Chemoreduction in the Management of Intraocular Retinoblastoma Using New International Classification

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Abstract

Purpose: To evaluate the effectiveness of chemoreduction (CRD) for globe saving in patients with intraocular retinoblastoma

Methods: In this interventional case series all patients with intraocular retinoblastoma were included and classified according to the international classification of retinoblastoma (ICRB) from group A to E. Six cycles of intravenous Vincristine, Etoposide and Carboplatin (VEC) were used for all groups, except for unilateral group A and E. After reduction of tumor volume adjuvant therapy was applied in all cases. Main outcome measure was CRD success, defined as globe salvage by avoidance of external beam radiotherapy or enucleation (EBRT).

Results: Forty-three eyes from 31 patients were enrolled, 12 patients had bilateral involvement. 5 eyes were in group A, 7 in group B, 6 in group C, 8 in group D and 15 in group E. Thirty-one eyes were treated with VEC protocol and aggressive focal consolidation. Successful response was observed in 24 patients, de-novo recurrences occurred in 6 eyes that treated with additional VEC and neoadjuvant therapy. Success rate was 100% for groups A, B and C and 55% for group D during 6-18 months (mean=11.4 months) follow-up. Overall 19 eyes were enucleated (group E=15 and group D=4).

Conclusion: CRD is an effective treatment modality for globe salvage in patients with intraocular retinoblastoma with a high success rate in groups B and C, and an acceptable success in group D.

Keywords: Chemoreduction, International Classification of Retinoblastoma, Adjuvant Therapy, Neoadjuvant Therapy

Introduction

Retinoblastoma is the most common primary intraocular tumor of children under 5-year-old with incidence of 1 in 15000-20000 live births every year. This tumor consists 3-4% of all children’s malignancies.\textsuperscript{1-3}

In recent years primary chemotherapy for reducing tumor volume (chemoreduction) has been used worldwide to ablate tumor by sequential aggressive local therapies to avoid enucleation and radiotherapy.\textsuperscript{13} Treatment has 3 goals: survival of the child, globe salvage and if possible preservation of child’s visual acuity (VA).

Chemoreduction (CRD) using new international classification of intraocular retinoblastoma from 1996 has opened new horizons of progress in the treatment of this dreadful tumor.\textsuperscript{1-6} International classification (ICRB) has been defined as below:

Group A- small tumor<3 mm in size and extramacular, group B- medium tumor>3 mm in size with macular involvement and subretinal fluid, group C- large tumor with localized seeding, group D- large tumor with diffuse seeding and group E- massive tumor that necessitates enucleation. The ICRB was designed to simplify retinoblastoma classification and to predict treatment success with current methods, specifically CRD. This classification was not intended to predict life prognosis or visual outcome. It was intended to predict ocular outcome, specifically, avoidance probability of enucleation and external beam radiotherapy or enucleation (EBRT) after CRD.\textsuperscript{5,9} The purpose of this study was to evaluate effectiveness of CRD plus aggressive adjuvant therapy (laser and cryo) and neoadjuvant therapy (subtenon and intravitreal injection of carboplatin) in the treatment of the intraocular retinoblastoma and, conservation of the globe using the new ICRB.

Methods

All of intraocular retinoblastoma cases from stage A to stage E (based on ICRB) referring to Farabi Eye Hospital between 2005 to early 2007 were included in the study. Exclusion criteria were trilateral, metastatic and invasive retinoblastomas.

All demographic data including age, gender, family history, and age at the time of diagnosis, were recorded, oral and written informed consent were obtained from the parents. Patients underwent general anesthesia (GA) with bilateral pupillary dilation and scleral depression for confirming the diagnosis and classification. In order to confirm the estimated size of tumor, ocular ultrasonography was utilized and for serial evaluation Ret-cam and fundus photography was done. In all cases both CT-Scan and ocular ultrasonography were performed.

Grouping and hereditability (multifocal, bilateral and positive family history) of tumor were established and the child was referred for systemic workup.

Thus for all unilateral (except group A and group E) and bilateral intraocular tumors 6 courses of VEC (Intravenous Vincristin 0.05 mg/Kg first day, Etoposide 5 mg/Kg first and second days, Carboplatin 18.6 mg/Kg first day) therapy was applied monthly by pediatric oncologist. For unilateral group A only focal therapies (laser and cryo) and unilateral group E only enucleation was done, however, if the pathologic report showed invasion of tumor to sclera and optic nerve stump, chemotherapy was applied.

The child was examined monthly during chemotherapies. After reduction of tumor size, focal aggressive consolidation was used and regressions and recurrences of the tumor were registered. For unilateral group A, focal therapies were administered and for unilateral group E, enucleation was performed. CRD success was defined as globe salvage by avoidance of EBRT.

Results

During 22 months (between early 2005 to late 2007), patients with suspected retinoblastomas referring to Farabi eye hospital were included in our study. They were 33 children. No one had trilateral retinoblastoma, with exclusion of 2 patients with unilateral group E that had been enucleated with negative pathologic answer for retinoblastoma, 31 patients remained in the study, 12 of them had bilateral involvement, therefore total 43 eyes were included.

The mean age of the children was 22.8 months, the median age was 25 months, the mean follow up time was 11.4 months and the median follow-up duration was 8.5 months.
Bilaterality in 39% and unilaterality in 61% was seen, 65% were males and 35% were females. Percentage of patients in each group is as follows: group E 34.9%, group D 20.9%, group B 18.6%, group C 14%, and group A 11.6%. The mean chemotherapy cycles were 6.5 courses.

The most common initial symptoms noticed by the parents were: leukocoria (64.2%), strabismus (22.6%), red eye (3.3%) and others such as megalocornea, microphthalmos and lack of vision (each 3.3%).

Chemotherapy (VEC therapy) for 6 courses was applied in all patients except unilateral group E.

In this study there was no unilateral group A, but there were 12 eyes with unilateral group E which were candidates for enucleation without chemotherapy. Thus CRD was done for only 31 eyes.

In bilateral cases in which one eye was in group E, chemotherapy was initiated and in 3 cases after 3 cycles of chemotherapy the worse eye did not respond to treatment. Thus enucleation was applied.

For group D if CRD was not successful neoadjuvant therapy with carboplatin 15-20 mg subtenon injection was applied monthly for 3 times. In these cases 4 of 9 eyes showed no response and were enucleated. All of these four eyes were in patients with bilateral involvement, and overall 19 eyes were enucleated.

One case had invasion of tumor to the orbital soft tissues 50 days after enucleation and was exenterated. The initial pathologic report was poorly differentiated retinoblastoma with extension to choroids and no extension to sclera and optic nerve. The child had received no chemotherapy.

There was no death or lost to follow-up and only in one patient bilateral enucleation was performed inevitably for the patient’s survival. External beam radiotherapy was not applied in order to prevent secondary neoplasms.

All patients with positive family history (3 bilateral and 2 unilateral) and bilaterally involved cases with multifocal tumors were considered as hereditable (9/31).

Twenty percent of patients had recurrences of tumors, with mean 5 months after completion of chemotherapy, all in hereditable patients. In 5 of these cases the tumor was seen before age one and only in one case in 2-5 year group. All recurrences were in the periphery of the eyes and de-novo. All recurrences were regressed with additional 3 to 6 cycles of chemotherapy, aggressive focal therapy, and neoadjuvant therapy.

In 6 eyes (of group D and C) subtenon injection of carboplatin and in 3 eyes (of group C) intravitreal injection of carboplatin was used. Both injections resulted in decrease or flattening of a and b waves of ERG.

Group A, B, and C responded to CRD but 4 eyes of group D (all hereditable) in spite of subtenon injections of carboplatin were unresponsive, and became candidates for enucleation.

Thus success rate was 100% in groups B, C and 55% in group D.

From 19 eyes which were candidates for enucleation only 10 eyes were enucleated. Histopathology reports were consistent with retinoblastoma in 8 eyes, one endophthalmitis and the other coat’s disease. In 9 patients the parents did not agree with informed consent for enucleation (one of them was a candidate for bilateral enucleation). All patterns of regression were seen in our patients. Close and near follow-ups were applied for hereditable disease and in patients with the disease initiated under one year old.

An interesting case was a child with unilateral group C retinoblastoma (Case: 5) with positive family history. The child had 12 sessions of VEC chemotherapy and 2 episodes of recurrence, treated with 3 intravitreal injections of 10 microgram carboplatin monthly. This led to complete regression of the tumor, flatness of ERG amplitudes a and b waves and 1.5 meter counting finger vision.

**Discussion**

In our study we used CRD based on ICRB. This classification was not intended to predict life prognosis or visual outcome. It was intended to predict ocular outcome, specifically, after CRD.6

In this study for all intraocular retinoblastomas (except unilateral group A and unilateral group E) CRD in the form of VEC protocol (monthly intravenous Vincristin 0.05 mg/Kg first day, Etoposide 5 mg/Kg first and second days, Carboplatin 18.6 mg/Kg first day) was used and followed by focal
consolidation therapies. We did not apply external beam radiotherapy in any case because of its morbidity and complications.

In short term follow-up with a mean 11.4 months the globe salvage rate was 100% for group B and group C and 55% in group D. In the study by Shields’ et al treatment success rate was achieved in 100% of the eyes in group A, 93% of group B, 90% of group C, and 47% of group D. Therefore patients within groups A, B, and C had a good chance for globe salvage and patients in group D had a lower chance for conserving the eye, and nearly half of them needed to be enucleated. In Schefler’s study with 3 years of follow-up, 100% success was obtained in groups I-IV Reese Ellsworth and 83% in group V.

Shields and associates had noted that after three years of follow-up of patients treated by CRD tumor recurrence was found in 51% of the eyes. Of those eyes with subretinal seeds at initial examination, subretinal seeds recurrence was found in 46% of the eyes, and of those with initial vitreous seeds, recurrence was detected in 62% of the eyes after three years of follow-up. These findings did not increase much after five years of follow-up. Therefore, it was presumed that most recurrence following CRD would be clinically visible by three years following the treatments.

Neoadjuvant therapies such as local carboplatin injections, both subtenon and intravitreal with different dosages and control of ERG were applied in refractory and complicated cases of group C and group D. In this study with ERG control 20 mg subtenon injection of carboplatin in patients induced retinal toxicity in 2 out of six cases.

Subtenon injection of carboplatin according to Murray, Abramson and Hayden has been used with different dosages in mice and human which has increased the rate of CRD success. On the contrary in a study by Karkhaneh et al using subtenon injection of carboplatin as adjuvant treatment in VEC protocol, had no additive effect on tumor regression.

In our study intravitreal injection of 10 µg carboplatin with ERG control induced retinal toxicity in one patient. According to the Harbours’ study intravitreal injection of carboplatin at dosage of 1.4 µg can inhibit development of tumor in 50% of transgenic murine. It can result in retinal toxicity in rabbits at dosage of 10 µg or higher. In Karkhaneh et al study, intravitreal injection of carboplatin in patients at dosage of 5 µg has increased the success rate of CRD.

Important points in our study are usage of aggressive focal therapy (laser and cryotherapy) during CRD and also usage of neoadjuvant therapy (subtenon and intravitreal injection of carboplatin) for resistant and recurrent cases.

As recurrences of tumor is common and frequent among children under 1 year and hereditary ones, urgent diagnosis is essential for successful treatment. Thus frequent follow-up exams under GA with precise inspection of the retinal periphery is important. Regarding early diagnosis of recurrences, chemotherapy is repeated for 3-6 sessions, and focal consolidation and neoadjuvant therapy can control all of the new tumors. As previously mentioned about case no. 5 that led to globe preservation and in spite of ERG flatness, the child has some useful vision.

There was only one case of rhegmatogenous retinal detachment in our case series due to aggressive usage of cryotherapy. Anagnoste has also reported the development of rhegmatogenous retinal detachment, with the retinal break adjacent to a cryotherapy scar, in three patients undergoing systemic chemotherapy for intraocular retinoblastoma.

In our study one patient was enucleated bilaterally and this result was estimated to be 1% in larger studies.

In this study there was no mortality in mean 11.4 months follow-up period. Of important aspects of our study are lack of radiotherapy, lack of major and serious chemotherapy complications, and aggressive local therapy with indirect laser even for macular region.

It seems that group D must be divided into two sub-groups; one with better response similar to group C and the other with worse behavior similar to group E.

The limitations of this study is short follow-up duration of the patients besides a high percentage of our patients have been referred to our clinic very late when they were in advanced groups (E and D), therefore early diagnosis and treatment and longer follow-up duration at least for 5 years is recommended.
Conclusion

In Conclusion regarding the high success rate of the new treatments in group A, B and C of retinoblastoma, the importance of screening and early diagnosis and treatment of tumor is critical. CRD plus aggressive adjuvant and neoadjuvant therapies are effective modalities for conserving the globe. Frequent follow-ups under GA is essential for detection of tumor recurrences and immediate treatment.

References