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Intra-Arterial Chemotherapy for Retinoblastoma

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Abstract

The management of retinoblastoma is challenging and complex. Preservation of the eyeball as well as vision, with minimum morbidity, is the aim in the initial stages. This has been made possible by the use of chemotherapy that is targeted to the eye in the form of selective intravitreal and intra-arterial chemotherapy which has shown promising results. The efficacy and safety of intra-arterial chemotherapy have been reported by many specialized centers. The aim of this article was to review the role of intraarterial chemotherapy in the management of retinoblastoma and its clinical outcomes. In addition, we will review the possible complications of the procedure. We were able to collect articles relevant to our research objectives by reviewing the title and abstract of each article. Irrelevant articles and those that did not meet the inclusion criteria were excluded. This yielded a total of 19 studies. The results indicated that intraarterial chemotherapy is an effective and new modality of treatment for retinoblastoma to salvage the eyeball and helps in the prevention of enucleation with minimal local and systemic complications that are mostly transient. For future work, we recommend conducting more prospective studies with large samples and the long duration of follow-up. Also, we recommend future studies focusing on assessing visual acuity, as most of the currently available studies did not assess the visual acuity, making the judgment on vision preservation with IAC difficult.

Keywords

Retinoblastoma, Intra-Arterial Chemotherapy, Intravitreal Chemotherapy, Eyeball Salvage

1. Introduction

The most common primary intraocular neoplasm in children is retinoblastoma, representing 3% of all malignancies in children and 10% - 15% of cancers that

develop in the first year of life [1]. In 1597, retinoblastoma was first mentioned by Peter Pawius of Amsterdam in the literature. Over the years, there were different views related to the origin of the tumor. In 1809, the Scottish surgeon James Wardrop deduced that the tumor arose from the retina [1]. The name "Retinoblastoma" was proposed by Verhoeff because the tumor is mainly made up of cells that resemble the cells of the undifferentiated embryo retina, called retinoblasts [2]. Retinoblastoma is deadly if untreated; however, the survival rate in developed countries reaches above 95% with current treatment modalities [1]. The management of retinoblastoma is both challenging and complex. There are three important goals of therapy that try to achieve whenever possible: life salvage, eyeball salvage and vision preservation [3]. The preservation of the eyeball as well as vision, with minimum morbidity, is the aim in the initial stage. This has been made possible with the use of chemotherapy that is targeted to the eye in the form of selective intravitreal and intra-arterial chemotherapy, and has shown promising results [3]. In selected cases, radiotherapy is beneficial either in the form of External Beam Radiotherapy (EBRT) or plaque brachytherapy [3]. Enucleation, which is the complete removal of the eyeball, represents the oldest surgical procedure in ophthalmology, but it remains an important option in the management of retinoblastoma [4]. The treatment of children with recurrent intra-ocular and advanced retinoblastoma by selective Ophthalmic Artery Chemotherapy (OAC) and Intra-Arterial Chemotherapy (IAC) has become the first line of treatment according to the report in 2008, due to its effectiveness in reducing enucleation and minimizing the toxicity of systemic chemotherapy [4]. In 1958, intra-arterial chemotherapy in retinoblastoma emerged for the first time by Reese, when he injected triethylene melamine into the internal carotid artery [1]. Unfortunately, this procedure was associated with a toxicity that was too high; thus, it was discontinued. In 2006, Gobin *et al.* used a guide wire to introduce the direct catheterization of the ophthalmic artery and called it "super selective intra-ophthalmic artery chemotherapy" [1]. The efficacy and safety of IAC have been reported by many specialized centers [4]. In this article, we will review the role of IAC in the management of retinoblastoma and its clinical outcomes, and will also review the possible complications of the procedure.

2. Disease Background

2.1. Pathophysiology

The main pathophysiology of retinoblastoma is a mutation in the retinoblastoma (RB1) gene found on the long arm of chromosome 13 [5]. This mutation has to occur on both alleles in order to cause retinoblastoma and can be inherited in the germline or spontaneous. RB1 is a tumor suppressor gene which encodes a protein called retinoblastoma (Rb), which plays a role in cell cycle regulation by preventing progression from the G1 phase to the S phase in cases of DNA damage [5]. Regarding the mode of inheritance, heritable retinoblastoma is an autosomal dominant disorder. A two-hit hypothesis was applied to explain the diffe-

rence between heritable and spontaneous retinoblastoma. In the heritable form of retinoblastoma, the germline mutation affects one allele in all body cells, which is considered the first hit. After that, a second hit can affect the other allele of chromosome 13 in retinal cells. This explains the possibility of inherited retinoblastoma having a bilateral presentation, and the increased risk of those patients developing osteosarcoma and pinealoma [5]. For spontaneous retinoblastoma, a sporadic mutation affects RB1 on both alleles of chromosome 13 in a single somatic retinal cell, meaning that this is rarely bilateral [5].

2.2. Clinical Presentation

Patients presenting with retinoblastoma are mostly under the age of 3 years, although the minority of them can present at the age of 7 years or older. Retinoblastoma has different presentations, and can be unilateral or bilateral [6]. The most commonly known presentations are leukocoria, strabismus, or pseudo-orbital cellulitis with marked periorbital edema [6]. Other presentations can include decreased vision (especially with bilateral cases), hypopyon, glaucoma, retinal detachment, or ocular pain. Occasionally, some patients might present with trilateral retinoblastoma, which is a pineal primitive neuroectodermal tumor (pinealoma) that occurs in concomitance with bilateral retinoblastoma [6].

Retinoblastoma features can also present in pediatric patients with 13q syndrome, in which they will be having other systemic features beside retinoblastoma, such as craniofacial dysmorphism, mental and growth retardation, and hand and foot anomalies. In some rare cases, pediatric patients might present with morning glory syndrome or retinopathy of prematurity that will be accompanied by retinoblastoma [6].

Regarding family history, there is no strong correlation with retinoblastoma, as only about 10% of diagnosed retinoblastoma patients have a positive family history [6].

2.3. Classification

Since the 1960s when External Beam Radiation Therapy (EBRT) was the primary conservative treatment for RB, the Reese-Ellsworth (RE) classification was designed to group eyes with intraocular retinoblastoma (**Table 1**) [7]. The system separates eyes regarding the presence or absence of several factors that complicate treatment with EBRT, such as large size, peripheral location and multifocality. The presence of these criteria in the tumor classifies it as more aggressive, therefore resulting in a higher RE grouping, which is group V [7]. The treatment of RB in the mid-1990s shifted from EBRT and enucleation as the first line to the use of chemo-reduction and focal consolidation [7]. The RB treatment challenges changed with this and a new classification system was created by a group of RB experts in mid-2003, the International Classification of Retinoblastoma (ICRB), to predict the successful of treatment with primary chemoreduction and focal consolidation (**Table 2**) [7] (see **Figure 1**).

Table 1. Reese-Ellsworth classification (RE).

Group	Description	Prognosis
I	1) Solitary tumor, <4 disc diameters in size, at or posterior to the equator of the eye (an imaginary line in the coronal plane that marks the division between the anterior and posterior halves of the eye); 2) Multiple tumors, none > 4 disc diameters in size, all at or behind the equator.	Very favorable
II	1) Solitary tumor, 4 - 10 disc diameters in size, at or behind the equator; 2) Multiple tumors, 4 - 10 disc diameters in size, behind the equator.	Favorable
III	1) Any lesion anterior to the equator; 2) Solitary tumors > 10 disc diameters behind the equator.	Doubtful
IV	1) Multiple tumors, some > 10 disc diameters in size; 2) Any lesion extending anteriorly to the ora serrata.	Unfavorable
V	1) Massive tumors involving over half of the retina; 2) Vitreous seeding.	Very unfavorable

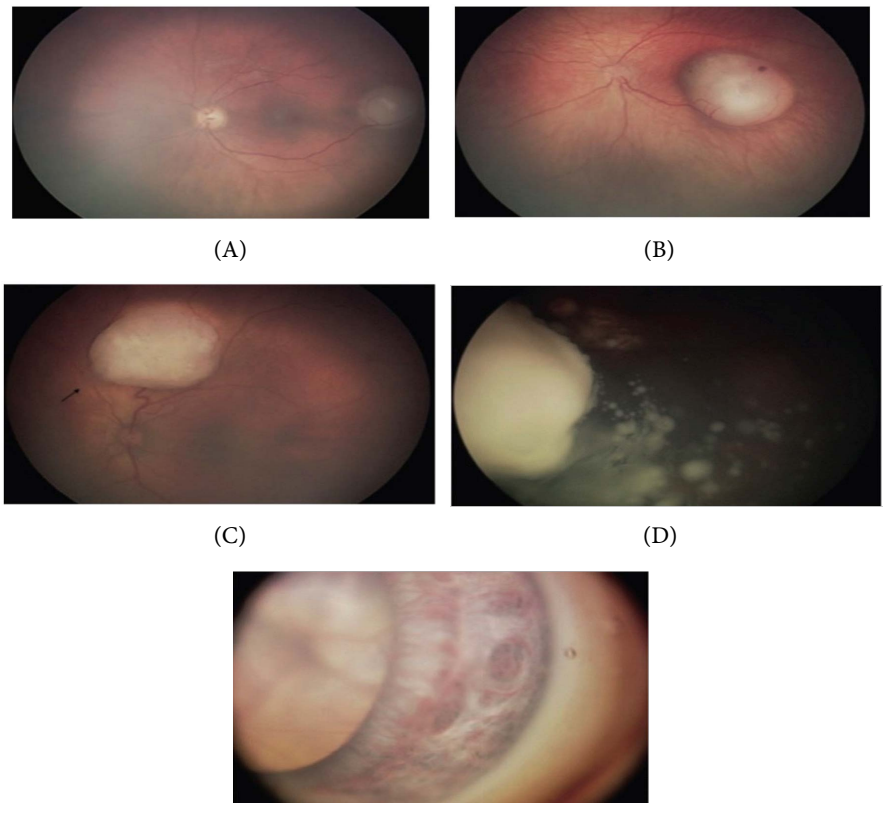

Figure 1. Grouping of retinoblastoma according to the international classification of retinoblastoma. Group A: Small tumors located away from the foveola; Group B: tumor at macular region; Group C: retinal tumor with local seeding; Group D: massive tumor with vitreous seeding; Group E: large tumor behind the lens and iris neovascularization.

Table 2. International classification of retinoblastoma (ICRB) [1].

Group	Description	Prognosis
A	Small tumors located away from the foveola or optic disc. Tumor ≤ 3 mm in basal dimension or thickness.	Very low risk
B	Retinal tumors of any size or location not in group A without vitreous or subretinal seeding. Tumor < 3 mm in basal dimension or thickness or any of the following: 1) Macular location ≤ 3 mm to foveola; 2) Juxtapupillary location ≤ 1.5 mm to disc; 3) Clear subretinal fluid ≤ 3 mm from margin.	Low risk
C	Retinal tumors of any size and location with focal vitreous or subretinal seeding. One of the following: 1) Subretinal seeds ≤ 3 mm from tumor; 2) Vitreous seeds ≤ 3 mm from tumor; 3) Both subretinal and Vitreous seeds ≤ 3 mm from tumor; 4) Less than one quadrant of subretinal fluid in the fundus.	Moderate risk
D	Massive tumor and/or diffuse vitreous or subretinal seeding One of the following: 1) Subretinal seeds > 3 mm from tumor; 2) Vitreous seeds > 3 mm from tumor; 3) Both subretinal and vitreous seeds > 3 mm from tumor; 4) Greater than one quadrant of subretinal fluid in the fundus.	High risk
E	Tumor has destroyed the eye anatomically or functionally Extensive retinoblastoma or one of the following: 1) Irreversible neovascular glaucoma; 2) Massive intraocular hemorrhage; 3) Invasion of post laminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber; 4) Tumor anterior to the anterior vitreous face; 5) Diffuse infiltrating tumor; 6) Phthisis bulbi or pre phthisis; 7) Aseptic orbital cellulitis.	Very unfavorable

2.4. Diagnosis

One of the first diagnostic tests to consider is fundoscopy, which can reveal a white-grey chalky mass in the retina, retinal detachment with visible retinal vessels behind the lens, and/or vitreous or subretinal seeding. Another important test to order is wide-field fundus photography and sdOCT (spectral domain optical coherence tomography) [6].

2.5. Treatment

Saving the patient's life is the main goal of the management of retinoblastoma [1]. However, with recent efficient treatment modalities, there is increased emphasis on improving visual outcomes, eye salvage and the prevention of secondary neoplasms [1]. In managing patients with retinoblastoma, a multidisciplinary

team is crucial. Various health care professionals should be included such as a pediatric ophthalmologist, pediatric oncologist, ocular oncologist, radiation oncologist, low-vision specialist, clinical geneticist, and nutritionist [1]. The management of retinoblastoma is individualized according to the stage of disease. There are various treatment modalities for intraocular retinoblastoma, including focal therapy (cryotherapy, laser photocoagulation, and thermotherapy), plaque brachytherapy, chemotherapy (local or systemic), external beam radiotherapy, and enucleation. External radiotherapy is associated with complications so it is no longer used as a first line treatment [1].

3. Intraarterial Chemotherapy

Saving the patient's life is the main goal of the management of retinoblastoma [1]. However, with recent efficient treatment modalities, there is increased emphasis on improving visual outcomes, eye salvage and the prevention of secondary neoplasms [1]. In managing patients with retinoblastoma, a multidisciplinary team is crucial. Various health care professionals should be included such as a pediatric ophthalmologist, pediatric oncologist, ocular oncologist, radiation oncologist, low-vision specialist, clinical geneticist, and nutritionist [1]. The management of retinoblastoma is individualized according to the stage of disease. There are various treatment modalities for intraocular retinoblastoma, including focal therapy (cryotherapy, laser photocoagulation, and thermotherapy), plaque brachytherapy, chemotherapy (local or systemic), external beam radiotherapy, and enucleation. External radiotherapy is associated with complications so it is no longer used as a first line treatment [1].

3.1. Technique

Prior to the procedure, to achieve anticoagulation, 50 - 100 IU/kg body weight of intravenous heparin is infused. Topical phenylephrine is applied on the distribution of the supratrochlear artery and intranasally to reduce the flow of chemotherapy onto the forehead and nose, respectively. With a French-pediatric arterial sheath, the ipsilateral side of the femoral artery is catheterized under aseptic precaution. The catheter is carefully advanced under fluoroscopy guidance up the aorta, into the carotid artery, then into the internal carotid artery, and finally to the ostium of the ophthalmic artery. Once an angiogram confirms the placement of the catheter at the ostium of ophthalmic artery, chemotherapeutic drugs diluted in 30 mL of normal saline are infused slowly in a pulsatile fashion over 30 min to ensure that the drugs are equally distributed along the targeted vascular anatomy. After the procedure, angiogram is repeated to exclude thromboembolic event and to evaluate brain vascularization integrity. In cases of bilateral (tandem IAC), withdrawal of the microcatheter is performed up to the aorta then redirected to the contralateral internal carotid artery up to the ostium of ophthalmic artery and similar procedure is continued. The microcatheter and guide wire are removed slowly and then the femoral artery is manually compressed for 15 minutes to reach he-

mostasis. This is followed by the application of a compressive bandage. Patients are observed for 4 - 6 hours, and if there are no concerns, they can be discharged on the same day as the procedure. Short-acting mydriatics along with topical steroids in tapering doses are prescribed. Some teams also recommended oral aspirin in the dose of 1 - 2 mg/kg body weight for 2 weeks postoperatively. After 7 - 10 days of IAC, a complete blood count is recommended for all patients to assess for neutropenia [1] [8].

3.2. Chemotherapeutic Agents and Dosage

According to the study of Inomato and Kaneko, melphalan was found to be the most effective agent for retinoblastoma when compared with other chemotherapeutic agents. Later, carboplatin and topotecan were added by Abramson *et al.*, putting forward the popular triple-drug regimen. Table 3 summarizes the types, doses and indications for each intraarterial chemotherapeutic agent. Side effects and complications of drugs depend mainly on the dosage of agents and should be titrated accordingly [8].

3.3. Treatment Protocol

A standardized treatment protocol has not yet been established regarding drugs and dosages for IAC [1]. However, among all agents, the most commonly used drug is melphalan [1]. The most common treatment approach is the administration of IAC for 3 sessions every 4 weeks [1]. In neonates and infants younger than 6 months, the IAC tends to be avoided due to difficulties in the cannulation of femoral artery [9].

3.4. Indications and Contraindications

It is important to note that intra-arterial treatment should not be used for the extraocular involvement of retinoblastoma; it is intended for intraocular disease [9]. Primary IAC is indicated in unilateral cases of retinoblastoma (group B, C and D), and also in bilateral retinoblastoma (group D, and E). However, in cases of bilateral retinoblastoma, some clinicians prefer systemic chemotherapy to ensure chemoprotection against metastasis and to avoid the unpredictable vascular

Table 3. Summary of IAC chemotherapeutic agents.

Name of drug	Type of drug	Standard dose and dose range in mg	Indications
Melphalan	Nitrogen mustard derivative alkylating agent	5 (3 - 7.5)	As a single agent for (group B and C).
Topotecan	Topoisomerase 1 inhibitor, semi-synthetic camptothecin derivative	1 (1 - 2)	Group (D and C) advanced retinoblastoma with diffuse vitreous seeds.
Carboplatin	Is a platinum-based derivative	20 (15 - 30)	Bilateral IAC to avoid the cumulative toxicity of melphalan. Recurrence after IAC, Suboptimal response to combination of melphalan and topotecan.

toxicity of IAC. Recurrent/persistent tumors or recurrent/persistent subretinal seeds are indications of secondary IAC [1]. IAC cannot always be performed due to several contraindications include, neovascular glaucoma, vitreous hemorrhage, hyphema, pre/post-septal cellulites, phthisis, optic nerve or scleral extension, extraocular or orbital extension, trilateral retinoblastoma or systemic metastasis, and it is also contraindicated in cases that can be treated with focal therapies [8].

4. Material and Methods

4.1. Methods

Multiple databases were used to collect sources for this review article. At the beginning, Google Scholar was used to take an initial look at the available articles by using different search terms such as "retinoblastoma and intraarterial chemotherapy", and "intraarterial chemotherapy in retinoblastoma". After that, we used an online library provided by Taibah University to complete our research and to provide us with access to full text articles, we also used PubMed for further research by applying the filter of free full text. The search terms used were: "intraarterial chemotherapy for retinoblastoma", "retinoblastoma and intraarterial chemotherapy", "intraarterial chemotherapy in retinoblastoma", "retinoblastoma intraarterial chemotherapy", and "ophthalmic artery chemosurgery". We were able to collect articles relevant to our research objectives by reviewing the title and the abstract of each article. Irrelevant articles and those that did not meet the inclusion criteria were excluded. This yielded to a total of 19 studies.

4.2. Inclusion and Exclusion Criteria

We included in our review human-based clinical trials, case reports, case series and cohort studies that discussed the outcomes of using intraarterial chemotherapy as a treatment for retinoblastoma and published during the last 10 years. We excluded Studies that focused on a specific outcome or complication of using intraarterial chemotherapy as a treatment for retinoblastoma.

5. Results

Several studies have published IAC outcomes in terms of eyeball salvage, tumor response, and treatment complications. This literature review includes nineteen studies. However, the techniques, choice of drugs and dosage vary widely among these studies. Table 4 summarizes the treatment outcomes across the analyzed studies.

5.1. Eyeball Salvage

Miaojuan Chen *et al.* retrospectively reviewed 107 eyes of 73 patients with RB undergoing IAC. The patients were classified as Group E (27.1%), Group D (52.3%), Group C (10.3%), and Group B (10.3%). Primary IAC was performed

in (28.1%) and as a secondary therapy in (71.9%). During follow up period the overall eyeball salvage rate was 78.5%. Included 100% Group B and C, 78.6% group D and 62% Group E [4]. Chee Chung Liu *et al.* analyzed the treatment outcomes of 13 eyes that successfully received IAC. At mean of 19 months follow-up the eyeball salvage rate of secondary IAC in study was 38% and most cases

Table 4. Review of intra-arterial chemotherapy main results in the analyzed studies.

Study (Year)	No. of eyes	No. of successful catheterizations (%success rate)	Drugs + Adjunct treatment	Indication (No. of eyes)	Overall eyeball salvage	Eyeball salvage by group	Ocular complications	Systemic complications	Metastasis	Death
David Abramson *et al.* (2016) [26]	112	NA	M, T, C	Primary (85.1) Bridge (85.7%)** Secondary (72.4%)	74%	74% group D	Eyelid edema Madarosis Retinal or choroidal vascular occlusion Phthisis Vitreous hemorrhage Ptosis Optic nerve swelling Retinopathy Cranial nerve palsy Ophthalmic artery vessel injury or sclerosis Suprachoroidal hemorrhage	Neutropenia Bronchospasm Allergy reaction Thrombocytopenia Fever Cardiorespiratory side effects Injection site complications (bleeding or thrombosis) Epistaxis	3	1
Chee Chung Liu *et al.* (2020)	14	23/32 (71.8%)	M	Primary (7%), secondary (93%)	38%	NA	Eyelid edema Conjunctiva chemosis Ophthalmic artery dissection Ophthalmic artery occlusion Retina artery occlusion Optic atrophy	Bronchospasm Hematoma	0	0
Miaojuan Chen *et al.* (2017)	107	338/343 (98.5%)	M, T	Primary (28.1%) Secondary (71.9%)	78.5%	Group B (100%), Group C (100%), Group D (78.6%), and Group E (62%)	Eyelid edema Bulbar conjunctiva congestion Excessive tearing Vitreous hemorrhage Subretinal hemorrhage Retinal vasculopathy Ophthalmic artery spasm	Fever Transient vomiting Transient myelosuppression	NA	NA
Pukhraj Rishi *et al.* (2019)	15	NA	M, T + VEC + TTT + IVitC + Cryo	Primary (6) Secondary (9)	67%	Group B (100%) Group C, (67%), Group D (67%), Group E (50%)	Posterior subcapsular cataract Vitreous hemorrhage Optic nerve disorder Branch retinal vein occlusion Sclerosed retinal vessels Iris atrophy with posterior synechiae Transient OA narrowing	Allergic skin reaction Forehead skin pigmentation Pancytopenia Leukopenia Thrombocytopenia Eosinophilia lymphocytopenia	0	0
Canan Akyüz *et al.* (2015)	56	NA	M	Primary (12) secondary (44)	66%	Secondary 64%	Eyelid edema Conjunctival chemosis Upper eyelid chemosis Redness over frontal area Limitation in ocular motility Mild proptosis Retinal pigment epithelium alteration Optic atrophy	0	NA	2
Pukhraj Rishi *et al.* (2017)	10	NA	M, T + VEC + TTT + IVitC + Cryo	Primary (2) Secondary (8)	80%	Group D 45% - 94%	Ophthalmic artery narrowing Branch retinal vein occlusion Sclerosed vessels Posterior subcapsular cataract Forehead skin Pigmentation Vitreous hemorrhage	Pancytopenia Leukopenia Thrombocytopenia		

Continued

Carol Shields *et al.* (2011)	17	16	M, C	NA	NA	NA	Eyelid edema Blepharoptosis Cilia loss Orbital congestion Dysmotility Ophthalmic artery stenosis Central or branch Retinal artery occlusion Retinal pigment epithelial mottling Choroidal atrophy Eyelashes loss Neovascularization of the iris Neovascular glaucoma	Cytopenia Internal carotid artery spasm	0	NA
Rojanaporn *et al.* (2019)	27	75 (94%)	M, C, T	Primary (7) Secondary (20)	52%	Group B, C (100%), Group D (75%), Group E (9%)	Occlusive vasculopathy Vitreous hemorrhage Retinal artery precipitation Strabismus	Transient ischemic attack	1	1
Pukhraj Rishi, *et al.* (2015)	6	NA	M, T	Primary (1) Secondary (5)	83%	NA	Diffuse choroidal atrophy Vitreous hemorrhage	0	0	NA
Hutchinson, *et al.* (2012)	1	1	M	Primary	100%	Group D	NA	NA	0	0
Pierre Gobin, *et al.* (2011)	95	255/259 (98.5%)	M, T, C, Mtx.	Primary (39) Secondary (56)	70%	81.7% primary 58.4% secondary Group V 66.5%.	Temporary inflammatory syndrome with redness and periocular edema Avascular retinopathy with total vision loss Cataract Temporary loss of eyelashes. Transient skin redness.	Neutropenia Fever Bronchospasm	2	0
Santiago Funes *et al.* (2018)	97	NA (99%)	M, C, T	Primary (35) Secondary (62)	65%	NA	Eyelid edema Focal alopecia Localized forehead erythema 3rd cranial nerve palsy Retinal and choroidal vascular occlusion Vision loss Ptosis	Hematopoietic toxicity Bronchospasm Femoral artery thrombosis	0	0
Khaqan *et al.* (2020)	3	NA	M	Primary	100%	100% in stage C 100% in stage D	Lid edema Skin hyperemia Orbital congestion	None.	NA	NA
Qiuying Chen *et al.* (2020)	231	NA	IAC: M, C, T IVC: C, E, V, Tn	NA	NA	IVC + IAC: D 71.7% E 33.3%. IAC alone: D 80%. E 32%.	NA	NA	Present but no set numbers	9
Evan B Selzer, *et al.* (2019) [27]	13	NA	M, C, T.	Primary (8). Secondary (5).	62%	NA	NA	NA	0	0
Samuray Tuncer, *et al.* (2016)	26	74/76 (97.3%)	M, C, T.	Primary	66.6%	NA	Retinal detachment. Localized chorioretinal atrophy. Diffuse chorioretinal atrophy. Vitreous hemorrhage. Ptosis. Eyelid edema. hyperpigmentation on the forehead.	Nausea and vomiting. Anaphylactoid reaction.	0	0

Continued

Miaojuan Chen *et al.* (2016)	13	27/28 (96%)	M, C, T	Primary	NA	NA	Ptosis Vitreous hemorrhage Phthisis Eyelid edema Choroidal infarction	Neutropenia	0	0
David H. Abramson, *et al.* (2016)	120	NA	M, T, C, Mtx.	Primary (60) secondary (60)	96.7%	ICRb: A-D 100% E 90%	NA	Fever Neutropenia	0	1
David H. Abramson, *et al.* (2012)	49	All except 1	NA	NA	100%	NA	NA	Hematological toxicity Febrile neutropenia.	0	0

NA = not available, M = melphalan, C = carboplatin, T = topotecan, E = etoposide, V = vincristine, Tn = teniposide, Mtx = methotrexate, IAC = intra-arterial chemotherapy, IVC = intravenous chemotherapy. **"bridge therapy: (intravenous carboplatin as a single agent until the infant old enough to undergo IAC)".

being bilateral, advanced, refractory retinoblastoma [10]. Rishi *et al.* found that the eyeball salvage achieved in 5 of 6 eyes (83%) with primary IAC in one case and secondary IAC in 5 cases. The study included 4 of 6 cases were advanced RB (Group D = 2, Group E = 2) [11]. Khaqan *et al.* study included 3 cases with a eyeball salvage rate of 100%, 2 of those 3 cases were of stage C, and 1 of stage D [12]. In a study conducted by Qiuying Chen *et al.*, patients were divided into 2 groups; the first group was patients receiving both Intravenous Chemotherapy (IVC) and Intra-Arterial Chemotherapy (IAC), and the eyeball salvage for this group was achieved in 66 out of 92 patients of group D eyes (71.7%), and 8 out of 24 patients of group E eyes (33.3%). The second group was patients receiving IAC alone, and the eyeball salvage for this group was achieved in 72 out of 90 patients of group D eyes (80%), and 8 out of 25 patients of group E eyes (32%) [13]. A case report of unilateral group D retinoblastoma was presented by Hutchinson *et al.* The case was treated with only two IAC cycles using melphalan, which resulted in tumor regression, resolution of subretinal fluid, and, most importantly, salvage of the life, and the eye [14].

In summary, the overall eyeball salvage rate ranges from 38%, as reported by Chee Chung Liu *et al.*, 12% to 100%, as stated by Khaqan *et al.* and Hutchinson *et al.* [12] [14]. However, there are several studies that did not report the overall eyeball salvage rate. Approximately half of the analyzed case series (eleven out of nineteen) propose that IAC can be considered an effective and safe therapeutic option for advanced cases and reduces the enucleation rate. **Table 4** describes in detail the overall eyeball salvage rate and eyeball salvage by groups covering analyzed studies.

5.2. Ocular Complications

An important indicator of localized IAC toxicity is ocular complications. In their study, Rishi *et al.* observed vitreous hemorrhage and diffuse choroidal atrophy in 1 eye each. No vascular occlusion or hypotony was observed in any eye.13 Another study of Rishi *et al.* reported 2 cases of subcapsular cataract, 3 cases of vit-

reous hemorrhage, 2 optic nerve disorders, and other eye disorders included, branch retinal vein occlusion, sclerosed retinal vessels and iris atrophy with posterior synechia were observed in 1 eye each [15]. In a study by Chee Chung Liu *et al.*, two patients experienced adverse events were related to repeated IAC cannulations. One of these patients had catheter-related OA dissection after four IAC sessions, causing an unsuccessful fifth attempt and the eye was enucleated; another patient had OA occlusion after two sessions of IAC procedure, which caused failure of the next IAC attempt. The same case also developed optic atrophy and was subsequently enucleated. Also, they reported one case which developed retinal ischemia secondary to central retinal artery occlusion (CRAO) after one IAC [10]. Pierre Gobin *et al.* reported 4 eyes of RE group V that developed avascular retinopathy with total loss of vision. All other reported complications in their study were temporary except for 3 eyes that developed cataract; also, it is worth mentioning that 2 of those eyes had recent radiation therapy [16]. Santiago Funes *et al.* reported 2 cases of 3rd cranial nerve palsy of grade 2, which were reversible [17]. All ocular complications are listed in **Table 4**.

Finally, there were a few studies that did not mention anything about ocular complications. On the other hand, the majority of reported complications were reversible, and eyelid edema was mentioned in almost all of the studies included. However, the fact that IAC has a specific procedure that is more complicated when compared to other treatment options carries a risk of multiple procedural complications, such as optic atrophy and ophthalmic artery spasm, which can prevent the patient from continuing the IAC option, eventually leaving them with no option but enucleation.

5.3. Systemic Complications

There is a significant reduction in systemic toxicity with IAC compared with IVC. Mostly, systemic complications after IAC depend on the dose of chemotherapeutic agent and tend to be transient. Some of the adverse events are related to the catheterization and include anaphylactoid reaction and autonomic response. **Table 4** presents all systemic complications.

Shields *et al.* found that the transient cytopenia presented in 6 cases with spontaneous recovery in all cases without the need for transfusion [18]. Rojanaporn *et al.* found one patient who developed a single episode of transient ischemic attack (TIA), but the patient recovered without any complications after treatment with intravenous methylprednisolone [19]. In the recent study of Rishi *et al.*, the most common complication observed was cytopenia. Other complications reported including allergic skin reaction and forehead skin pigmentation 1 case each [15]. Chee Chung Liu reported one case who developed bronchospasm along with apnea and bradycardia thus, the procedure was abandoned which is potentially a life-threatening condition [10]. In the Pierre Gobin *et al.* study, they reported 18 cases of chemotherapy toxicity that presented as significant neutropenia, which happened after 29 of the 255 sessions (11.4%); however, at the same time, only

one patient needed admission to receive parenteral antibiotic due to fever [16]. Moreover, hematopoietic toxicity was reported in 24 cycles of chemotherapy (6%) in the study conducted by Santiago Funes *et al.* [17]. They also had a patient who developed grade 3 femoral artery thrombosis, which was managed by anticoagulation therapy. For the recent study conducted by Miaojuan Chen *et al.*, systemic complications were observed in 1 patient only, who developed grade 3 - 4 neutropenia and received a transfusion of red blood cells [20]. The transfusion of blood products was also required for 3 patients (3 out of 60) in the study conducted by Abramson *et al.* They also had to hospitalize 2 patients due to fever/neutropenia [21]. Apart from hematological toxicity, Abramson *et al.* did not mention any other systemic complications in their older study [22].

Interestingly, according to studies conducted by Khaqan *et al.* and Akyüz *et al.*, no systemic side effects were detected [12] [23], which is in agreement with the findings of Rishi *et al.* in their first report that included 6 patients [11]. Finally, it was clear that systemic complications of IAC were all manageable and only few cases needed to be hospitalized. At the same time, it was hard to ignore the potentially life-threatening complications caused by the procedure itself.

5.4. Metastasis and Death

According to Chee Chung Liu *et al.*, Hutchinson *et al.* [10] [14] and three studies conducted by Rishi *et al.*, there were no secondary neoplasms, no patients developed metastasis, or pinealoblastoma and no death during the follow-up period [11] [15] [24]. Abramson *et al.* reported three patients who developed metastases over the course of their follow-up. However, all three were successfully treated and all survived [21]. The other study of Abramson *et al.* reported 2 cases that developed pineoblastoma [22]. In the study of Rojanaporn *et al.*, one patient died, whose IAC cannulation failed so enucleation was performed but who later developed a fatal brain metastasis [19]. Pierre Gobin *et al.* reported metastatic disease in 2 children, but no trilateral retinoblastoma [16]. On the other hand, metastasis was the main cause of mortality in the study by Qiuying Chen *et al.*, where they reported a mortality rate of 3.9% in their IVC plus IAC group (4/103), which reached 4.5% in the IAC group (5/110). 15 According to Samuray Tuncer *et al.*, there were 3 eyes with a recurrence of the main solid tumor within 6 - 15 months after finishing the treatment [25].

Overall, the majority of the analyzed studies did not report cases of metastasis (twelve out of nineteen). Also, there are several studies which did not mention the rates of metastasis and death.

6. Conclusion

In conclusion, IAC is an effective and new modality of treatment for retinoblastoma to salvage the eyeball and helps in the prevention of enucleation with minimal local and systemic complications that are mostly transient. Although IAC is a complicated procedure, all studies revealed high salvage and success rates and

low mortality rates, giving IAC an advantage over other modalities. For future work, we recommend conducting more prospective studies with large samples and long follow-up duration. Also, we recommend future studies focus on assessing visual acuity, as most of the currently available studies did not assess visual acuity, making the judgment on vision preservation with IAC difficult. During the collection of the included articles, we were not able to find studies conducted in Saudi Arabia regarding IAC in retinoblastoma, so local studies are needed to evaluate this modality of treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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