Original article

Multidisciplinary management of retinoblastoma: Experience in 37 eyes

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A B S T R A C T

Objective: To report the results of the multidisciplinary management of patients with retinoblastoma, including survival, enucleation rate, and systemic chemoreduction success.

Methods: A retrospective study was conducted on 27 patients (37 eyes) diagnosed with retinoblastoma, and treated by a multidisciplinary team in San Juan de Dios Hospital. Demographic information, clinical characterization, survival, local and systemic treatments were included in the analysis. Patients treated with intra-arterial chemotherapy (IAC) were also reviewed.

Results: The study included 14 male patients (52%). The median of age at presentation was 8 months (0.16–90). The median follow-up time was 33 ± 21 months. The diagnosis was made in 10 (37%) cases after 15 months old, with a median of 35 months (24–90). 17 (63%) patients had unilateral retinoblastoma, and 10 (37%) bilateral retinoblastoma. Leukocoria, isolated or associated with other signs, was the most frequent reason for referral (63%). Global enucleation rate was 57% (n = 21), being the primary treatment in 15 (55%) patients. Enucleation rate in unilateral retinoblastoma was 76.5%, and for bilateral retinoblastoma, it was 60% for one eye and 10% for both. Systemic chemotherapy was prescribed in 17 (63%) patients, with a mean number of cycles of 5.3 ± 2.1. The overall success of chemoreduction and focal therapy in order to avoid external radiotherapy and/or enucleation was 68%. Three patients were treated with IAC as a salvage therapy, controlling the tumor in 2 patients at 6 months of follow-up. These are the first cases reported in Chile. Survival rate was 100%.

Conclusion: Multidisciplinary management of retinoblastoma led to a survival rate and morbidity comparable with international reports.

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Manejo multidisciplinario en retinoblastoma: experiencia en 37 ojos

RESÚMEN

Objetivos: Reportar los resultados del manejo multidisciplinario de pacientes con retinoblastoma, incluyendo supervivencia global, tasa de enucleación y éxito de la quimiorreducción sistémica.

Métodos: Estudio retrospectivo 27 pacientes (37 ojos) con diagnóstico de retinoblastoma, tratados por un equipo multidisciplinario en el Hospital San Juan de Dios. Se incluyeron información demográfica, características clínicas, supervivencia, tratamiento local y sistémico. Se realizó además un subanálisis de tratamiento con quimioterapia intraarterial (QIA).

Resultados: Catorce pacientes (52%) fueron de sexo masculino. La mediana de edad al ingreso fue de 8 meses (0,16-90). La mediana ± desviación estándar de seguimiento fue de 33 ± 21 meses. Diez casos (37%) se diagnosticaron después de los 15 meses de edad, con una mediana de 35 meses (24-90). En 17 (63%) pacientes fueron retinoblastomas unilaterales, mientras 10 (37%) tuvieron retinoblastoma bilateral. La leucocoria, aislada o asociada a otros signos, fue el motivo de consulta más frecuente (63%). La tasa global de enucleación fue del 57% (n = 21), siendo el tratamiento primario en 15 (55%) pacientes. La tasa de enucleación en retinoblastoma unilateral fue del 76,5% y en retinoblastoma bilateral del 60% de un ojo y el 10% de ambos. Diecisiete (63%) pacientes recibieron quimioterapia sistémica (media de ciclos: 5,3 ± 2,1). El éxito global de la quimiorreducción sistémica y la terapia focal fue del 68%. Tres pacientes fueron tratados con QIA como terapia de rescate, logrando controlar el tumor en 2 pacientes a 6 meses de seguimiento, siendo los primeros casos en Chile. La supervivencia fue del 100%.

Conclusión: El manejo multidisciplinario del retinoblastoma permite una supervivencia y una morbimlidad comparable con la literatura internacional.

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Introduction

Retinoblastoma is a curable ocular cancer which, if not treated, could cause death within 2 years. Its incidence is close to 1 for every 16,000 live births, although it can reach one for every 34,000. It is estimated that 13 new cases arise every year in Chile. Most of these cases are cared for by the public system by means of the Explicit Health Guarantees (Garantías Explícitas en Salud, GES). The San Juan de Dios Hospital is a tertiary oncology referral center where these patients are treated by a multidisciplinary team.

The main goal of retinoblastoma management is patient survival, in addition to preserving the compromised eye and visual function as far as possible. It involves a complex clinical process for discarding simulating lesions, detection of disseminated disease, selection of personalized therapy and strict follow-up for diagnosing recurrences. There is a range of treatments comprising systemic management with several modes of chemotherapy and focal ophthalmological treatments.

The primary objective of the present study is to report the result of multidisciplinary management of patients with retinoblastoma in our hospital, including overall survival, enucleation rate and success of systemic chemoreduction. The secondary goal is to report the characterization of ophthalmological variables, the range of treatments in this series, including the first cases of intra-artery chemotherapy (IAC) carried out in Chile.

Methods

Retrospective study of clinical histories which included patients diagnosed for retinoblastoma admitted to the San Juan de Dios Hospital between August 2007 and March 2014. The study excluded patients with retinoblastoma-simulating lesions (pseudo-retinoblastoma) and patients with retinoblastoma diagnostic but were in follow-up when the study began. The data collected comprised demographic data, reason for the visits, follow-up, family history, supplementary examinations, characterization of tumors, staging, classification, systemic treatments (chemotherapy modes) and local treatments (including laser, cryotherapy, brachytherapy, IAC [topotecan 1 mg, melfalan 4 mg] enucleation), relapses and dissemination. The results of available biopsies were reviewed. The study was approved by the Ethics Committee of the institution. The genetic study was carried out in an international laboratory (Impact Genetics Inc., Canada). The statistical analysis was made with SPSS 16.0 2007 for Mac (SPSS Inc., Chicago, USA), utilizing T for Student and Chi square tests.
Results

The study included 37 eyes of 27 patients, with a mean of 5.5 admissions per year (range 2–6). The mean ± standard deviation for follow-up time was 33 ± 21 months. Only 3 patients had less than 6 months follow-up (4, 5 and 5, respectively) but these were enucleation cases, all stage I in Classification of tumors based on histology (Grabowski-Abramson). Fourteen patients (52%) were male. The mean age at admittance was 8 months (0.16–90). One case was diagnosed in a 5-day old infant and 10 cases (37%) were diagnosed after 15 months of age, with a mean value of 5 months (24–90).

Family history

Seven patients (26%) exhibited positive family history for retinoblastoma (4 parents, 3 siblings), 2 of them being unilateral.

Reason for visit

The most frequent reason for visiting the consulting room was leukocoria in 17 cases (63%), which was the only sign in 13 patients (48%). Strabismus was the second reason for visit with 5 patients (19%), followed by for patients with multiple signs (15%; 3 leukocoria + strabismus; 1 leukocoria + strabismus + proptosis), 3 with family history of retinoblastoma (11%) and 2 with other signs (8%; red eye and trauma).

Laterality and focality

Seventeen patients (63%) exhibited unilateral retinoblastoma while 10 patients (37%) exhibited bilateral retinoblastoma. The mean age of bilateral tumor diagnostics was 5.5 months (0.16–24), whereas the mean age of bilateral tumor diagnostics was 11 months (6–90) (p = 0.05).

Number and location of tumors

All bilateral cases (100%) exhibited multifocal tumors and in only 2 patients compromise was unilateral. The mean tumors per eye in bilateral cases were of 3 (range 1–6). In eyes with non-massive tumors and defined edges at admittance (n = 18), location was: 5 eyes (28%) tumors compromising the optic nerves, 5 eyes (28%) tumors in the juxtapapillary region, and 6 (33%) in the macular region. In addition, 3 eyes (17%) had tumors compromising the optic nerve as well as the macula. When comparing the enucleation frequency between patients with juxtapapillary compromise (3/5) with those with optic nerve compromised (5/5), the difference was statistically significant (p = 0.002).

Clinical classification of tumors

The classification of the present series, based on the International Classification of Intraocular Retinoblastoma (ICIRB) are shown in Table 1. Table 2 shows the staging of patients according to ICIRB.

<table>
<thead>
<tr>
<th>Table 1 – Classification of tumors according to the International Classification of Intraocular Retinoblastoma.</th>
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<tr>
<td>Group</td>
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</tr>
<tr>
<td>A</td>
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<td>B</td>
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<tr>
<td>C</td>
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<tr>
<td>D</td>
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<td>E</td>
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<th>Table 2 – Stage of patients according to the International Classification.</th>
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<td>Stage</td>
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<td>0</td>
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<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IVa</td>
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<td>IVb</td>
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</tbody>
</table>

Supplementary examinations

All the patients were examined with orbit and brain magnetic resonance, finding in one patient (4%) a nodular region in the pineal gland, which was interpreted as benign due to its stable behavior in time, one case (4%) exhibited compromised post-laminar nerve up to the chiasm, and one patient (4%) exhibited juxtascleral orbit compromise. Lumbar puncture was carried out in 5 patients (19%), with all samples being negative for tumoral cells.

Enucleation

The overall enucleation rate was 57% (21 of 37 eyes were enucleated). The enucleation rate in unilateral retinoblastoma was 76.5% (13 of 17 eyes). In bilateral retinoblastoma, 60% of cases required enucleation of at least one eye (6 out of 10 patients) and only one patient (one out of 10 cases) was submitted to bilateral enucleation. A summary of the treatments received by each eye is shown in Table 3. Fig. 1 shows enucleated patients according to the ICIRB.

Out of 21 enucleation surgeries, all with primary implant, 2 cases presented with moderate orbit hematoma immediately after surgery (9.5%), in addition to 2 moderate ptosis (9.5%) and 2 cases with orbit implant extrusion associated to orbit cellulitis (9.5%).

<table>
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<th>Table 3 – Types of treatment.</th>
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<tr>
<td>Management</td>
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<tr>
<td>Primary enucleation</td>
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<tr>
<td>Chemoreduction</td>
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<tr>
<td>Neoadjuvant CMT</td>
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<tr>
<td>Secondary enucleation</td>
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<tr>
<td>IAC</td>
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IAC: intra-artery chemotherapy; CMT: chemotherapy.
* Twenty-two eyes of 7 patients.
Overall, chemotherapy was prescribed in 2 patients with unilateral retinoblastoma. In one patient, homozygote deletion was found in a tumor sample but not in blood (c.1962_1963delGT), discarding germinal mutation. In a second patient, the genetic study carried out only in blood also discarded the presence of a germinal condition. All the tumors were sent to the Tumor Bank for eventual study.

**Genetic study**

A genetic study was requested for 2 patients with unilateral retinoblastoma. In one patient, homozygote deletion was found in a tumor sample but not in blood (c.1962_1963delGT), discarding germinal mutation. In a second patient, the genetic study carried out only in blood also discarded the presence of a germinal condition. All the tumors were sent to the Tumor Bank for eventual study.

**Histopathology**

All the enucleated eyes (n = 21) were sent for histopathological study (Fig. 2). Table 4 summarizes the available studies (n = 16).

**Chemotherapy**

Overall, 7 patients (63%) received systemic chemoreduction with vincristine, etoposide and carboplatin (VEC). The mean number of cycles was 5.3 (±2.1). Out of 13 patients with unilateral retinoblastoma and primary enucleation, co-adjuvant chemotherapy was indicated in only 3 (11%): in one case due to massive choroidal compromise after histopathology, in another due to optic nerve postlaminar compromise and in the third due to previous vitrectomy performed in another hospital with doubtful diagnostic.

The overall success of systemic chemoreduction and focal therapy for avoiding external radiotherapy and/or enucleation was 68% (1 of 2 eyes in 17 patients). Causes of chemoreduction failure were: 5 patients with primary failure (tumoral control) and 2 patients with untreatable relapse.

Five patients (18.5%) exhibited minor chemotherapy complications: one case of non-anaphylactic moderate allergy, one case of paralytic ileus, one case of neutropenic enteropathy and 2 cases of febrile neutropenia.

One case (4%) successfully completed autogon bone marrow transplant (metastatic retinoblastoma with bone marrow compromise). Systemic chemotherapy did not give rise to major complications or demise.

**Intra-artery chemotherapy**

Three patients (11%) received IAC as rescue treatment due to systemic chemoreduction failure (Fig. 3). In 2 out of 3 cases, IAC with topotecan and melfalan was able to control relapses and prevent enucleation (6 months follow-up). One of said successful cases was a patient with bilateral retinoblastoma and relapse in a non-enucleated single eye, being the first case of IAC use in Chile. No major complications associated to IAC arose, and only one of the patients exhibited transient ptosis which was resolved within 3 months.

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**Fig. 1 – Distribution of eyes according to the International Classification of Intraocular Retinoblastoma based on enucleated and non-enucleated eyes.**

**Fig. 2 – Suspected active residual tumor on optic nerve, after completing 6 VEC chemoreduction cycles (left). Enucleation is performed and the pathological anatomy exhibits pre-laminar optic nerve compromise with feasible tumoral cells up to the lamina cribosa (right).**

<table>
<thead>
<tr>
<th>Stage</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Ia</td>
<td>3 (19)</td>
</tr>
<tr>
<td>I b</td>
<td>8 (50)</td>
</tr>
<tr>
<td>I c</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>IIa</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>IIIa</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>IVb</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>IVa</td>
<td>0 (0)</td>
</tr>
<tr>
<td>IVb</td>
<td>0 (0)</td>
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* For stages I–IV table shows only those with eyes; Id, IIb, IIIb, IVa, Va and Vb did not exhibit samples.
Consolidation therapy and supplementary management

Eighteen eyes (49%) were given focal laser treatment (treatment mean ± standard deviation of 6.2 ± 2.8), 11 (30%) with cryotherapy (treatment mean 2.5 ± 1.9). Subtenon chemotherapy injection was utilized in 7 eyes (19%; treatment mean 2.7 ± 1.4.3 carboplatin, 4 topotecan). Three patients received focal therapy with I125 brachytherapy for treating tumor relapses, achieving success in 2 out of 3 cases (Fig. 4).

Radiotherapy

One patient with bilateral retinoblastoma was administered radiotherapy in one advanced eye after all other therapies failed. There was no response and the residual eye was enucleated.

Relapses

Seven eyes (19%) exhibited relapses, which were early (<6 months) in 5 eyes, 3 of which were multiple in the same eye. In the 4 remaining eyes, the relapse occurred in the original location. In 3 eyes, enucleation was finally necessary, with 2 of these exhibiting multiple relapses.

Mortality and dissemination

All the patients in the series remain alive. All those exhibiting extra-ocular retinoblastoma were rescued with chemotherapy as per the protocol for each stage, and at the time of completing this review remained in remission (one case exhibited post-laminar and chiasmatic optic nerve compromise, and a further one bone marrow and juxtascleral orbit compromise).

Examination under anesthesia

The mean number of examinations under anesthesia was 7.5 (range 2–19).

Discussion

Retinoblastoma is an intraocular cancer which affects the pediatric population and can threaten survival if left untreated. Its management is a challenge that requires a multidisciplinary team with experience in striking a balance between the treatment objectives: survival, ocular globe preservation and finally preservation of vision.

At the world level, the reported retinoblastoma survival rate ranges between 30% and 97% depending on the economy.
of each country, and is consistently over 95% in developed countries which carry out high screening levels and are virtually free of restrictions as regards the best available treatment options.

Initial signs of this disease are crucial for an early diagnostic. Said signs depend on the level of ocular involvement at diagnostic. The publications that have studied this report that the most frequent debut signs include leukocoria (47–56%), strabismus (24%) or poor vision (8%). The mean presentation age of retinoblastoma is 5 months. In less developed countries, initial signs at the first visit vary, with the main sign being prophosis (55%) or buphthalmos (56%). The majority of our cases with familial retinoblastoma history were bilateral, which matches the literature. Of all patients with presumably germinal retinoblastoma (progenitors and/or siblings affected, bilateral and/or multifocal tumors), 2 patients presented with unilateral compromise (16%), which also matches the values found in the literature. The present paper utilized a screening and demographic profile similar to that found in highly developed countries.

Retinoblastoma can simulate a number of lesions which could reach up to 22% of visits, the most frequent being Coats disease and the persistence of fetal vasculature. These findings match reports in local literature. Even though the authors did not review the lesions included in the pseudo-retinoblastoma group, it is important to emphasize that precise diagnostics preempt unnecessary treatments, particularly those involving chemotherapy and its potential adverse effects.

ICIRB is applied specifically to the chemotherapy results through the intravenous pathway due to the predictability of success. The authors did not use the Reese-Ellsworth classification, which is mainly useful for predicting prognosis when retinoblastoma is treated with external radiotherapy, because it did not match the circumstances of this series. Current management of intraocular retinoblastoma and dissemination prevention continues to be systemic chemotherapy. VEC, the most widely used protocol, is effective for managing intraocular retinoblastoma and preventing metastasis, pinealoblastoma and other expressions of cancer. The local protocol of the authors did not utilize chemoreduction and conservative therapy in patients with ICIRB E (enucleation). Chemotherapy is rarely healing on its own. In general, discrete and advanced tumors, either multifocal or recurring, require consolidation with focal therapy. This includes a range of described alternatives, the most used of which are indirect laser therapy (argon or diode, around and over the tumor), cryotherapy and brachytherapy. The primary enucleation frequency in this series was of 55%, mainly indicated in eyes with group E retinoblastoma. However, the majority of eyes that were administered chemoreduction involved smaller tumors with better response to treatment.

The results of this series portray an improvement in retinoblastoma diagnostic and screening in the country. Compared with the most recent local study in which the mean age of patients at first visit was 21 months, 93% with primary enucleation, 26% with ocular extension and a survival rate of 85%, this series obtained a mean presentation age of 8 months, 55% primary enucleation, 8% extracocular extension and 100% survival rate. However, the mean follow-up time of Trincado et al. was 56 months compared to the mean follow-up time of this study of 3 months. The authors wish to point out that the central tendency measure applied was the median and not the average, mainly due to the heterogeneous distribution of the sample. These findings make these numbers comparable with those reported in the literature of more developed countries, and higher than in previous reports in Latin America (80–94%). Survival is associated to the development stage of the disease. The factors associated to metastasis are: advanced disease with choroidal invasion exceeding 3 mm, optic nerve compromise beyond the lamina cribosa and scleral or orbital compromise.

Previous publications discussed the clinical relevance of tumor location as diagnostic is more probable in red pupil for tumors involving the posterior pole or the half periphery. It is worthwhile pointing out that macular compromise with affect central vision while optic nerve compromise leads to the suspicion of higher risk of treatment failure, partly due to the limitations in management with local measures. It is noteworthy that the 5 eyes with optic nerve compromise in this series required enucleation, while the other 5 eyes with optic juxtapapillary tumors did not.

According to the ICIRB success of intraocular retinoblastoma treatment per eye was achieved in 100% for group A, 93% for group B, 90% for group C, 47% for group E and 25% for group F. Additional treatments such as subtotal therapy or IAC have improved said percentages. Systemic chemotherapy has demonstrated its usefulness for controlling associated retina detachment, prevention of metastasis and other tumors, reducing morbidity and lower incidence of pinealoblastoma. All the complications observed in our patients were managed without additional morbidity.

In the present series, the enucleation rate in unilateral retinoblastoma (76.5%) was comparable to that of other series published in Toronto (82%), Philadelphia (65%) and Birmingham (89%). In addition, it represents an improvement vis-à-vis the 100% enucleation rate for unilateral retinoblastoma previously reported in our country. This rate is probably related to early diagnostic and access to new treatments techniques such as IAC.

In what concerns enucleation complications, the present series reports a post-surgery ptosis incidence of 9.5% as compared to 18.2% in a recently published report (Choi et al., 2013). Orbital implant extrusion associated to infection appeared in 2 patients (9.5%) of the present series, as compared to 21–35% of other series, depending on the previous treatment. However some reports had no extrusion cases. IAC has demonstrated to be a safe and effective alternative for managing retinoblastoma in selected cases. Gobin reported 82% ocular survival 2 years after primary treatment and 58% with secondary treatments. A research publication reported 72% ocular survival in primary treatment and 62% in secondary treatments, with good results for the ICIRB group in primary management (group B [100%], group C [100%], group D [94%] and group E [36%]). The 3 cases reported herein represent the first experience in Chile, all indicated as rescue therapy for eyes with chemoreduction and local treatment failure. During the 6 months follow-up, only one case required enucleation. The low rate of complications and success in the remaining 75% of cases gives rise to high expectations for...
managing selected cases in the future. To our knowledge, the other active IAC programs in Latin America are in Argentina, Colombia, Brazil and Mexico.

The present work exhibits the limitations inherent in retrospective analysis of clinical histories, which represents the actual situation in a referral center in our country. This does not mean that the conclusions of this study should be applied to the entire country as the efforts for promoting screening at the primary level and education in retinoblastoma will never be enough. In order to demonstrate the effectiveness and safety of the practices reported herein and therapeutic alternatives, prospective, collaborative and multicenter protocols seem to be the best option.

Success in the treatment of retinoblastoma is the result of a sequence of multiple factors involving diagnostic and treatment. The authors firmly believe that the improvement in the socioeconomic conditions of the population have facilitated an earlier diagnostic of the disease, and that the development of study techniques and treatment at the local level explain the improvement in results at all levels (survival, ocular and visual preservation). The management of these patients should be in charge of a specialized interdisciplinary team with experience in treating this disease.

Conflict of interest

No conflict of interest has been declared by the authors.

REFERENCES


