Impact of Chemoreduction for Conservative Therapy for Retinoblastoma in Argentina

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Background. Few studies were reported from developing countries regarding patient outcome and ocular survival in children with bilateral retinoblastoma treated with chemoreduction compared to external beam radiotherapy (EBRT). ***Procedure.*** We undertook a retrospective study of three treatment eras: (1) (1988–1995) n = 68 when EBRT was used as primary conservative therapy; (2) (1995–2003) n = 46 when carboplatin-based systemic chemoreduction was introduced and (3) (2003–2009) (n = 83) when additional periocular chemotherapy was added for advanced tumors and pre-enucleation chemotherapy was given for those with massive buphthalmia. ***Results.*** The probability of 5-year disease-free survival was 0.94 (95% confidence interval [CI] 0.91–0.98%) without significant differences among the three eras. Chemoreduction reduced the use of EBRT from 84.6% to 68.7% in eras 1 and 3, respectively ($P = 0.008$), which was more evident in cases with less advanced disease. Chemoreduction also significantly improved the 5-year probability of preservation of eyes with advanced disease from 0.13 (95% CI 0.04–0.27) during era 1 to 0.49 (95% CI 0.34–0.62) in era 3 ($P < 0.0001$). Chemoreduction was not associated with changes in the probability of extraocular relapse, which was reduced after the introduction of pre-enucleation chemotherapy. Second malignancies occurred in nine cases, acute myeloid leukemia being the most fatal one. Trilateral retinoblastoma occurred in three cases and all of them had been exposed to chemotherapy. ***Conclusions.*** Chemoreduction reduced the need for EBRT in eyes with less advanced disease and improved the preservation of eyes with advanced disease while its effects on secondary malignancies or trilateral disease remain unclear. Pediatr Blood Cancer

Key words: chemotherapy; developing countries; retinoblastoma; second malignancies

INTRODUCTION

Conservative therapy for retinoblastoma evolved from the classical treatment with external beam radiotherapy (EBRT) to chemotherapy-based regimens in the mid 1990s. Following the initial experience of Kingston et al. [1], chemoreduction with carboplatin-based protocols was used as primary treatment for intraocular disease not amenable for local therapy aiming to decrease tumor size and make the tumors suitable for local therapy [2]. The major achievement of this treatment was to avoid EBRT and its mutagenic potential in a substantial number of children [3]. With chemoreduction, most patients with less advanced disease, which were grouped as groups A, B, and C in the international classification responded favorably to chemotherapy [4], so that enucleation and EBRT could be avoided in most cases. On the other hand, patients with advanced intraocular tumors (group D), especially those with vitreous seeds, ocular salvage rates were substantially lower and consolidation with EBRT and usually enucleation was required [4]. In order to improve the results in this population, different treatment modalities such as periocular administration of chemotherapy [5] and more recently, intra-arterial chemotherapy [6] have been subsequently employed. Chemoreduction treatment needs trained personnel, sophisticated equipment for local therapy among others [7] all which are not always available in developing countries, so publications are relatively scarce [8–10]. This particular situation needs to be addressed in order to make treatment strategy decisions relevant to each setting. Thus, the paradigm for abandoning EBRT, which is highly efficacious for conservative therapy of retinoblastoma, based on the potentially lower long-term toxicity of chemotherapy-based regimens may not be so clear in middle income countries because of the relative weight of the above-mentioned problems. To our knowledge, no report from a large cohort, even including referral centers in developed countries, have compared the results of conservative therapy with EBRT and that of chemoreduction.

Thus, the aims of this study were to analyze patient outcome and ocular survival in patients with bilateral retinoblastoma treated with chemoreduction compared to EBRT in a large referral center in Argentina.

METHODS

Setting

The Hospital JP Garrahan is a tertiary care public pediatric center and all treatments are subsidized by the Government or social security and are free of charge for all patients except for brachytherapy, which was only available for insured patients. However, there were many intervals where the availability of local therapies such as lasers was limited because of lack of equipment. Approval from our Human Investigations Committee was obtained for this study.

Patients

All patients with bilateral retinoblastoma registered and treated at our center from January 1988 to December 2009 were included. In the first two eras, the Reese–Ellsworth (RE) classification [11] was used for extent of intraocular disease evaluation and replaced by the International Classification (original version [12]) in the third era. For this study, the clinical charts were retrospectively reviewed

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and each eye was re-classified according to the International Classification based upon fundoscopy drawings. Outcome was analyzed according to the International Classification.

Conservative Treatment

It was divided into three eras:

1. January 1988 to April 1995: All group E and most group D eyes were initially enucleated and those with groups A–C disease were given upfront EBRT using a lens-sparing technique delivering 45 Gy through a 10 MeV linear accelerator [13].
2. May 1995 to April 2003: In this era, chemoreduction therapy was introduced. Those tumors that could not be controlled with chemoreduction and local therapy, received EBRT at the same dose and fields and those failing EBRT were enucleated. The decision of conservation of an affected eye with EBRT was also influenced by the status of the contralateral eye, so that children with a fellow eye with less advanced disease were usually enucleated without receiving EBRT. No second line chemotherapy regimen was available and no local chemotherapy was used. The number of cycles was not fixed and chemotherapy was stopped when tumors became inactive as per ophthalmological criteria. All E eyes were enucleated initially and the decision of attempting conservative therapy for group D eyes was made individually, depending on the status of the contralateral eye and the disease extension.
3. May 2003 to December 2009: The same strategy of the second era was followed for less advanced eyes. For group D eyes, upfront periocular chemotherapy with carboplatin or topotecan concomitantly with chemoreduction in the first 3–4 cycles was given. In these children, the number of cycles of systemic chemotherapy was fixed to 6 and EBRT was used as consolidation in most cases. All eyes of group E were enucleated upon diagnosis, however, those presenting with glaucoma and buphthalmia received neo-adjuvant therapy followed by secondary enucleation and adjuvant therapy regardless of the pathology report. These children received a more intensive chemotherapy regimen [14].

Extent of Disease Evaluation

In the first two eras, all children underwent a brain and orbit contrast-enhanced CT scan which was gradually replaced by standard MRI for all patients in the third one. Bone marrow aspiration and CSF examination were done in all patients in the first era and limited to high risk patients (but including biopsy of two sites) from the second one onwards [15].

Chemotherapy Treatment

The chemoreduction regimen was tailored to disease extension including carboplatin 18.7 mg/kg (or 500 mg/m^2 for children weighing more than 12 kg) on Day 1 with vincristine 0.05 mg/kg (or 1.5 mg/m^2 for children weighing more than 12 kg, maximum dose 2 mg) for children with eyes of the R-E I–III. Etoposide at a dose of 3.3 mg/kg/day (or 100 mg/m^2 for children weighing more than 12 kg) (Days 1 and 2) was added for those with groups IV and V and those eyes with groups I–III that failed to be controlled with two cycles of the vincristine and carboplatin combination [10]. In treatment era 3, all children with group D eyes that underwent conservative therapy received periocular injections of 20 mg of carboplatin (2003–2008) which was replaced by topotecan (2 mg) after a phase I study was completed (2008–2009). In both cases, periocular chemotherapy was started after the second cycle of intravenous chemoreduction and given for up to four doses administered after 7 days of each cycle of intravenous chemotherapy.

Adjuvant therapy was indicated when pathology risk factors were present after enucleation, both for eyes initially or secondarily enucleated. The following pathology risk factors were considered for adjuvant therapy: any degree of scleral invasion, most cases with postlaminar optic nerve involvement [16] and tumor at the resection margin of the optic nerve, who also received adjuvant orbital radiotherapy (45 Gy) up to the chiasm. The chemotherapy regimens used for adjuvant therapy were previously published [13,14,17].

Patient Follow-up

All patients were followed by our group at least until age 18. In all patients receiving chemotherapy, audiological evaluation was scheduled on a yearly basis from age 5 onwards for 3–5 years after that time. All surviving patients have at least one complete audiological evaluation.

Statistical Analysis

Contingency tables were constructed and chi-square or Fisher exact tests were used for categorical variables and Mann–Whitney test was used for continuous variables. Survival status was updated to August 2013. Curve comparison was done with the Log Rank Test (Mantel Cox).

RESULTS

During the study period, a total of 197 evaluable children with bilateral retinoblastoma were registered. Another 25 patients with bilateral retinoblastoma were seen at our center in this period, but they were considered not evaluable because they were second opinions of patients diagnosed and treated elsewhere. Two additional patients were diagnosed at our center, but opted for treatment at another institution. Out of the 197 evaluable children (Table I), 22 (11.3%) presented with unilateral tumors but had an asynchronic bilateral tumor. A total of 177 patients (89.8%) received conservative therapy to at least 1 eye and are analyzed for conservative therapy.

Initial Treatment

Bilateral enucleation was needed in nine cases (4.6%), conservative therapy to both eyes was attempted in 69 (35%) (58 with chemoreduction, 7 with bilateral EBRT, 4 with local therapy), initial unilateral enucleation and conservative therapy of the fellow eye was attempted in 105 cases (53.2%) (50 with chemoreduction, 40 with EBRT, 8 with local therapy, and 7 cases underwent initial enucleation and developed metachronous involvement in the fellow eye treated with local therapy). Thirty-two of the initially enucleated eyes presented pathology risk factors warranting adjuvant therapy (Table I) and 13 had a residual tumor in the resection margin of the optic nerve. Four patients with postlaminar optic nerve invasion and concomitant sclera invasion in the third era

TABLE I. Clinical Characteristics and Outcome According to Treatment Era

	First era (n = 68)	Second era (n = 46)	Third era (n = 83)	*P*
Age (mean) in months	13.4 (0.7–61)	15.8 (1–41)	13.3 (0–114)	NS
Follow-up in months (median, range)	202 (33–290)	157.3 (62–223)	71.5 (13–129)	ND
Family history	10 (14.7%)	4 (8.7%)	13 (15.7%)	NS
No. of patients with metastatic disease at diagnosis	2 (2.9%)	2 (4.3%)	4 (4.8%)	NS
Initial bilateral enucleation	4 (5.9%)	2 (4.3%)	3 (3.6%)	NS
Intraocular grouping	A–C = 62 D = 32 E = 42	A–C = 31 D = 39 E = 22	A–C = 64 D = 59 E = 43	NS
Conservative therapy attempted in at least 1 eye	59 (86.8%)	42 (91.3%)	76 (91.6%)	NS
% receiving chemotherapy	50.7%	93.5%	98.8%	<0.001
% receiving EBRT	84.6%	58.7%	68.7%	0.008
Age at the moment of EBRT (mean) in months	14 (2–61)	20.9 (8–55)	18.3 (5–47)	<0.001
Event description	- Second malignancy = 6 - Extraocular relapse = 3 - Metastatic-extraocular disease progression = 4	- Extraocular relapse = 3 - Death of toxicity = 1 - Second malignancy = 2 - Metastatic disease progression = 2	- Trilateral retinoblastoma = 3 - Metastatic disease progression = 3 - Second malignancy = 1 - Extraocular relapse = 1	
Patients with pathology risk factors in initially enucleated eyes warranting adjuvant therapy	PLONI = 8 Tumor at the resection margin of optic nerve = 11	PLONI = 9 Scleral invasion = 1 Tumor at the resection margin of optic nerve = 2	PLONI = 12 Scleral invasion = 2	ND

NS, Not significant; ND, not done; EBRT, external beam radiotherapy; PLONI, post-laminar optic nerve invasion.

received a more intensive regimen including higher dose carboplatin and etoposide alternating with cyclophosphamide, idarubicin, and vincrsitine [17]. These cases were not analyzed for chemotherapy toxicity. Twelve patients (6.1%) received neo-adjuvant therapy for the treatment of overt extraocular disease in eight and massive buphthalmia in four. Two patients (1%) received palliative care because of advanced metastatic disease.

Extent of Intraocular Disease at Diagnosis

Of the 177 children that underwent conservative therapy, 25 (14.1%) presented with both eyes belonging to the groups A–C, 58 (32.8%) had one eye group D and the fellow eye groups A–C, 48 (27.1%) had one eye group E and the fellow eye groups A–C, 19 (10.7%) had both eyes group D and 27 (15.3%) had one eye group D and the fellow eye group E. There were no significant differences according to treatment era (Table I).

Eye Preservation

At the time of this analysis, of a total of 162 living children in whom conservative therapy was attempted, 109 (67.3%) retain at least one eye with useful vision, 27 (16.7%) retain both eyes while 26 (16%) have undergone bilateral enucleation. The probability of eye preservation avoiding EBRT at 5 years for eyes belonging to the groups A–C at the latest two eras (n = 95) was 0.49 (95% CI 0.39–0.6) since many patients had to receive EBRT for the treatment of the fellow eye, usually of group D. In order to evaluate the preservation of eyes with less advanced disease treated with chemoreduction avoiding this confounding effect, we evaluated separately those patients presenting with both eyes of groups A–C (n = 16) and those with a fellow eye of group E that was enucleated initially (n = 25) together. The probability of avoiding EBRT at 5 years was 0.73 (95% CI 0.62 to 0.91) in this particular population. The 5-year probability of eye preservation according to treatment era and grouping of the enucleated eye is shown in Figure 1. For this estimation, all eyes from patients with no metastatic disease, including those initially enucleated were included.

Patient Survival

With a median follow-up of 115 months (range 31–290), the probability 5-year overall survival for the whole group was 0.94 (95% confidence interval (CI) 0.91–0.98%), with no significant differences among treatment periods.

Results of Pre-Enucleation Chemotherapy in Children With Buphthalmia

Four children presenting with massive buphthalmia received pre-enucelation chemotherapy. All of them showed regression of disease manifestations and were enucleated after 1–3 cycles of chemotherapy. Pathological examination of enucleated eyes include: complete necrosis in a case, post laminar optic nerve invasion in one case, prelaminar invasion in one case and focal choroidal invasion in the remaining one. All are alive and disease-free with a median follow-up of 72 months (range 31–120).

Description of Events

Extraocular relapse or progression occurred in 16 patients (8.1%). Nine of them had progression or relapse of metastatic disease present at diagnosis. Cases with non-metastatic disease that

had an extraocular relapse are described in Table II. Three children developed trilateral disease (1.5%) and two of them died despite treatment with high dose chemotherapy and autologous stem cell rescue. All of them belonged to the third era and had received chemotherapy before the occurrence of trilateral disease (Table III). Nine children had a secondary malignancy (Table III) (seven of them outside the radiotherapy field) and five of them died. One patient who was receiving adjuvant therapy because of tumor at the resection margin of the optic nerve, died as a consequence of chemotherapy toxicity because of sepsis during a neutropenic episode. An additional patient died of sepsis during therapy for metastatic retinoblastoma.

Chemotherapy Toxicity

Seventy-seven patients had no episode of fever and neutropenia during treatment and there was no significant differences between treatment era 2 and 3 and the occurrence of fever and neutropenia (5.7% of cycles in the second era vs. 6.8% in the third). There were a total of 18 severe documented infections and 10 patients required transfusion support. Two children had abnormal audiology evaluations but no therapeutic intervention was required.

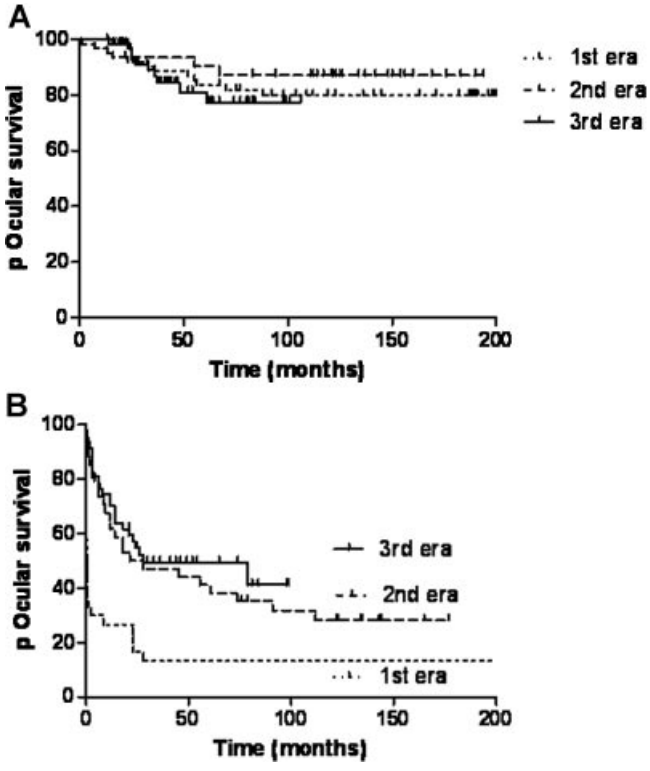

Fig. 1. Probability of ocular survival at 5 years according to group and treatment era (eyes of patients that died of toxicity or second malignancies are excluded). **A**: Groups A–C eyes. The probability of ocular survival at 5 years for the first treatment (n = 62) era was 0.83 (95% CI 0.71–0.9), for the second treatment era (n = 31) 0.9 (95% CI 0.73–0.97), and for the third treatment era (n = 62) 0.8 (95% CI 0.71–0.98). $P = 0.52$. **B**: Group D eyes. The probability of ocular survival at 5 years for the first treatment (n = 30) era was 0.13 (95% CI 0.04–0.27), for the second treatment era (n = 34) 0.38 (95% CI 0.23–0.54), and for the third treatment era (n = 47) 0.49 (95% CI 0.34–0.62); $P < 0.0001$.

DISCUSSION

While the introduction of systemic chemoreduction in our program did not affect overall or disease-free survival, it significantly reduced the use of EBRT for the treatment of eyes with less advanced disease, improved the preservation rate of eyes with more advanced disease and delayed the use of EBRT in those children requiring it.

The 5-year disease-free survival rate of children with bilateral retinoblastoma has been over 90% for the past two decades in our center [13,14] and the introduction of chemoreduction did not make a significant change in survival results. Despite the suggestion that chemoreduction may have a positive effect in preventing systemic metastasis in high risk children because systemically-administered chemotherapy would be useful to manage microscopically disseminated disease [18], no such effect was evident in our population. In the EBRT era, 28 patients were managed without receiving chemotherapy and no extra-ocular relapse was seen. In fact, extraocular relapse only occurred in children already identified as high risk who were receiving chemotherapy for residual tumor in the optic nerve. According to our data, additional protection is not apparent if adjuvant therapy is tailored to pathology risk factors of the enucleated eyes. In our population, the major differences in the occurrence of extraocular relapse between the cohorts of EBRT treated and chemoreduction-treated patients are based on the possible prevention of the occurrence of a tumor residue in the retrolaminar optic nerve by the use of pre-enucleation chemotherapy [19] since this complication was possibly prevented by pre-enucleation chemotherapy in the third era. In our series, in four out of the seven patients developing extraocular relapse, the relapsed tumor originated from an eye that was treated with conservative therapy in families that did not accept timely enucleation of the affected eye. Our rate of refusal of 2.3% is relatively low for a developing country [20]. The use of chemoreduction-based regimens did not affect significantly the decision of acceptance of enucleation in our setting.

Although there is no evident advantage in the eye preservation rate, as reported from developed countries, children with less advanced disease were significantly less likely to receive EBRT if chemoreduction was given. However, EBRT was used more frequently in our setting, probably because it was needed for a contralateral group D eye, or by lack of availability of brachytherapy or laser therapy or when problems of follow-up were anticipated and EBRT was felt to be a safer alternative. Hence, when only those eyes with bilaterally less advanced disease or those with an enucleated fellow eye were evaluated, the use of EBRT was only slightly higher than the reported international figures which are in the range of 20% [21].

Our patient cohort includes a substantial number of children presenting with bilaterally advanced disease with high risk of blindness, thus in this population we felt it was justified to introduce periocular chemotherapy and consolidation with EBRT upfront in our third era. A favorable impact of chemoreduction for eyes with advanced disease of group D was evident. However, even though the preservation rate at 5 years doubled that of EBRT alone, the occurrence of late relapses or ocular complications leading to enucleation narrowed these differences in the long term and we could not definitely determine the positive long-term effect of this treatment in this cohort.

TABLE II. Description of Extraocular Relapses in Non-Metastatic Patients

Patient (era)	Event	Treatment received for retinoblastoma	Outcome	Comment
6 (2)	Extraocular relapse form an eye treated with conservative intent	Chemoreduction and EBRT	Orbital progression, CNS extension and death after treatment with high dose chemotherapy and ASCR	Family initially declined enucleation of second eye and was treated elsewhere. Came back with orbital disease
7 (2)	Extraocular relapse form an eye treated with conservative intent	Chemoreduction and EBRT	Orbital progression followed by CNS extension and death	Family refused bilateral enucleation
49 (2)	Extraocular relapse form an eye treated with conservative intent	Chemoreduction and EBRT Orbital exenteration after an orbital relapse	Orbital relapse, CNS extensión and death	Patient showed chemoresistance from the diagnosis
54 (1)	Extraocular relapse form an eye treated with conservative intent	Enucleation and EBRT of the fellow eye	Orbital progression followed by CNS extension and death	Family abandoned treatment
78 (1)	Extraocular relapse form an enucleated eye	Bilateral enucleation, adjuvant EBRT and chemotherapy	CNS metastasis	CNS relapse and death
191 (1)	Extraocular relapse form an enucleated eye	Enucleation, adjuvant EBRT and chemotherapy	CNS metastasis	Temporary abandonment followed by CNS relapse
197 (3)	Extraocular relapse form an eye treated with conservative intent	Initial chemoreduction to both eyes, EBRT and enucleation	CNS metastasis	Death during a septic episode

TABLE III. Description of Secondary Malignancies and Trilateral Retinoblastoma

Patient (era)	Second malignancy	Retinoblastoma treatment	Lag time[a]	Treatment for second malignancy/trilateral	Outcome
26 (1)	Lower limb osteosarcoma	Enucleation-EBRT[c]	10 years	Chemotherapy-surgery	Alive and disease-free for 10 years
41 (2)	AML	Enucleation-EBRT[c] Chemotherapy[d]	3 months	Chemotherapy	Dead of progressive disease
48 (1)	Lower limb Ewing sarcoma (metastatic)	Enucleation-EBRT[c]	5 years	High dose chemotherapy and autologous stem cell rescue	Dead of progressive disease
51 (1)	Spinal ependymoma	Enucleation-EBRT[c] Chemotherapy[e]	12 years	Surgery	Alive and disease-free for 3 years
79 (1)	Soft tissue sarcoma	EBRT to both eyes	19 years	Surgery chemotherapy	Dead of progressive disease
82 (1)	Hemispheric low grade glioma	Enucleation, chemotherapy[d] and EBRT[c]	6 years	Surgery	Alive and disease-free for 7 years
92 (1)	Upper limb osteosarcoma	Enucleation, chemotherapy[d] and EBRT[c]	17 years	Chemotherapy and surgery	Alive and disease-free for 1 year
154 (3)	AML[b]	Chemotherapy[e] and EBRT	2 years	Chemotherapy	Dead of progressive disease
45 (2)	AML	Neoadjuvant chemotherapy[e], EBRT[c], bilateral enucleation	2 years	Chemotherapy	Dead of progressive disease
142 (3)	Trilateral	Initial bilateral enucleation adjuvant chemotherapy[f]	19 months	High dose chemotherapy and ASCR	Dead of progressive disease
182 (3)	Trilateral	Chemotherapy[e] and EBRT	15 months	High dose chemotherapy and ASCR	Dead of progressive disease
196 (3)	Trilateral	Initial enucleation, chemotherapy[e]	8 months	Conventional chemotherapy	Alive with disease

ASCR, Autologous stem cell rescue. [a]Lag time was defined as the interval between the date of diagnosis of retinoblastoma and that of a second malignancy or trilateral disease; [b]A molecular re-arrangement of the 11q23 MLL gene was detected; [c]EBRT: External beam orbital radiotherapy (45 Gy) up to the chiasma; [d]Chemotherapy for extraocular disease; [e]Chemoreduction; [f]Adjuvant chemotherapy because of pathology risk factors.

The acute toxicity of chemoreduction regimens was manageable and no toxic death was attributed to them. The patients that died because of septic complications in our cohort had extraocular disease and were receiving a more intensive regimen. Severe, life-threatening complications occurred in less than 10% of the cases receiving standard chemoreduction, but even though they were managed successfully by our team, the situation may not be similar in other settings with less resources and experience since toxic mortality has been reported in children receiving standard chemoreduction [9]. Significant ototoxicity was evident in less than 2% of the cases and no other unexpected toxicity occurred.

The occurrence of chemotherapy-induced acute leukemias is an uncommon but potentially fatal complication of chemoreduction [22]. Second to sarcomas, AML accounted for one third of the cases of secondary tumors and about two-thirds of the fatalities for second malignancies in our cohort. Individuals with germline Rb1 mutations do not show an increased susceptibility for AML and most reported cases are therapy-related [22]. In one of our cases, MLL rearrangements were detected, linking it to etoposide but the relationship with chemotherapy exposure is more difficult to determine in the remaining two children [23]. The overall rate of secondary malignancies was relatively low in our population and only two irradiated children had secondary malignancies in the irradiation field, which may be influenced by the relatively short follow-up. The mortality of children affected with secondary solid tumors was lower than those with secondary leukemias. There are scant data about secondary malignancies in children with retinoblastoma treated with chemoreduction. Turaka et al. [24] reported that 4% of their 187 cases with retinoblastoma and germ line mutations developed a secondary malignancy, which is comparable to our data if our complete cohort is considered. Thus, no definitive conclusions on the comparative effect of chemotherapy on secondary malignancies can be elicited from our data. As previously reported, children receiving chemotherapy and radiotherapy appear to be at higher risk for second malignancies as those receiving either of these alone. Since EBRT could be significantly delayed in children receiving chemoreduction, radiation-induced tumors may be less common since an age-dependent effect was reported for the mutagenic potential of EBRT in these children [25].

The occurrence of trilateral retinoblastoma was 1.5% in our series, which is in line with current estimations [26,27] but lower than previous studies from other groups that reported an incidence of 6–15% [28,29]. The apparent reduction in the number of trilateral cases in recent years was attributed to a potential protective effect of chemotherapy [30]. Shields et al. [30] reported that none out of 99 susceptible cases treated with chemotherapy developed trilateral disease, compared to 1 case in 18 in susceptible children without chemotherapy exposure. In our series, 3 of 159 children who received chemotherapy developed trilateral disease, compared to 0 of 38 that did not receive chemotherapy, which may suggest the opposite. It may be argued that some cases with trilateral retinoblastoma might have been missed in our initial series when only CT scans were done for extent of disease evaluation. However, all cases that died of CNS dissemination of retinoblastoma in our first era had received chemotherapy and no CNS event occurred in any other case not receiving chemotherapy. The evaluation of our cases that died of CNS events was not consistent with pineal or sellar masses but from progression via the optic nerve in children with tumor at the resection margin. Since trilateral retinoblastoma is fatal without therapy [29], it is very unlikely that these cases were missed. Our hypothesis is that given the low prevalence of trilateral retinoblastoma, the possible role of chemotherapy in its prevention or induction cannot reliably be supported from the available data based on relatively low numbers, requiring a much larger cohort to confirm any of these hypothesis.

To conclude, the implementation of a program of systemic chemoreduction was feasible and associated with manageable toxicity in our setting. It was effective in significantly reducing the use of EBRT in eyes with less advanced tumors. For patients with more advanced disease, there was a significant increase in the eye preservation rate compared to EBRT, but the addition of periocular chemotherapy followed by consolidation with EBRT did not significantly increased eye preservation.

REFERENCES

1. Kingston JE, Hungerford JL, Madreperla SA, et al. Results of combined chemotherapy and radiotherapy for advanced intraocular retinoblastoma. Arch Ophthalmol 1996;114:1339–1343.
2. Murphree AL, Villablanca JG, Deegan WF III, et al. Chemotherapy plus local treatment in the management of intraocular retinoblastoma. Arch Ophthalmol 1996;114:1348–1356.
3. Shields CL, Mashayekhi A, Cater J, et al. Chemoreduction for retinoblastoma. Analysis of tumor control and risks for recurrence in 457 tumors. Am J Ophthalmol 2004;138:329–337.
4. Shields CL, Mashayekhi A, Au AK, et al. The International Classification of Retinoblastoma predicts chemoreduction success. Ophthalmology 2006;113:2276–2280.
5. Marr BP, Dunkel IJ, Linker A, et al. Periocular carboplatin for retinoblastoma: Long-term report (12 years) on efficacy and toxicity. Br J Ophthalmol 2012;96:881–883.
6. Gobin YP, Dunkel IJ, Marr BP, et al. Intra-arterial chemotherapy for the management of retinoblastoma: Four-year experience. Arch Ophthalmol 2011;129:732–737.
7. Wilson MW, Haik BG, Rodriguez-Galindo C. Socioeconomic impact of modern multidisciplinary management of retinoblastoma. Pediatrics 2006;118:e331–e336.
8. Antoneli CB, Ribeiro KC, Steinhorst F, et al. Treatment of retinoblastoma patients with chemoreduction plus local therapy: Experience of the AC Camargo Hospital, Brazil. J Pediatr Hematol Oncol 2006;28:342–345.
9. Naseripour M, Nazari H, Bakhtiari P, et al. Retinoblastoma in Iran: Outcomes in terms of patients' survival and globe survival. Br J Ophthalmol 2009;93:28–32.
10. Chantada GL, Fandino AC, Raslawski EC, et al. Experience with chemoreduction and focal therapy for intraocular retinoblastoma in a developing country. Pediatr Blood Cancer 2005;44:455–460.
11. Reese AB, Ellsworth RM. The evaluation and current concept of retinoblastoma therapy. Trans Am Acad Ophthalmol Otolaryngol 1963;67:164–172.
12. Linn Murphree A. Intraocular retinoblastoma: The case for a new group classification. Ophthalmol Clin North Am 2005;18:41–53, viii.
13. Schvartzman E, Chantada G, Fandino A, et al. Results of a stage-based protocol for the treatment of retinoblastoma. J Clin Oncol 1996;14:1532–1536.
14. Chantada G, Fandino A, Davila MT, et al. Results of a prospective study for the treatment of retinoblastoma. Cancer 2004;100:834–842.
15. Chantada GL, Rossi J, Casco F, et al. An aggressive bone marrow evaluation including immunocytology with GD2 for advanced retinoblastoma. J Pediatr Hematol Oncol 2006;28:369–373.
16. Chantada GL, Casco F, Fandino AC, et al. Outcome of patients with retinoblastoma and postlaminar optic nerve invasion. Ophthalmology 2007;114:2083–2089.
17. Chantada GL, Fandino AC, Guitter MR, et al. Results of a prospective study for the treatment of unilateral retinoblastoma. Pediatr Blood Cancer 2010;55:60–66.
18. Shields CL, Kaliki S, Rojanaporn D, et al. Intravenous and intra-arterial chemotherapy for retinoblastoma: What have we learned? Curr Opin Ophthalmol 2012;23:202–209.
19. Bellaton E, Bertozzi AI, Behar C, et al. Neoadjuvant chemotherapy for extensive unilateral retinoblastoma. Br J Ophthalmol 2003;87:327–329.
20. Bakhshi S, Gupta S, Gogia V, et al. Compliance in retinoblastoma. Indian J Pediatr 2010;77:535–540.
21. Shields CL, De Potter P, Himelstein BP, et al. Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthalmol 1996;114:1330–1338.
22. Gombos DS, Hungerford J, Abramson DH, et al. Secondary acute myelogenous leukemia in patients with retinoblastoma: Is chemotherapy a factor? Ophthalmology 2007;114:1378–1383.
23. Sampor C. Secondary acute myeloblastic leukemia in a child who was treated with chemoreduction. In Oncopedia, Edition. 2009.
24. Turaka K, Shields CL, Meadows AT, et al. Second malignant neoplasms following chemoreduction with carboplatin, etoposide, and vincristine in 245 patients with intraocular retinoblastoma. Pediatr Blood Cancer 2012;59:121–125.
25. Abramson DH, Frank CM. Second nonocular tumors in survivors of bilateral retinoblastoma: A possible age effect on radiation-related risk. Ophthalmology 1998;105:573–579, discussion 579–580.
26. Ramasubramanian A, Kytasty C, Meadows AT, et al. Incidence of pineal gland cyst and pineoblastoma in children with retinoblastoma during the chemoreduction era. Am J Ophthalmol 2013;156:825–829.
27. Antoneli CB, Ribeiro Kde C, Sakamoto LH, et al. Trilateral retinoblastoma. Pediatr Blood Cancer 2007;48:306–310.
28. Kivela T. Trilateral retinoblastoma: A meta-analysis of hereditary retinoblastoma associated with primary ectopic intracranial retinoblastoma. J Clin Oncol 1999;17:1829–1837.
29. Blach LE, McCormick B, Abramson DH, et al. Trilateral retinoblastoma—Incidence and outcome: A decade of experience. Int J Radiat Oncol Biol Phys 1994;29:729–733.
30. Shields CL, Meadows AT, Shields JA, et al. Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral retinoblastoma). Arch Ophthalmol 2001;119:1269–1272.