Original Article

Recent Decreasing Frequency of Enucleation for Intraocular Retinoblastoma in Upper Egypt

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Abstract

Purpose: To evaluate the efficacy of combined systemic chemotherapy (chemoreduction) and local ophthalmic therapy (LT) in preventing or delaying external-beam radiotherapy (EBRT) and enucleation in patients with intraocular retinoblastoma.

Patients and Methods: This was a prospective, nonrandomized, single-institution, clinical study. Twenty-eight patients (37 eyes) with newly diagnosed intraocular retinoblastoma were included in this study. Primary enucleation was performed for 7 eyes with advanced intraocular retinoblastomas at presentation before starting chemoreduction. Using Reese-Ellsworth (RE) staging for RB, the remaining 30 eyes were as follows: Two in group I, 4 in group II, 8 in group III, 7 in group IV, and 9 in group V. All the 30 eyes were initially treated with 6 cycles of chemoreduction using vincristine, etoposide, and carboplatin, repeated every 3 weeks. After total of 6 cycles, each tumor was re-evaluated to decide on the next mode of therapy. In cases where the tumor was reduced enough, LT (Thermotherapy, or cryotherapy, but plaque radiotherapy was unavailable) was applied. In cases where the tumor was reduced but insufficient for LT, we added another 3 cycles of the same regimen in some patients; or we performed chemothermotherapy (CTT) for others, according to the size of the residual tumor. Eyes failed to respond tochemoreduction and LT, received EBRT or were enucleated.

Results: Following 6 cycles of chemoreduction, all tumors showed an initial regression, and all vitreous and subretinal seeds showed calcification or disappearance of most of them. Among the 30 eyes, 12 eyes achieved complete response (CR), and 18 eyes achieved partial response (PR). Only 7 eyes (Stages I to III) showed sufficient reduction of tumor size for the LT to be applied, for which, TTT (4 eyes), and cryotherapy (3 eyes) were performed. Chemothermotherapy (CTT) was performed for 9 patients (13 eyes, 15 tumors). At the end of the follow-up period, 14 of total 30 eyes (46.7%) could not be salvaged with chemoreduction and LT and required EBRT, enucleation, or both (5 eyes in group IV, and 9 eyes in group V). Toxicities from chemotherapy were mild and included cytopenias (84%), fever and neutropenia (32%), infection (11%), and gastrointestinal symptoms, dehydration, and vincristine neurotoxicity (39%). No patients developed a second malignancy, metastatic disease, or ototoxicity.

Conclusion: The author concludes that in appropriately selected patients with RE groups I, II, and III intraocular retinoblastomas, chemoreduction and local ophthalmic therapy are effective and carry little morbidity. However, other treatment options need to be developed for group IV and V patients.

Key Words: retinoblastoma, chemoreduction, chemotherapy, plaque radiotherapy, enucleation

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Retinoblastoma (RB) is the most common primary intraocular (IO) malignancy in childhood. It is a highly malignant tumor that requires an early and accurate diagnosis and prompt treatment. It characteristically arises multicentrically in one or both retinae,

and if left untreated, is almost invariably fatal. It occurs in hereditary and nonhereditary forms. The hereditary form is usually bilateral and multifocal, whereas the nonhereditary form is unilateral and unifocal.[1] The incidence of RB worldwide ranges from 1 in 15,000 to 1 in 30,000 live births.[2-5]

The management of RB has gradually changed over the past few decades. It was rare that a child survived RB at the beginning of the twentieth century. With advances in therapy, survival has risen from 30% in the 1930s to nearly 95% in the 1990s in the reference centers.[6] A decade ago, enucleation, generally performed on the affected eye in children with unilateral sporadic RB and on the more severely affected eye in bilateral disease, was the standard strategy in treatment of RB in our locality. EBRT was used for less advanced disease, especially for RB associated with diffuse vitreous seeding. Enucleation is a simple way of treatment of IO RB, however, it inevitably brings loss of the globe and vision of the affected eye, together with later psychotic problems. EBRT provides a good local control of RB, especially when used in conjunction with local therapy.[7] However, it has significant local side effects, including xerophthalmia, cataract, retinopathy, and keratopathy. It can adversely affect orbital growth and often associated with cosmetic deformities.[8] Moreover, publications in the early 1990s showed an increased risk for non-ocular malignancies after EBRT in RB patients with a germline mutation. This cumulative risk for secondary cancers was estimated to be 58% overall, compared with 27% in those not treated with radiation therapy.[9] This effect may be age dependent, with the greatest risk in those RB patients with hereditary disease treated under 1 year of age.[10,11]

For these reasons, there has been a substantial decrease in the frequency of enucleation or EBRT over the recent years, a great portion of which is attributable to advances in diagnostic tools with subsequent earlier diagnosis,[12-16]and refinements in the conservative local therapeutic methods such as episcleral plaque radiotherapy,[17-19] photocoagulation,[20,21] cryotherapy,[22,23] and diode laser transpupillary thermotherapy (TTT),[24,25] and chemothermotherapy.[25-27]

Since May 1999 our strategy of management of RB has been changed. The purpose of this study was to identify indications, complications, and limitations of the new treatment modalities, and to evaluate the possibility of avoiding EBRT and enucleation for patients with IO RB treated at our hospital.

Table 1. Reese-Ellsworth Classification of Intraocular Retinoblastoma

Group	Description
Ia	Solitary tumor <4 dd; behind the equator
Ib	Multiple tumors <4 dd; behind the equator
IIa	Solitary tumor 4-10 dd; behind the equator
IIb	Multiple tumors 4-10 dd; behind the equator
IIIa	Any lesion anterior to equator
IIIb	Solitary tumor >10 dd; behind the equator
IVa	Multiple tumors >10 dd
IVb	Any lesion anterior to ora serrata
Va	Tumor involving >50 percent of the eye
Vb	Vitreous seeding

dd = Disc diameters

PATIENTS AND METHODS

Newly diagnosed patients with unilateral or bilateral IO RB treated at the Ophthalmology Department and Oncology Center, Sohag University Hospital, Sohag, Egypt, during the period between January 1999 & May 2005 were eligible for this study, with a follow-up period ranged between 6-30 months (median of 18 months). Children with extraocular RB, metastatic RB, or prior treatment for RB; and those with inadequate renal or liver function were excluded from the study.

When a child with IO RB was seen for the first time, complete history was recorded; and a detailed ocular examination including slitlamp biomicroscopy and indirect ophthalmoscopy with scleral indentation was performed under general anesthesia after maximal mydriasis. Each eye was assessed for laterality of involvement (unilateral, bilateral), overall tumor growth pattern (endophytic, exophytic, diffuse), and total number of retinal tumors per eye. Each retinal tumor was measured for greatest basal dimension (mm) using indirect ophthalmoscope, and thickness (mm) using A-scan and B-scan ultrasonography. Tumor size was recorded as 'tumor base x tumor thickness' in millimeters. Discrete retinal masses were enumerated, and the location and extent of each were documented on a detailed fundus drawing and fundus photography when possible. The presence of subretinal fluid and tumor seeding was recorded. Each eye was categorized according to the Reese-Ellsworth classification system (Table 1).

In addition, several clinical variables were defined as follows; eyes were considered to have diffuse vitreous seeding if individual cells or clumps were seen in the anterior vitreous and there was at least one ophthalmoscopically visible tissue clump disconnected from any retinal mass. Presence of extensive subretinal fluid was

Table 2. Pretreatment Ocular Characteristics of 24 Patients with Intraocular Retinoblastoma

Patient No.	Age	Sex	Affected Eye	RE Group	Total No. of Tumors	No. of Tumors > 10 mm	Vitreous Seeding	Extensive Subretinal Fluid	Foveal Involvement
1	32	M	R	II	2	-	-	-	-
2	21	F	R, L	Enuc, IV	5	2	+	+	+
3	37	M	L	V	4	1	+	-	-
4	18	M	R, L	III, II	3	1	-	-	-
5	24	M	R, L	V, III	5	2	+	-	+
6	36	F	R	II	2	-	-	-	-
7	33	F	L	I	I	-	-	-	-
8	27	M	R, L	IV, V	6	3	+	+	+
9	39	F	R	III	2	1	-	-	-
10	36	M	R	III	3	1	-	-	-
11	25	F	R, L	III, V	3	1	+	-	+
12	15	M	R, L	IV, Enuc	4	2	+	+	-
13	31	M	L	I	2	-	-	-	-
14	37	F	R	IV	3	1	-	-	-
15	11	M	R, L	IV, III	2	1	-	-	-
16	40	F	R	III	2	1	-	-	-
17	36	M	L	V	2	1	+	-	+
18	34	M	R	II	1	-	-	-	-
19	18	F	R, L	V, V	3	2	+	-	+
20	32	M	L	IV	5	2	-	-	+
21	29	M	R, L	Enuc, V	3	1	+	+	-
22	31	F	R	IV	3	1	-	-	-
23	24	M	R	III	1	1	-	-	-
24	38	M	L	V	4	2	+	-	+

considered if there was retinal detachment more than 3 mm from any tumor. Foveal involvement was defined as occupation or obscuration of the center of the foveal pit by tumor or detached retina. Optic nerve head involvement was defined as obscuration of any portion of the optic disc by the tumor or detached retina.

Computed tomography (CT) and/or magnetic resonance imaging (MRI) of the orbits and brain were performed to exclude gross optic nerve and CNS involvement. Additional metastatic work-up in selected cases included bone scan, lumbar puncture, and bone marrow aspirates.

All patients were considered for chemoreduction, provided that they had no absolute indication for enucleation. chemoreduction was started within one week of diagnosis in the form of systemic chemotherapy regimen named "VEC" including vincristine (1.5 mg/m^2), etoposide (150 mg/m^2), and carboplatin (560 mg/m^2). These drugs were given intravenously by the Oncologist with hospitalization for management of side effects. During the period of treatment, blood cell count (particularly absolute neutrophil count and platelets) were obtained at 2-week intervals. Renal function, liver function, and general clinical status were monitored closely. After 3 cycles of 3-week interval chemoreduction, the affected eye was thoroughly examined to evaluate for objective reduction in tumor volume. Tumor response was estimated as the percent reduction in tumor base and thickness. If objective reduction in tumor volume was achieved, the same regimen was repeated for additional 3 cycles. After total of 6 cycles, each tumor was re-evaluated to decide on the next mode of therapy. In cases where the tumor was reduced enough, LT (TTT, cryotherapy, but plaque radiotherapy was unavailable)

was applied. In cases where the tumor was reduced but insufficient for LT, we added another 3 cycles of the same regimen in some patients; or we performed chemothermotherapy (CTT) for others, according to the size of the residual tumor. Chemotherapy was stopped either when local treatment (LT) could be applied, or in the case of treatment failure (TF).

The LT selected for each tumor or seed depended on several factors including the tumor or seed location, status of the opposite eye, visual acuity in the involved and opposite eye, and most important, tumor or seed size. In our hospital, cryotherapy, argon laser photocoagulation, and diode laser thermotherapy were only available as LT measures, but episcleral plaque radiotherapy was unavailable.

Transpupillary thermotherapy (TTT) was used for small lesions located posterior to the equator. It was applied as a primary treatment or if growth subsequently occurred. It was performed while patients under general anesthesia, after maximal mydriasis, using the infrared diode laser attached to indirect ophthalmoscope delivery system in combination with a 20 D lens. Following published recommendations,[25-27] laser settings were selected as follows: median intensity of 400 mW (treatment started with 400-450 mW for tumors of a thickness of 3-4 mm, and 500-700 mW for larger tumors); median spot size of 1.2 mm (range, 0.3-2.0 mm); and median number of cycles required to obtain tumor control was 3 (2 to 4 applications in separate treatment sessions, one month apart, were applied depending on the size of the lesion). The planned duration of treatment varied between 10 minutes for small tumors and approximately 20 minutes for larger tumors. The aiming beam of the laser was focused on the surface in the centre of the tumor during the whole treatment session.

Chemothermotherapy (CTT) was used for tumors located posterior to the equator. It consisted of a combination of TTT delivered one hour after intravenous injection of carboplatin (560 mg/m^2). Each tumor was treated separately. Laser intensity, spot size, and duration were adapted to the size of each tumor and clinical response. At day 8, TTT was repeated alone. This cycle was repeated from 1-5 times every 28 days. The choice between TTT and CTT depended on the initial size of the tumor. TTT was used for tumors of ≤ 3mm in thickness, and CTT was used for larger tumors.

Cryotherapy was mainly applied for small peripheral tumors located anterior to the equator, usually near the ora serrata. It was most successful if limited to tumors measuring ≤ 3.5 mm in diameter and ≤ 2.0 mm in thickness, with no evidence of vitreous seeds. It was applied by the triple freeze-thaw technique, using the cryoprobe as a scleral depressor. Freezing (-80^o) was applied until both the tumor and the surrounding retina turned white, then the tumor was allowed to thaw. Three successive freeze-thaw applications are usually adequate. The eye was re-examined within 3-4 weeks, and when there was any ophthalmoscopic evidence of viable tumor, the treatment was repeated.

Tumor response was determined as follows: Complete response (CR) was defined as complete regression of all apparent tumors and absence of residual tumor activity; partial response (PR) was defined as greater than 50% reduction in the size of all apparent retinal tumors and vitreous seeds, but less than complete regression; and treatment failure (TF) was defined as local relapse that required a change of treatment strategy. Progressive disease was defined as increase in retinal tumor size greater than 25%, vitreous or subretinal seed progression, or new tumor formation. Eyes failed to respond to chemoreduction and LT, received EBRT or were enucleated.

RESULTS

Patients

Between May 1999 and December 2004, 28 patients (37 eyes) with newly diagnosed IO RB were included in this study. Seventeen patients were males and 11 were females. Two patients were living in Sohag city, and 26 patients were referred from other cities in Upper Egypt for treatment. The mean age overall at the time of diagnosis was 24.8 months (from 11 - 40 months); with mean of 27.6 months in unilateral cases, and 16.5 months in bilateral cases. The modes of presentation included leukocoria (31 eyes, 78.6%), buphthalmos (2 eyes, 7.1%), strabismus (one eyes, 3.6%), hyphema (one eye, 3.8%), orbital cellulitis-like picture (one eye, 3.6%), and endophthalmitis-like picture (one eye, 3.6%). Nineteen cases (67.9%) had unilateral RB, and 9 cases (32.1%) had bilateral disease, for a total of 37 eyes. Of these 37 eyes, 7 with advanced IO RB at presentation were enucleated before starting treatment with systemic chemotherapy "CR". Using Reese-Ellsworth (RE) staging for RB, the 30 eyes treated with CR were as follows: Two in group I, 4 in group II, 8 in group III, 7 in group IV, and 9 in group V. Pretreatment ocular characteristics of the remaining 24 patients are summarized in Table 2.

Tumor response to chemotherapy (VEC) was observed in all eyes after 6 cycles of CR. All tumors

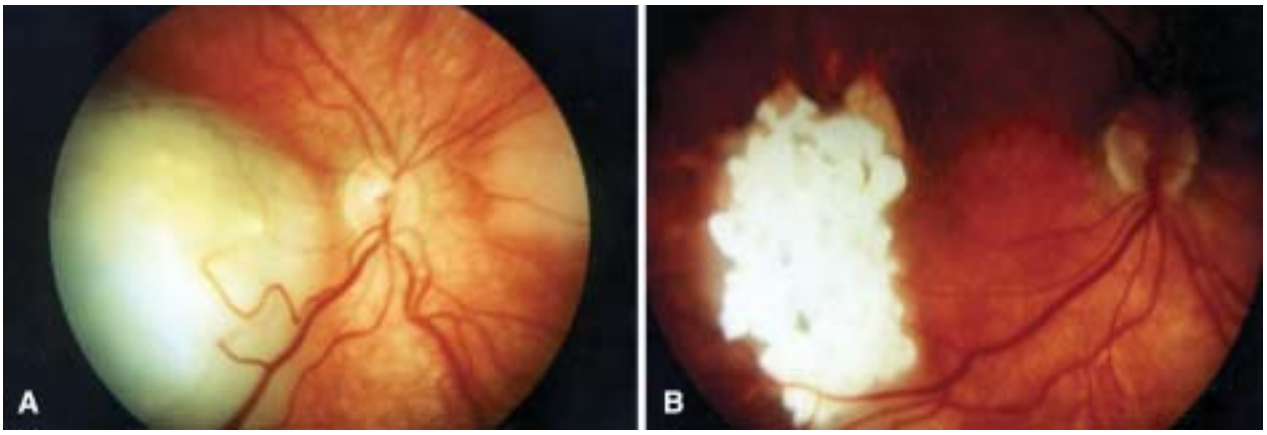

Figure 1. A solitary large intraocular retinoblastoma treated with 6 cycles of chemoreduction followed by 3 cycles of chemothermotherapy (A) Pre-treatment (B) One year post-treatment fundus photograph showing type I tumor regression.

showed initial regression with CR. All vitreous and subretinal seeds showed an initial favorable response, with calcification or disappearance of most of the seeds. Among the 30 eyes, 12 eyes achieved complete response (CR), and 18 eyes achieved partial response (PR). Only 7 eyes showed sufficient reduction of tumor size for the LT to be applied, for which, TTT (4 eyes), and cryotherapy (3 eyes) were performed. Six eyes (3 patients with bilateral disease No. 8, 12 & 19), stages IV & V showed treatment failure and needed salvage treatment by EBRT, and subsequent enucleation of 3 of these eyes. Four eyes (patients No. 2 & 21) had received additional 3 cycles (total of 9 cycles) of CR due to persistent retinal detachment. However, enucleation of the other eye in the patient no. 21 was indicated due to progression of the disease and extensive retinal detachment.

Chemothermotherapy (CTT) was performed for 13 eyes, with tumor thickness ranged between 4 -10 mm. To achieve complete tumor regression, 1-5 sessions of CTT was required according to the size of the tumor (One session for one eye, 2 for 3 eyes, 3 for 5 eyes (Figure 1), 4 for 2 eyes, and 5 sessions for 2 eyes. At the end of CTT, 4 tumors showed a type I regression (26.7%), 2 tumors a type II regression (13.3%), 6 tumors a type III regression (40.0%), and 3 tumors showed a flat scar (20.0%). A local tumor recurrence after CTT occurred in 4 tumors of the 15 (26.7%). The mean interval between the end of CTT and the diagnosis of tumor recurrence was 3.1 months (range

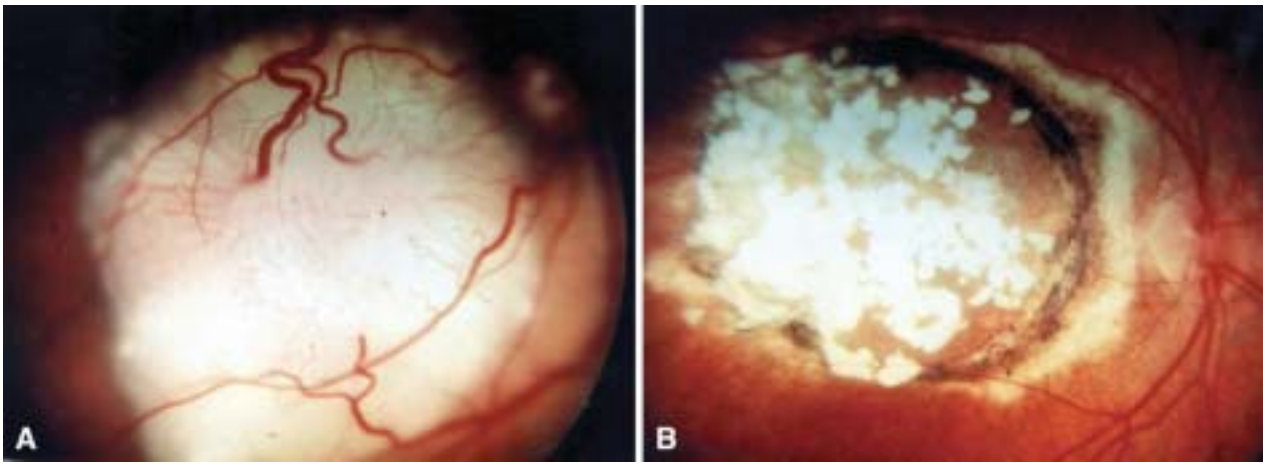

Figure 2. A Solitary juxtapapillary huge intraocular retinoblastoma treated with 6 cycles of chemoreduction followed by 5 cycles of chemothermotherapy. Recurrence occurred at the margin of the tumor remnant treated with argon laser photocoagulation (A) Pre-treatment (B) Post-treatment fundus photograph showing tumor regression.

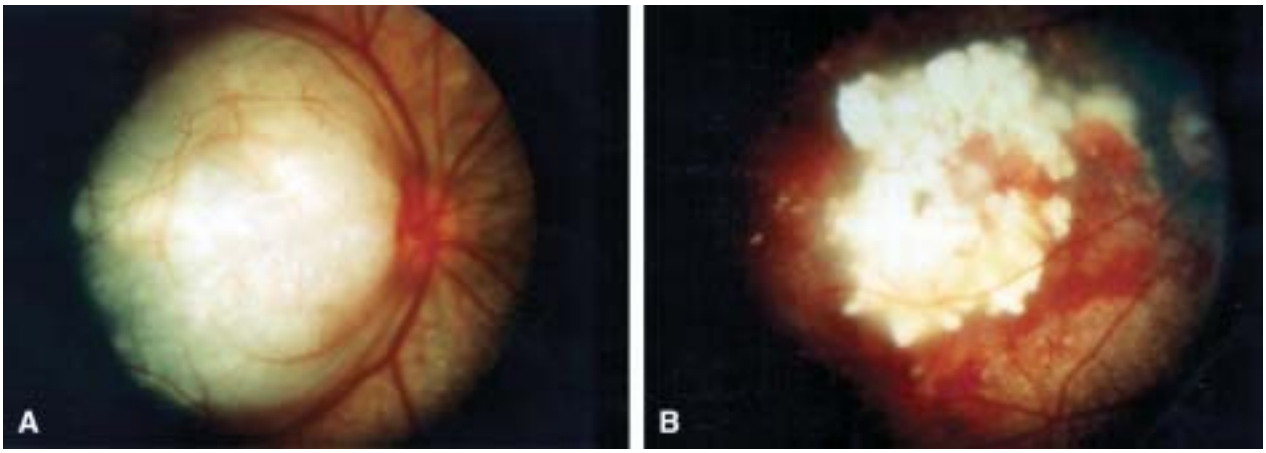

Figure 3. A Solitary juxtapapillary huge intraocular retinoblastoma treated with 6 cycles of chemoreduction followed by 4 cycles of chemothermotherapy, then EBRT due to massive tumor recurrence (A) Pre-treatment (B) Post-treatment fundus photograph showing tumor regression following EBRT.

3 weeks to 12 months). Recurrences at the margins of the tumor remnants were treated with argon laser photocoagulation for 3 tumors (Figure 2), and cryotherapy was used for one tumor with recurrence at the apex of the tumor remnant (treatment of choice is plaque radiotherapy which was unavailable in our study). After additional treatment complete tumor regression was observed in 14 of the 15 tumors initially treated with CTT. Enucleation was indicated in one eye with a massive tumor recurrence in virtually blind eye (patient no. 24).

TREATMENT OUTCOME

At the end of the follow-up period, 14 of the total 30 eyes (46.7%) could not be salvaged with chemoreduction and LT and required EBRT (Figure 3), enucleation, or both (Nine eyes in group V, and 5 eyes in group IV). Toxicities from chemotherapy were mild and included cytopenias (84%), fever and neutropenia (32%), infection (11%), and gastrointestinal symptoms, dehydration, and vincristine neurotoxicity (39%). No patients developed a second malignancy, metastatic disease, or ototoxicity.

DISCUSSION

The management of any specific patient with RB can be extremely complex. The goals of treatment are, first and foremost, to save the child's life and, second, to save the eye and/or vision if possible. It is impossible to establish absolute guidelines regarding treatment. Each case must be individualized according to many factors including, laterality of the disease, size and location of the tumor(s), threat of metastatic disease, risks for second cancers, systemic status, and ultimate predicted visual potential.[1] Prior to starting treatment in this study, there was one main aim, to avoid EBRT and/or enucleation as a primary therapeutic modality for IO RB except if it is absolutely indicated, or after failure of chemoreduction and LT.

The term chemoreduction has been recently used to describe the technique of using chemotherapy over a short course to reduce the size of RB so that subsequent conservative adjuvant less damaging therapeutic measures can be applied for ultimate tumor control.[28,29] Although efficient in reducing tumor volume, chemoreduction alone cannot cure RB and needs to be followed by intensive LT, such as TTT, cryotherapy, and plaque radiotherapy.[30-33] Despite nearly uniform agreement that chemoreduction is effective for reduction in size of IO RB, there is still a controversy regarding the number of cycles of chemotherapy necessary for tumor and seed control. In a pilot study, Shields et al.[28] used a 2-cycle regimen of chemoreduction (VEC) for IO RB, and reported a 49% reduction in the tumor thickness and 35% in tumor base after this treatment. In another more recent study, Shields et al. reported that the use of 6 cycles of chemotherapy provided tumor consolidation with little further tumor size reduction, and that 76% of eyes with RB associated with total retinal detachment achieved complete retinal reattachment after chemoreduction.[34] Furthermore, they found that less than 6 cycles of chemoreduction alone may not be sufficient to completely destroy subretinal

seeds. Also, they reported that 6 cycles of chemoreduction alone may not be sufficient to completely treat active vitreous or subretinal seeds because these eyes showed recurrence of vitreous seeds in 75% and subretinal seeds in 67% of cases in the same study. However, the addition of carefully selected LT to the regressed seeds added significantly improved control of the seeds with 0% recurrence.[30]

In this study, the initial treatment with chemoreduction started within one week of diagnosis in the form of 6 cycles of chemotherapy (VEC). Following the 6 cycles, all tumors showed initial regression. All vitreous and subretinal seeds showed an initial favorable response, with calcification or disappearance of most of them. Among the 30 eyes treated with chemoreduction, 12 eyes achieved complete response (CR), and 18 eyes achieved partial response (PR). The adjuvant LT selected for each tumor or seed depended on several factors including, the tumor or seed location, status of the opposite eye, visual acuity in the involved and opposite eye, and most important, tumor or seed size. The treatment decision was complex, based on the extensive clinical variation of each tumor or seed and was individually tailored to each tumor mass, with respect to the remainder of the eye. Regarding size, if a tumor or seed was 3 mm or less in base, then the adjuvant therapeutic options included TTT, or laser photocoagulation if the tumor was posterior to the equator, and cryotherapy if it was anterior to the equator. If the base was 3 - 12 mm, then CTT was applied preferentially (plaque radiotherapy was unavailable in this study). For larger residual tumors, and those associated with active, incompletely regressed, or recurrent vitreous or subretinal seeds, the above adjuvant treatment plans were altered. In these cases, if the seeds were focal (< 6 clock hours subretinal or local vitreous seeds), then plaque radiotherapy was the treatment of choice, however, it was unavailable in this study, and instead EBRT was performed. If the seeds were diffuse (> 6 clock hours subretinal or diffuse midvitreous seeds), then EBRT or enucleation was recommended according to the condition. At the end of the follow-up period, 14 of the total 30 eyes (46.7%) initially treated with chemoreduction, required EBRT, enucleation, or both after failure of chemoreduction and LT (Nine eyes in group V, and 5 eyes in group IV).

This study confirmed the reported sensitivity of IO RB to first-line chemotherapy (CR) associated with intensive LT. This treatment strategy can be considered as treatment of choice for patients with RB groups I to III not accessible to primary LT. However, this type of therapy was less effective for group IV patients, who had unfavorable results with respect to successful salvage treatment avoiding EBRT and enucleation.

The group V patients, with or without vitreous seeds, represented the greatest obstacle to cure with combined CR and LT. Retinoblastoma with vitreous seeding has been one of the most challenging conditions for eye preservation therapy. Several modalities for treating vitreous seeding were reviewed in order to analyze the problems associated with them. External beam radiotherapy has been the most reliable method to treat vitreous seeding. However, recurrence after external beam radiotherapy needs other types of treatment to preserve the eyeballs. Systemic chemotherapy can rarely cure vitreous seeding, but local chemotherapy using vitreous injections of melphalan can preserve about 50% of the eyeballs with vitreous seeding. Currently, animal experiments being conducted to study the efficacy and safety of intravitreal injection of anticancer drugs (e.g. thiotepa and melphalan) for eradication of vitreous seeds and maintenance of visual function.[35]

Children with metastatic retinoblastoma are considered to have a poor prognosis after conventional chemotherapy. Kremens et al[36] have reported the use of high-dose chemotherapy (HDC) with peripheral hematopoietic stem cell transplantation in such patients in an attempt to improve their survival.

CONCLUSION

We conclude that in appropriately selected patients with RE groups I, II, and III intraocular retinoblastomas, chemoreduction and local ophthalmic therapy are effective and carry little morbidity. However, other treatment options need to be developed for group IV and V patients.

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