treatment were introduced including chemotherapy. At one time, chemotherapy was used mainly to manage metastatic retinoblastoma, but later the interest of scientists and clinicians shifted to the use of this treatment strategy for non-metastatic retinoblastoma. As the interest of experts grew and the demand for better overall outcome increased, multiple interesting treatment strategies were developed and refined. Now, four main routes of administration of chemotherapy are present, and these are: intravenous chemotherapy (IVC), intra-arterial chemotherapy (IAC), intravitreal chemotherapy (IVitC) and periocular chemotherapy (POC).

Today, chemotherapy is regarded as one of the indispensable pillars of treatment of retinoblastoma. In fact, retinoblastoma is currently one of the most commonly curable childhood malignant tumors universally. In developed countries, the rates of expected survival exceed 95% whereas the rates in developing countries are

lower due to the limited healthcare resources [1]. The different chemotherapy treatment strategies outlined above will be discussed thoroughly in the upcoming sections.

2. Intravenous chemotherapy for retinoblastoma

The era of chemotherapeutic treatment for retinoblastoma began in 1953 when Carl Kupfer reported the successful use of intravenous nitrogen mustard along with irradiation to treat a child with recurrent retinoblastoma [2]. Thereafter, the use of triethylene melamine, a chemotherapeutic alkylating agent, via different routes (oral, intramuscular, intravenous and intra-arterial) became more widespread between clinicians until the late 1960s given that it allowed the reduction of radiotherapy dose which was associated with multiple potential side effects [3–6]. In the following years, the use of systemic chemotherapy fluctuated until the early 1990s when the use of systemic chemotherapy was popularized and strongly advocated by the leading retinoblastoma treatment centers worldwide and the use of external beam radiation was restricted in favor of chemotherapy due to the considerable risk of secondary tumors in patients receiving radiotherapy.

The management of retinoblastoma should be carried out by an experienced team as these children need meticulous bilateral ocular examination, usually under anesthesia, in parallel with systemic evaluation by a pediatric oncologist with experience in ocular oncology and appropriate systemic imaging by magnetic resonance imaging (MRI) must be standardly performed to rule out metastasis. These steps are vital to accurately classify the disease in accordance with the more recent International Classification of Retinoblastoma (ICRB). This will direct the treatment to either systemic chemotherapy or local therapies (thermal, cryotherapy and chemotherapy) or a combination of both.

Understating the effect of systemic chemotherapy on the different forms of retinoblastoma (solid tumor, subretinal tumor and vitreous seeds) is essential as it helps in guiding the treatment. Moreover, the likely complications and systemic toxicities of IVC are important to be looked at carefully before commencement as this will help in individualizing the treatment in this vulnerable subset of patients so as to reduce systemic morbidities without jeopardizing the treatment success [7]. In this section, we will highlight the principal characteristics of this treatment modality.

2.1 Indications

The use of IVC varies slightly between different treatment centers worldwide; but generally speaking, the umbrella of IVC usage encompasses its use in patients with intraocular disease only and in patients with or at high risk of extraocular disease. When the disease is limited to the eyes, IVC aims at shrinking the size of the tumor to expedite cure and lessen the damage induced by consolidating local therapies to follow, especially when the tumor involves sensitive retinal areas such as the macula. This has been termed chemoreduction and it had been shown to achieve adequate tumor control (alone or along with focal consolidating therapies) and eliminate the need for enucleation or external beam radiation (EBR) in more than 75% of patients in a large series (n = 457, group A–D). The risk of recurrence in this series was 22% and these were usually detected in the first year after starting the treatment; yet; none occurred by 4 years of follow up [8, 9]. This is probably the most important concern arising with the use of chemoreduction; though continuous surveillance of these children partly helps in overcoming this shortcoming.

Moreover, one study suggested that the administration of chemoreduction might minimize the risk of pineoblastoma where none of the children (n = 147) receiving this therapy developed trilateral retinoblastoma [10].

IVC is used also as an adjuvant therapy after enucleation in patients with extraocular disease (metastasis) as well as patients with intraocular disease associated with high-risk histopathological features (e.g., optic nerve invasion beyond the lamina cribrosa and choroid invasion >3 mm) demonstrated on histopathological examination of the enucleated eye [11]. It is speculated that patients with high-risk features might presumably have micro-metastasis and administering systemic chemoprophylaxis helps in improving their prognosis. Evidence in the literature supports the use of prophylactic IVC in high-risk patients where it was shown that it is safe and effective in decreasing the risk of metastasis [12, 13].

Patients with extraocular disease receiving IVC can be divided into three categories: those with orbital and/or regional spread to the preauricular lymph nodes or optic nerve cut, those with central nervous system (CNS) dissemination and those with distant extracranial metastasis [14]. In patients presenting with orbital retinoblastoma, IVC is a valuable treatment. This holds true when it is predominantly administered in combination with other therapies (multimodal therapy: surgery, radiotherapy and chemotherapy) as its effect is usually inadequate when given alone [15]. Patients who have CNS involvement usually have a very poor prognosis with low survival rate. The usual approach to these patients consists of platinum-based IVC with agents having good CNS penetration along with focal CNS treatments such as radiotherapy. Some studies suggested using high doses of IVC followed by autologous hematopoietic progenitor cell rescue; yet, this technique is controversial [16]. Distant metastasis usually occurs to the bone and a small series (n = 14) on stage 4A patients showed promising results using intense induction chemotherapy followed by high dose consolidating chemotherapy and autologous hematopoietic progenitor cell rescue [17].

2.2 Chemotherapeutic protocol

Over the past decades, multiple chemotherapeutic agents were used, and multiple chemotherapy protocols were implemented, some of which are now outdated. In the meantime, the most commonly employed IVC therapy is the VEC protocol consisting of three main chemotherapeutic agents (Vincristine, Etoposide, Carboplatin) in standard doses based on the body weight. Higher doses may be used in patients with more advanced disease (bilateral group D or E) [7, 18]. This three-drug regimen is the most popular combination preferred by many experts and this stems from its proven effect on neuronal tumors in the pediatric age group as well as its good penetration into the eye [19]. The patient usually receives 6–9 cycles on a monthly basis and once the tumor shrinks in size, then focal consolidating treatments can follow [7].

2.3 Complications

Common side effects, which are usually observed with any systemic chemotherapy, include transient pancytopenia owing to bone marrow suppression, fever and alopecia. The occurrence of these side effects is usually limited to the treatment period. Although carboplatin, a platinum based agent, had been linked to ototoxicity and nephrotoxicity, these serious side effects are rare as they are dose-dependent [20, 21]. There was an underlying concern that etoposide may induce acute myelogenous leukemia especially with high multiple doses; yet, the results of several studies on this topic were reassuring [7, 22]. With regards to secondary tumors, it

does not seem that IVC increases the risk ominously. A long term follow-up study demonstrated that the rate of secondary tumors in germline retinoblastoma patients treated with systemic chemotherapy was 4%, which is less than expected for this vulnerable subset of patients [23].

2.4 Outcomes and success rate

The introduction of systemic chemotherapy resulted in an improved eye salvage rate, not to mention the enhanced visual outcome. Chemoreduction success can be predicted in patients with retinoblastoma following the ICRB classification as following: 100% in group A, 93% in group B, 90% in group C and <50% in group D and E [24]. The success rate in the advanced stages can be augmented when combining IVC with other modalities of treatment such as IAC or IVitC. Long-term studies have shown that chemotherapy with or without adjunctive therapies maintains ambulatory vision of ≥6/60 in almost two-thirds of the patients, particularly those with multiple tumors and/or no foveolar tumors [25]. Furthermore, IVC seems to exert a protective effect against pineoblastoma as its occurrence is usually very low in patients receiving it [26].

The effect of systemic chemotherapy as a monotherapy appears to be satisfactory especially in patients with less advanced disease whereas in patients with advanced disease, its remedial action is complementary to the selective recent therapies. A recently published meta-analysis comparing IVC to the more selective IAC revealed that both methods are equivalent in terms of tumor recurrence and metastasis. IAC evidently had a higher total success rate and ocular sparing effect in group D patients compared to IVC [27]. Despite this, we believe that IVC will continue to be an integral part of the treatment regimen of retinoblastoma.

3. Intra-arterial chemotherapy for retinoblastoma

Intra-arterial chemotherapy (IAC), also known as ophthalmic artery chemosurgery (OAC), is an important treatment strategy for retinoblastoma that evolved rapidly and gained popularity worldwide. Today, this modality of treatment is being performed in many retinoblastoma treatment centers located in more than 45 countries across the globe [28]. This treatment modality was initially explored by Reese et al. [3] who directly injected the alkylating agent triethylene melamine (TEM) into the internal carotid artery; nevertheless, it was not until 2006 when Abramson and Gobin introduced the novel technique of super-selective ophthalmic artery catheterization via transfemoral artery approach which allowed immediate and effectual delivery of the administered agent (melphalan) into the diseased eye [29]. Thereafter, many oncology centers adopted this technique and started publishing their experience. In this section, we will be shedding the light on the important aspects and most recent results of IAC.

3.1 Indications

IAC opened the door to a new era in the treatment of retinoblastoma. The key exciting factor behind this local therapy is its ability to achieve adequate therapeutic intraocular concentrations of the delivered chemotherapeutic agents while minimizing the systemic toxicity induced by these infused drugs such as neutropenia and secondary tumors [30]. In view of this, IAC is utilized mainly in treating patients with intraocular disease without local or systemic spread. Previous studies on IAC have shown that it can be used successfully as a primary retinoblastoma treatment in

naïve eyes (no previous therapy employed) or as a secondary treatment in eyes with recurrent or residual tumor after trying other treatment modalities such as systemic chemotherapy, external beam radiotherapy and others [29, 31–37]. Currently, the common indications for IAC in retinoblastoma patients include unilateral retinoblastoma that cannot be halted by local treatments alone (e.g., cryotherapy or laser photocoagulation) and advanced unilateral retinoblastoma (such as group D and E based on the ICRB) [30]. Several studies had previously reported the following advantages of using IAC in patients with group D retinoblastoma: better eye conservation rates and greater visual acuity compared to systemic chemotherapy, shorter treatment period and ability to repeat the therapy several times using multiple agents without endangering the patients' life and vision [28, 38]. It is also noteworthy to mention that IAC can save naïve eyes with advanced retinoblastoma from enucleation particularly when subretinal seeding is present (2 year ocular survival rate of 83%) [39]. Furthermore, IAC has a proven benefit even in patients presenting with advanced disease such as those having retinoblastoma-induced total or partial retinal detachment in which it can successfully achieve retinal re-attachment and thus help in preserving the eye and the life with the least possible side effects [40, 41].

Simultaneous IAC (tandem therapy) to both eyes consecutively is also a valuable and safe treatment method in patients with bilateral germline retinoblastoma whether used primarily or secondarily. This was demonstrated in two recent studies, which reported excellent globe salvage rates (ocular survival rate > 90%) even in patients with advanced disease. Despite that the safety profile of this simultaneous therapy was considerably high where no treatment-associated deaths occurred, these children were still at risk of secondary tumors such as pineoblastoma and this is probably attributed to their inherent genetic predisposition [42, 43].

3.2 IAC technique

The technique of IAC is carried out on patients who are generally anesthetized and is usually coordinated by a specialized and experienced oncology/radiology team. The common femoral artery on the ipsilateral treatment side is usually used to gain access to the internal carotid artery and then the ophthalmic artery (OA) is selectively catheterized under fluoroscopic guidance at its ostium (origin) while heparin is infused intravenously to prevent coagulation. Then, in order to verify the proper placement of the microcatheter, selective angiography is done by contrast infusion to delineate the vascular anatomy and ocular perfusion. Due to the variability of vascular territory anatomy and blood flow patterns, OA catheterization might fail and other routes are available, however, this is out of the scope of this chapter [34].

3.3 Chemotherapeutic agents

The most commonly used intra-arterial chemotherapeutic agent is melphalan, a potent alkylating agent. Melphalan is by far the strongest chemotherapeutic drug acting effectually against human retinoblastoma cells [44]. It is very safe when administered locally but very toxic when infused systemically due to the resultant severe myelosuppression [45]. In fact, it is currently considered an ideal agent due to its favorable safety profile, short half-life and ability to be used in combination with other agents to achieve greater tumor control when needed [34, 46]. Topotecan, a topoisomerase inhibitor, and carboplatin, an alkylating agent, are other agents that have been used alone or as a part of a multi-drug regimen in advanced cases that fail to respond to melphalan solitarily or in bilateral tandem therapy where the dose of melphalan is decreased to prevent systemic side effects [34].

3.4 Complications

Despite being a less invasive therapeutic intervention, IAC does carry some risk of complications, as it would be expected with any medical interventional procedure. Complications occurring after IAC are attributed either to the procedure itself or to the chemotherapeutic agent/agents or both. Complications developing from the procedure include endovascular complications occurring intraoperative, allergy to iodine and hematoma at the site of entry into the femoral artery. Systemic thromboembolic and hemorrhagic events (stroke, limb ischemia) are possible but their current reported overall occurrence is extremely scarce [30, 44]. Up to date, no procedure-related deaths had been reported. Theoretically speaking, since IAC targets chiefly the intraocular pathology, the risk of metastasis and secondary neoplasms remains unchanged or even might be increased, as this treatment is not intended to reach the systemic circulation in high concentrations. Experts studied the incidence of death due to retinoblastoma-associated metastasis in a cohort of patients treated over a 10-year period by IAC primarily or secondarily and found it to be negligible (<1%) [47]. Likewise, IAC was not associated with an increased rate of second primary malignancies (SPM) in a group of patients with germline retinoblastoma from one treatment center studied over a 10-year period (2006–2016) [48]. However, IAC is relatively a recent therapy; therefore, it is still premature to derive definite conclusions regarding the potential risk and studies with longer follow up periods are required.

Neutropenia is another important complication that should be recognized and managed early to prevent devastating complications. The local distribution of the drug has helped in limiting its occurrence to <15% [34, 49]. On the other hand, minor ocular side effects are common and these include: lids edema, blepharoptosis, temporary loss of the eyelashes and forehead hyperemia along the distribution of the supratrochlear artery [50]. Ocular vascular complications are among the universally feared local side effects. A recent review of 16 published studies reported that <2.5% had ophthalmic artery obstruction or occlusion, choroidal ischemia or atrophy and vasospasm [49]. These vascular events should be interpreted in the context of the clinical case given that these are usually sick eyes that might have received other local treatments that might contribute to the occurrence of such events. A recently published study looked at the incidence of vascular events and the variability of their occurrence when IAC is given primarily or secondarily and reported the following: overall vascular complications occur in 5% of eyes per infusion and no difference was observed when IAC is used as a primary or secondary therapy [51].

3.5 Outcomes and success rate

The body of evidence in the literature supporting the use of IAC has been growing persistently in the past decade. Impressively, the reported globe salvage rate is currently exceeding 90% without compromising patient's survival and the enucleation rate dropped to <10% [35, 52–54]. Even the rate of orbital recurrence was significantly higher in patients with advanced disease treated with enucleation compared to IAC and this further emphasizes the gainful outcome of IAC [55].

A major concern about the risk of recurrence after IAC treatment remains in spite of the success achieved by this treatment modality. A recent study from one of the pioneering centers utilizing IAC with 10 years experience reported that around 25% of eyes treated primarily with IAC might develop recurrence. The recurrence of the disease was observed to occur mainly in the first 12 months post-treatment; and therefore, close follow up with serial meticulous examination is recommended during this period. Surprisingly, the rate of recurrence was higher in eyes that

received the drug through routes other than OA and in eyes with widely spaced treatments more than 4 weeks. The risk of recurrence was <10% by 2 years in eyes remaining disease free in the first year after IAC [52].

4. Intravitreal chemotherapy for retinoblastoma

Intravitreal chemotherapy (IVitC) is another well-established targeted therapy accounting for one of the important current treatment modalities for retinoblastoma manifesting vitreous seeds. Initial reports on IVitC date back to the 1960s where thiotepa was injected into the vitreous cavity of six eyes with retinoblastoma; yet the results were inconclusive due to the limited number of treated eyes [56]. Later, this method was revived by Kaneko and Suzuki who injected melphalan intravitreally in 41 eyes along with ocular hyperthermia to cure vitreous seeding with a notable resultant eye preservation rate of 51.3% [57]. The choice of melphalan was essentially based on in-vitro testing of 12 anti-neoplastic drugs, and melphalan proved to be the most effective against retinoblastoma cells [45]. Implementing this technique into current practice took several years and perhaps the major limiting factor was the fear of disseminating the cancer cells during injection with the risk of subsequent extraocular spread causing metastasis and death. This section will elaborate on the key qualities of this relatively new therapy.

4.1 Indications and contraindications for intravitreal chemotherapy

This local therapeutic technique is intended essentially to achieve the highest concentration of the delivered tumoricidal drug into the confined intraocular space adjacent to the tumor. IVitC is used as an adjunctive therapy to chemoreduction with systemic chemotherapy and IAC. The main indications for this treatment modality are the presence of active vitreous seeds that are either refractory to standard therapy or recurrent after pervious standard therapy [7]. The use of IVitC had also expanded lately to include patients with retinal and subretinal tumors where it had been shown to be successful in salvaging the globe of such patients [58].

On the other hands, contraindications preventing the execution of this procedure include tumors involving the ciliary body or extending up to the anterior segment, tumors filling the globe, retinal detachment and vitreous hemorrhage.

4.2 Intravitreal chemotherapy technique

Before proceeding with this treatment, it is critical to meticulously evaluate the pars plana clinically in all quadrants 360° looking for any tumor foci as that could pose a threat to safety if present due to the risk of spread while injecting. If visualization is difficult, then ultrasound biomicroscopy can be used to help in detection and affirmation [59].

The procedure is usually carried out in the operating room under sterile conditions while the child is under general anesthesia. The anti-cancerous drug, typically melphalan, is injected through the pars plana 3–3.5 mm from the limbus into the vitreous cavity using a small needle, preferably a 32 gauge-needle. This creates the smallest needle track that helps in reducing the risk of dissemination. The injection is rather done in a seed-free quadrant, 2 o'clock hours away from vitreous seeds to prevent the undesirable exteriorization of tumor cells. Furthermore, some experts advocate reducing the pressure inside the eye by paracentesis before inserting the needle to prevent the possible risk of microscopic tumor seeding. After injecting the drug and before exiting the tumor-harboring globe, triple freeze-thaw cryotherapy

should be carried out concurrently at the injection site while withdrawing the needle. Then, uniform intraocular distribution of the drug is achieved by gentle shaking of the eye using forceps. Examination is usually performed at the end of the procedure to rule out possible acute complications such as retinal detachment and bleeding. The ocular surface is then washed with balanced salt solution to remove any remnant chemotherapeutic agent that could be toxic. The child is usually discharged in the same day and the family is instructed to avoid touching the eye [59]. The procedure may vary minimally between different specialized treatment centers.

4.3 Chemotherapeutic agents

Melphalan hydrochloride is the principal drug injected into the vitreous cavity in retinoblastoma patients. It is a cytotoxic nitrogen mustard derivative that inhibits the synthesis of DNA and RNA together [59]. Its effective dosage range was studied and set at 20–30 μg per injection as low doses (8 μg) were not adequate to control and eradicate the disease while high doses (50 μg) controlled the disease but resulted in local toxicity (cataract, posterior segment hemorrhage, hypotony and phthisis bulbi) [60]. The number of injections is governed by the response. In general, Shields et al. proposed giving a total of six injections weekly or every 2 weeks [7].

Topotecan, a topoisomerase-1 inhibitor, is another potent intravitreal agent that had been employed in the treatment of retinoblastoma with vitreous seeds. Experimental animal studies showed that topotecan produce high and stable levels in the vitreous [61]. One of the distinguishable advantages of topotecan is its ability to attain a vitreous-to-plasma concentration five times more than melphalan [62]. Previous studies have shown that it is an effective anti-tumor drug with good safety profile and low ocular toxicity [63]. It had been used intravitreally in combination with melphalan in humans with encouraging results where this multi-agent regimen managed to achieve notable vitreous seeds regression with fewer injections [64]. Topotecan can also be used effectively in patients with recurrent or resistant viable vitreous seeds according to a recent study on 17 eyes which demonstrated control of these seeds in all treated eyes (100%) in the absence of ocular or systemic side effects and with a lower number of injections [65].

4.4 Complications

Extraocular tumor dissemination through the needle track with subsequent metastasis was perhaps the most feared serious event limiting the use of this treatment modality in the past. However, a meta-analysis examining published studies on this matter revealed that the risk of systemic spread is very low (two cases out of 1304 injections, proportion of extraocular spread secondary to injections was 0.007) especially when the appropriate safety enhancing injection techniques are applied. Therefore, IVitC can be utilized unreservedly whenever needed after proper patient selection [66].

Ocular side effects are generally uncommon in patients receiving IVitC. The major factor influencing the risk of complications and local ocular toxicity is the dose of administered medication where toxicity is more likely with melphalan doses higher than 30 μg [67]. Among the most frequent side effects is retinal pigment epithelium changes (salt and pepper retinopathy), which is believed to represent a form of chemical burn to the retinal at the area where the drug is concentrated the most [68, 69]. Retinal function decline due to toxicity, usually highlighted on electroretinography (ERG), is a possible complication of melphalan although the results are conflicting in the literature where one study showed no effect on ERG (dose:

20–30 μg) while another reported non-progressive decreased ERG amplitudes of approximately 5 μV (equivalent to 5% retinal response) with every 30 μg melphalan injection [70–72]. ERG can actually be a useful tool to monitor these patients for cumulative retinal toxicity.

Other major ocular complications that were highlighted in a systematic review with a total of 1287 intravitreal injections given to 306 eyes include: iris depigmentation and atrophy, chorioretinal atrophy with vitreous hemorrhage and retinal detachment [67]. Fortunately, there are no reports of endophthalmitis after IVitC; nonetheless, all protective measures should be taken to prevent this possible devastating complication.

With regards to serious systemic side effects, namely significant neutropenia of grade 3 and 4, these were not observed when analyzing 46 blood samples withdrawn from patients receiving IVitC (despite some patients received concurrent IAC) [71]. Again, this accentuates the benefit of local therapies in these young children.

4.5 Outcomes and success rate

Treating retinoblastoma with vitreous seeding can be really challenging due to the avascular nature of the vitreous; and therefore, drug delivery through systemic routes may not be sufficient sometimes. Besides this, it tends to be resistant to external radiation and systemic chemotherapy [68, 73]. In the past two decades, a quantum leap forward in the management of advanced retinoblastoma was reached with the help of IVitC. The reported vitreous seeding control rates of IVitC (melphalan with or without topotecan) ranges between 60 and 100% [60, 68, 71, 72, 74]. Additionally, the attained globe salvage rates are also impressive reaching up to 100% as reported in one study on 11 eyes receiving a total of 55 intravitreal melphalan injections [69].

5. Periocular chemotherapy for retinoblastoma

Periocular chemotherapy (POC) administration was designed to allow delivery of a higher concentration of the tumoricidal drugs locally. This route was firstly tested in retinoblastoma animal models using carboplatin and it had been shown that this route produces vitreous concentrations 8–10 folds more than the intravenous route [75, 76]. These preclinical results led to the conduction of a trial in which children with retinoblastoma were treated using subconjunctival carboplatin and the results were promising [77]. Thereafter, POC grew in popularity and it was consequently incorporated into the multimodal treatment algorithm of retinoblastoma. Currently, it is a part of the prospective multicenter Children's Oncology Group trials for retinoblastoma. In this section, POC will be tackled comprehensively.

5.1 Indications for periocular chemotherapy

POC is used predominantly as an adjunctive therapy to systemic chemotherapy as presently there is no evidence promoting it as a stand-alone therapy [78]. It is indicated principally in patients with recurrent localized tumor and in advanced disease (group D and E) where chemotherapy can be desirably infused in higher concentrations without exposing the patient to increased systemic toxicity [7]. It can also be utilized in patients who are not fit to receive systemic chemotherapy as well as patients with recurrent or persistent viable non-calcified vitreous seeds [78].

5.2 Chemotherapeutic agents

The common chemotherapeutic agents that are mostly used are carboplatin and topotecan. Experimental work showed that carboplatin peaks in the vitreous after 30 min of periocular injection and lasts for hours. Its concentration in the vitreous is approximately seven times more than that achieved by intravenous chemotherapy [76]. Several periocular drug administrative devices were explored and these include: plain liquid, Lincoff balloon, fibrin sealant, nanoparticles and iontophoresis [76, 79–81].

5.3 Complications

This treatment modality fortunately has no systemic side effects. Ocular complications do occur, and these mostly affect the periorbital tissue possibly owing to local toxicity. The most common observed side effects are lid edema, lid erythema, periorbital pseudocellulitis, ptosis, orbital fat atrophy, optic nerve atrophy and muscle fibrosis causing ocular motility changes [7, 77, 78, 82, 83]. Concerns were raised regarding the toxic effect on the extraocular muscles; yet, a study examining the effect of sub-tenon topotecan on the extraocular muscles of 10 eyes concluded that it had no toxic effect on the muscles and it is a safe and effective alternative [84].

5.4 Outcomes and success rate

Although the number of studies on POC is limited overall, it had been shown that POC is principally effective when combined with other modalities of anti-neoplastic therapies. One long-term follow up study demonstrated that 39% (n = 33 eyes) of the enrolled eyes were saved when treated with POC in addition to other concurrent treatment modalities. The same report indicated that two eyes treated by POC as monotherapy were cured and remained disease free on follow up [82].

6. Conclusions

In the last two decades, significant new approaches have been employed in the treatment of retinoblastoma which is a curable disease when diagnosed early. Modalities to avoid enucleation and minimize the short and long term effects of exposure to systemic chemotherapy and radiation therapy continue to evolve and now set the platform in the treatment of retinoblastoma. Despite new techniques such as selective intra-arterial and intravitreal chemotherapy, it is paramount to individualize therapy according to multiple factors including patient age, tumor location, stage of disease, size, and extension, along with realistic visual expectations. Personalized medicine will be able to tailor therapy with the best response and safety in children with retinoblastoma.

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Conflict of interest

The authors have no conflict of interest to disclose.

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References

[1] Shields CL, Shields JA. Diagnosis and management of retinoblastoma. Cancer Control. 2004;**11**:317-327

[2] Kupfer C. Retinoblastoma treated with intravenous nitrogen mustard. American Journal of Ophthalmology. 1953;**36**(12):1721-1723

[3] Reese AB, Hyman GA, Merriam GR Jr, Forrest AW, Kligerman MM. Treatment of retinoblastoma by radiation and triethylenemelamine. A.M.A. Archives of Ophthalmology. 1954;**53**(4):505-513

[4] Reese AB, Hyman GA, Tapley NA, Forrest AQ. The treatment of retinoblastoma by X-ray and triethylene melamine. A.M.A. Archives of Ophthalmology. 1958;**60**(5):897-906

[5] Krementz ET, Schlosser JV, Rumage JP, Herring L. Retinoblastoma: Behavior and treatment with fractional irradiation and intra-arterial triethylenemelamine. Annals of the New York Academy of Sciences. 1964;**114**(2):963-975

[6] Hyman GA, Ellsworth RM, Feind CR, Tretter P. Combination therapy in retinoblastoma: A 15-year summary of methods and results. Archives of Ophthalmology. 1968;**80**(6):744-746. DOI: 10.1001/archopht.1968.00980050746012

[7] Shields CL, Lally SE, Leahey AM, et al. Targeted retinoblastoma management: When to use intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Current Opinion in Ophthalmology. 2014;**25**(5):374-385. DOI: 10.1097/ICU.0000000000000091

[8] Shields CL, De Potter P, Himelstein B, Shields JA, Meadows AT, Maris JM. Chemoreduction in the initial management of intraocular retinoblastoma. Archives of Ophthalmology. 1996;**114**:1330-1338

[9] Shields CL, Mashayekhi A, Cater J, Shelil A, Meadows AT, Shields JA. Chemoreduction for retinoblastoma: Analysis of tumor control and risks for recurrence in 457 tumors. Transactions of the American Ophthalmological Society. 2004;**102**:35-44. discussion 44-45

[10] Shields CL, Meadows AT, Shields JA, Carvalho C, Smith AF. Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral retinoblastoma). Archives of Ophthalmology. 2001;**119**(9):1269-1272. DOI: 10.1001/archopht.119.9.1269

[11] Eagle RC Jr. High-risk features and tumor differentiation in retinoblastoma: A retrospective histopathologic study. Archives of Pathology & Laboratory Medicine. 2009;**133**(8):1203-1209. DOI: 10.1043/1543-2165-133.8.1203

[12] Honavar SG, Singh AD, Shields CL, et al. Postenucleation adjuvant therapy in high-risk retinoblastoma. Archives of Ophthalmology. 2002;**120**(7):923-931

[13] Kaliki S, Shields CL, Rojanaporn D, et al. High-risk retinoblastoma based on international classification of retinoblastoma: Analysis of 519 enucleated eyes. Ophthalmology. 2013;**120**(5):997-1003. DOI: 10.1016/j.ophtha.2012.10.044

[14] Rodriguez-Galindo C, Orbach DB, VanderVeen D. Retinoblastoma. Pediatric Clinics of North America. 2015;**62**(1):201-223. DOI: 10.1016/j.pcl.2014.09.014

[15] Honavar SG, Manjandavida FP, Reddy VAP. Orbital retinoblastoma: An update. Indian Journal of Ophthalmology. 2017;**65**(6):435-442

[16] Namouni F, Doz F, Tanguy ML, et al. High-dose chemotherapy with carboplatin, etoposide and cyclophosphamide followed by a haematopoietic stem cell rescue in patients with high-risk retinoblastoma: A SFOP and SFGM study. European Journal of Cancer. 1997;**33**(14):2368-2375

[17] Dunkel IJ, Khakoo Y, Kernan NA, et al. Intensive multimodality therapy for patients with stage 4a metastatic retinoblastoma. Pediatric Blood & Cancer. 2010;**55**:55-59

[18] Shields CL, Fulco EM, Arias JD, et al. Retinoblastoma frontiers with intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Eye (London, England). 2013;**27**(2):253-264. DOI: 10.1038/eye.2012.175

[19] Shields CL, Meadows AT, Leahey AM, Shields JA. Continuing challenges in the management of retinoblastoma with chemotherapy. Retina. 2004;**24**(6):849-862

[20] Lambert MP, Shields C, Meadows AT. A retrospective review of hearing in children with retinoblastoma treated with carboplatin-based chemotherapy. Pediatric Blood & Cancer. 2008;**50**(2):223-226

[21] Leahey A. A cautionary tale: Dosing chemotherapy in infants with retinoblastoma. Journal of Clinical Oncology. 2012;**30**(10):1023-1024. DOI: 10.1200/JCO.2011.39.4254

[22] Gombos DS, Hungerford J, Abramson DH, et al. Secondary acute myelogenous leukemia in patients with retinoblastoma: Is chemotherapy a factor? Ophthalmology. 2007;**114**:1378-1383

[23] Turaka K, Shields CL, Meadows AT, Leahey A. Second malignant neoplasms following chemoreduction with carboplatin, etoposide, and vincristine in 245 patients with intraocular retinoblastoma. Pediatric Blood & Cancer. 2012;**59**(1):121-125. DOI: 10.1002/pbc.23278

[24] Shields CL, Mashayekhi A, Au AK, et al. The international classification of retinoblastoma predicts chemoreduction success. Ophthalmology. 2006;**113**(12): 2276-2280

[25] Narang S, Mashayekhi A, Rudich D, Shields CL. Predictors of long-term visual outcome after chemoreduction for management of intraocular retinoblastoma. Clinical & Experimental Ophthalmology. 2012;**40**(7):736-742. DOI: 10.1111/j.1442-9071.2012.02757.x

[26] Ramasubramanian A, Kytasty C, Meadows AT, Shields JA, Leahey A, Shields CL. Incidence of pineal gland cyst and pineoblastoma in children with retinoblastoma during the chemoreduction era. American Journal of Ophthalmology. 2013;**156**(4):825-829. DOI: 10.1016/j.ajo.2013.05.023

[27] Chen Q, Zhang B, Dong Y, et al. Comparison between intravenous chemotherapy and intra-arterial chemotherapy for retinoblastoma: A meta-analysis. BMC Cancer. 2018;**18**(1):486. DOI: 10.1186/s12885-018-4406-6

[28] Abramson DH, Daniels AB, Marr BP, et al. Intra-arterial chemotherapy (ophthalmic artery chemosurgery) for group D retinoblastoma. PLoS One. 2016;**11**(1):e0146582. DOI: 10.1371/journal.pone.0146582

[29] Abramson DH, Dunkel IJ, Brodie SE, Kim JW, Gobin YP. A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. Ophthalmology.

2008;**115**(8):1398-1404. 1404.e1. DOI: 10.1016/j.ophtha.2007.12.014

[30] Zanaty M, Barros G, Chalouhi N, et al. Update on intra-arterial chemotherapy for retinoblastoma. Scientific World Journal. 2014;**2014**:869604. DOI: 10.1155/2014/869604

[31] Abramson DH, Dunkel IJ, Brodie SE, Marr B, Gobin YP. Superselective ophthalmic artery chemotherapy as primary treatment for retinoblastoma (chemosurgery). Ophthalmology. 2010;**117**(8):1623-1629. DOI: 10.1016/j.ophtha.2009.12.030

[32] Aziz HA, Boutrid H, Murray TG, et al. Supraselective injection of intraarterial melphalan as the primary treatment for late presentation unilateral multifocal stage Vb retinoblastoma. Retina. 2010;**30**(4 Suppl):S63-S65. DOI: 10.1097/IAE.0b013e3181cbda0f

[33] Say EA, Iyer PG, Hasanreisoglu M, et al. Secondary and tertiary intra-arterial chemotherapy for massive persistent or recurrent subretinal retinoblastoma seeds following previous chemotherapy exposure: Long-term tumor control and globe salvage in 30 eyes. Journal of AAPOS. 2016;**20**(4):337-342. DOI: 10.1016/j.jaapos.2016.05.009

[34] Gobin YP, Dunkel IJ, Marr BP, Brodie SE, Abramson DH. Intra-arterial chemotherapy for the management of retinoblastoma: Four-year experience. Archives of Ophthalmology. 2011;**129**(6):732-737. DOI: 10.1001/archophthalmol.2011.5

[35] Shields CL, Manjandavida FP, Lally SE, et al. Intra-arterial chemotherapy for retinoblastoma in 70 eyes: Outcomes based on the international classification of retinoblastoma. Ophthalmology. 2014;**121**(7):1453-1460. DOI: 10.1016/j.ophtha.2014.01.026

[36] Shields CL, Say EA, Pointdujour-Lim R, Cao C, Jabbour PM, Shields JA. Rescue intra-arterial chemotherapy following retinoblastoma recurrence after initial intra-arterial chemotherapy. Journal Français d'Ophtalmologie. 2015;**38**(6):542-549. DOI: 10.1016/j.jfo.2015.03.004

[37] Shields CL, Kaliki S, Shah SU, et al. Minimal exposure (one or two cycles) of intra-arterial chemotherapy in the management of retinoblastoma. Ophthalmology. 2012;**119**(1):188-192. DOI: 10.1016/j.ophtha.2011.06.036

[38] Munier FL, Mosimann P, Puccinelli F, et al. First-line intra-arterial versus intravenous chemotherapy in unilateral sporadic group D retinoblastoma: Evidence of better visual outcomes, ocular survival and shorter time to success with intra-arterial delivery from retrospective review of 20 years of treatment. The British Journal of Ophthalmology. 2017;**101**(8):1086-1093. DOI: 10.1136/bjophthalmol-2016-309298

[39] Abramson DH, Marr BP, Dunkel IJ, et al. Intra-arterial chemotherapy for retinoblastoma in eyes with vitreous and/or subretinal seeding: 2-year results. The British Journal of Ophthalmology. 2012;**96**:499-502

[40] Rowlands MA, Mondesire-Crump I, Levin A, et al. Total retinal detachments due to retinoblastoma: Outcomes following intra-arterial chemotherapy/ophthalmic artery chemosurgery. PLoS One. 2018;**13**(4):e0195395. DOI: 10.1371/journal.pone.0195395

[41] Shields CL, Kaliki S, Shah SU, Bianciotto CG, Jabbour P, Shields JA. Effect of intraarterial chemotherapy on retinoblastoma-induced retinal detachment. Retina. 2012;**32**(4):799-804. DOI: 10.1097/IAE.0b013e31823d8e1e

[42] Francis JH, Roosipu N, Levin AM, et al. Current treatment of bilateral retinoblastoma: The impact of intraarterial and intravitreous chemotherapy. Neoplasia. 2018;**20**(8):757-763. DOI: 10.1016/j.neo.2018.05.007

[43] Abramson DH, Marr BP, Francis JH, et al. Simultaneous bilateral ophthalmic artery chemosurgery for bilateral retinoblastoma (tandem therapy). PLoS One. 2016;**11**(6):e0156806

[44] Jabbour P, Chalouhi N, Tjoumakaris S, et al. Pearls and pitfalls of intraarterial chemotherapy for retinoblastoma. Journal of Neurosurgery. Pediatrics. 2012;**10**(3):175-181. DOI: 10.3171/2012.5.PEDS1277

[45] Inomata M, Kaneko A. Chemosensitivity profiles of primary and cultured human retinoblastoma cells in a human tumor clonogenic assay. Japanese Journal of Cancer Research. 1987;**78**(8):858-868

[46] Shields CL, Bianciotto CG, Jabbour P, et al. Intra-arterial chemotherapy for retinoblastoma: Report No. 1, control of retinal tumors, subretinal seeds, and vitreous seeds. Archives of Ophthalmology. 2011;**129**(11):1399-1406. DOI: 10.1001/archophthalmol.2011.150

[47] Abramson DH, Shields CL, Jabbour P, et al. Metastatic deaths in retinoblastoma patients treated with intraarterial chemotherapy (ophthalmic artery chemosurgery) worldwide. International Journal of Retina and Vitreous. 2017;**3**:40. DOI: 10.1186/s40942-017-0093-8

[48] Habib LA, Francis JH, Fabius AW, Gobin PY, Dunkel IJ, Abramson DH. Second primary malignancies in retinoblastoma patients treated with intra-arterial chemotherapy: The first 10 years. The British Journal of Ophthalmology. 2018;**102**(2):272-275. DOI: 10.1136/bjophthalmol-2017-310328

[49] Wyse E, Handa JT, Friedman AD, Pearl MS. A review of the literature for intra-arterial chemotherapy used to treat retinoblastoma. Pediatric Radiology. 2016;**46**(9):1223-1233. DOI: 10.1007/s00247-016-3554-6

[50] Abramson DH. Chemosurgery for retinoblastoma: What we know after 5 years. Archives of Ophthalmology. 2011;**129**(11):1492-1494. DOI: 10.1001/archophthalmol.2011.354

[51] Ancona-Lezama D, Dalvin LA, Lucio-Alvarez JA, Jabbour P, Shields CL. Ophthalmic vascular events after intra-arterial chemotherapy for retinoblastoma: Real-world comparison between primary and secondary treatments. Retina. Sep 7, 2018. DOI: 10.1097/IAE.0000000000002315 [Online ahead of print]

[52] Francis JH, Levin AM, Zabor EC, Gobin YP, Abramson DH. Ten-year experience with ophthalmic artery chemosurgery: Ocular and recurrence-free survival. PLoS One. 2018;**13**(5):e0197081. DOI: 10.1371/journal.pone.0197081

[53] Abramson DH, Shields CL, Munier FL, Chantada GL. Treatment of retinoblastoma in 2015: Agreement and disagreement. JAMA Ophthalmology. 2015;**133**(11):1341-1347

[54] Abramson DH, Fabius AW, Issa R, et al. Advanced unilateral retinoblastoma: The impact of ophthalmic artery chemosurgery on enucleation rate and patient survival at MSKCC. PLoS One. 2015;**10**(12):e0145436. DOI: 10.1371/journal.pone.0145436

[55] Yannuzzi NA, Francis JH, Marr BP, et al. Enucleation vs ophthalmic artery

chemosurgery for advanced intraocular retinoblastoma: A retrospective analysis. JAMA Ophthalmology. 2015;**133**(9):1062-1066

[56] Ericson LA, Rosengren BH. Present therapeutic resources in retinoblastoma. Acta Ophthalmologica. 1961;**39**:569-576

[57] Kaneko A, Suzuki S. Eye-preservation treatment of retinoblastoma with vitreous seeding. Japanese Journal of Clinical Oncology. 2003;**33**:601-607

[58] Abramson DH, Ji X, Francis JH, Catalanotti F, Brodie SE, Habib L. Intravitreal chemotherapy in retinoblastoma: Expanded use beyond intravitreal seeds. The British Journal of Ophthalmology. 2019;**103**(4):488-493. DOI: 10.1136/bjophthalmol-2018-312037

[59] Manjandavida FP, Shields CL. The role of intravitreal chemotherapy for retinoblastoma. Indian Journal of Ophthalmology. 2015;**63**(2):141-145

[60] Ghassemi F, Shields CL. Intravitreal melphalan for refractory or recurrent vitreous seeding from retinoblastoma. Archives of Ophthalmology. 2012;**130**(10):1268-1271

[61] Buitrago E, Del Sole MJ, Torbidoni A, et al. Ocular and systemic toxicity of intravitreal topotecan in rabbits for potential treatment of retinoblastoma. Experimental Eye Research. 2013;**108**:103-109. DOI: 10.1016/j.exer.2013.01.002

[62] Nemeth KM, Federico S, Carcaboso AM, et al. Subconjunctival carboplatin and systemic topotecan treatment in preclinical models of retinoblastoma. Cancer. 2010;**117**(2):421-434

[63] Schaiquevich P, Carcaboso AM, Buitrago E, et al. Ocular pharmacology of topotecan and its activity in retinoblastoma. Retina. 2014;**34**(9):1719-1727. DOI: 10.1097/IAE.0000000000000253

[64] Ghassemi F, Shields CL, Ghadimi H, Khodabandeh A, Roohipoor R. Combined intravitreal melphalan and topotecan for refractory or recurrent vitreous seeding from retinoblastoma. JAMA Ophthalmology. 2014;**132**(8):936-941. DOI: 10.1001/jamaophthalmol.2014.414

[65] Rao R, Honavar SG, Sharma V, Reddy VAP. Intravitreal topotecan in the management of refractory and recurrent vitreous seeds in retinoblastoma. The British Journal of Ophthalmology. 2018;**102**(4):490-495. DOI: 10.1136/bjophthalmol-2017-310641

[66] Smith SJ, Smith BD. Evaluating the risk of extraocular tumour spread following intravitreal injection therapy for retinoblastoma: A systematic review. The British Journal of Ophthalmology. 2013;**97**(10):1231-1236. DOI: 10.1136/bjophthalmol-2013-303188

[67] Smith SJ, Smith BD, Mohney BG. Ocular side effects following intravitreal injection therapy for retinoblastoma: A systematic review. The British Journal of Ophthalmology. 2014;**98**(3):292-297. DOI: 10.1136/bjophthalmol-2013-303885

[68] Munier FL, Gaillard MC, Balmer A, et al. Intravitreal chemotherapy for vitreous disease in retinoblastoma revisited: From prohibition to conditional indications. The British Journal of Ophthalmology. 2012;**96**(8):1078-1083

[69] Shields CL, Manjandavida FP, Arepalli S, Kaliki S, Lally SE, Shields JA. Intravitreal melphalan for persistent or recurrent retinoblastoma vitreous seeds: Preliminary results. JAMA Ophthalmology. 2014;**132**(3):319-325

[70] Brodie SE, Munier FL, Francis JH, Marr B, Gobin YP, Abramson DH.

Persistence of retinal function after intravitreal melphalan injection for retinoblastoma. Documenta Ophthalmologica. 2013;**126**(1):79-84

[71] Francis JH, Schaiquevich P, Buitrago E, et al. Local and systemic toxicity of intravitreal melphalan for vitreous seeding in retinoblastoma: A preclinical and clinical study. Ophthalmology. 2014;**121**(9):1810-1817

[72] Francis JH, Brodie SE, Marr B, Zabor EC, Mondesire-Crump I, Abramson DH. Efficacy and toxicity of Intravitreous chemotherapy for retinoblastoma: Four-year experience. Ophthalmology. 2017;**124**(4):488-495. DOI: 10.1016/j.ophtha.2016.12.015

[73] Francis JH, Habib LA, Abramson DH. Vitreous disease in retinoblastoma: Clinical findings and treatment. Advances in ophthalmology and optometry. 2017;**2**(1):177-195

[74] Suzuki S, Aihara Y, Fujiwara M, Sano S, Kaneko A. Intravitreal injection of melphalan for intraocular retinoblastoma. Japanese Journal of Ophthalmology. 2015;**59**(3):164-172. DOI: 10.1007/s10384-015-0378-0

[75] Harbour JW, Murray TG, Hamasaki D, et al. Local carboplatin therapy in transgenic murine retinoblastoma. Investigative Ophthalmology & Visual Science. 1996;**37**:1892-1898

[76] Mendelsohn ME, Abramson DH, Madden T, Tong W, Tran HT, Dunkel IJ. Intraocular concentrations of chemotherapeutic agents after systemic or local administration. Archives of Ophthalmology. 1998;**116**(9):1209-1212

[77] Abramosn DH, Frank CM, Dunkel IJ. A phase I/II study of subconjunctival carboplatin for intraocular retinoblastoma. Ophthalmology. 1999;**106**(10):1947-1950

[78] Kaliki S, Shields CL. Retinoblastoma: Achieving new standards with methods of chemotherapy. Indian Journal of Ophthalmology. 2015;**63**(2):103-109

[79] Hayden B, Jockovich ME, Murray TG, et al. Iontophoretic delivery of carboplatin in a murine model of retinoblastoma. Investigative Ophthalmology & Visual Science. 2006;**47**(9):3717-3721

[80] Martin NE, Kim JW, Abramson DH. Fibrin sealant for retinoblastoma: Where are we? Journal of Ocular Pharmacology and Therapeutics. 2008;**24**(5):433-438. DOI: 10.1089/jop.2007.0110

[81] Kang SJ, Durairaj C, Kompella UB, O'Brien JM, Grossniklaus HE. Subconjunctival nanoparticle carboplatin in the treatment of murine retinoblastoma. Archives of Ophthalmology. 2009;**127**(8):1043-1047. DOI: 10.1001/archophthalmol.2009.185

[82] Marr BP, Dunkel IJ, Linker A, Abramson DH. Periocular carboplatin for retinoblastoma: Long-term report (12 years) on efficacy and toxicity. The British Journal of Ophthalmology. 2012;**96**(6):881-883. DOI: 10.1136/bjophthalmol-2011-300517

[83] Mulvihill A, Budning A, Jay V, et al. Ocular motility changes after subtenon carboplatin chemotherapy for retinoblastoma. Archives of Ophthalmology. 2003;**121**(8):1120-1124. DOI: 10.1001/archopht.121.8.1120

[84] Yousef YA, Halliday W, Chan HS, Héon E, Gallie BL, Dimaras H. No ocular motility complications after subtenon topotecan with fibrin sealant for retinoblastoma. Canadian Journal of Ophthalmology. 2013;**48**(6):524-528. DOI: 10.1016/j.jcjo.2013.05.018