INTRA-ARTERIAL CHEMOTHERAPY IS MORE EFFECTIVE THAN SEQUENTIAL PERIOCULAR AND INTRAVENOUS CHEMOTHERAPY AS SALVAGE TREATMENT FOR RELAPSED RETINOBLASTOMA

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ABSTRACT

BACKGROUND: There are few options for retaining an eye with retinoblastoma failing systemic chemoreduction and external beam radiotherapy. This study was done to compare the efficacy and toxicity of intra-arterial ophthalmic artery chemotherapy (IAO) to our historical cohort of sequential periocular and systemic chemotherapy in such patients.

PATIENTS AND METHODS: Eighteen eyes (15 consecutive patients) were retrospectively evaluated. Eight eyes received IAO for a median of 4 cycles (range 2 to 9) including melphalan alone (n=3) or after topotecan and carboplatin (n=4) or topotecan and carboplatin without melphalan (n=1). Ten eyes received a median of 2 cycles (range 1 to 3) of periocular topotecan (n=9) or carboplatin (n=1) followed by intravenous topotecan and cyclophosphamide in 3 patients if at least stable disease was achieved. Both groups were comparable in terms of disease extension and prior therapy.

RESULTS: No extraocular dissemination or second malignancy occurred and all patients are alive. The probability of enucleation-free survival at 12 months was 0.87 for the IAO group, compared to 0.1 for the periocular group ($p<0.01$). Ocular toxicity was mild and similar in both groups (mostly mild orbital edema). Systemic toxicity was low for IAO and periocular injection, but children who received sequentially intravenous chemotherapy (n=12 cycles) had 5 episodes of grade IV neutropenia, 3 of which resulted in hospitalizations. No case in the IAO group presented these complications.

CONCLUSIONS: IAO is significantly superior to sequential periocular-intravenous topotecan-containing regimens in eyes with relapsed intraocular retinoblastoma with a more favorable toxicity profile.

INTRODUCTION

Treatment of advanced retinoblastoma relapsing after failure of systemic chemoreduction and focal therapies traditionally included external beam radiotherapy (EBRT) [1] that may rescue up to 83% of affected eyes. However, when tumor relapses after EBRT, the treatment is more challenging and most cases are ultimately enucleated [2]. Cases with vitreous relapse [3] or those whose tumors are not amenable for local therapy are difficult to cure and most these eyes ultimately need enucleation. There are mostly anecdotal reports on treatment options for these eyes, including a second course of irradiation [2] the same drugs with different schedule[4] or second line chemotherapy with non-cross resistant agents[5, 6], usually administered peri-ocularly in order to prevent long term toxicity attributable to prolonged chemotherapy exposure[7]. Intravitreal injection of chemotherapy was recently reported as effective for eyes with relapsed-resistant vitreous seeding but the cases reported were not given EBRT [8].

The Rb1 gene germinal mutation carried by these patients predisposes them to secondary malignancies, which are critically influenced by the treatment received (chemotherapy and radiotherapy)[9], so every effort to protect them from this by reducing the exposure to potentially carcinogenetic treatments should be done. This is especially important since enucleation of the affected eye would be curative. However, when the eye in treatment is the single remaining eye or when both eyes are in the same situation, the need of eye and visual preservation becomes critical. Patients with bilateral retinoblastoma in our setting present more frequently with advanced disease [10, 11], so in Argentina this dilemma is faced more often than in North America.

In order to find alternatives for the treatment of these eyes, our group evaluated the activity of periocular topotecan in a phase 1 trial including eyes that had failed systemic chemoreduction and EBRT[7]. This study was completed in 2008[7] but even though the drug proved to be safe, the results in terms of eye preservation were disappointing [7]. The use of periocular carboplatin was equally ineffective as salvage therapy[12]. In recent years, after the introduction of superselective intra-arterial administration of

chemotherapy via the ophthalmic artery (IAO), our group explored this treatment for salvage of eyes failing chemoreduction and EBRT. This technique was developed initially by the New York group for the treatment of children with unilateral disease needing enucleation as first line therapy [13], but subsequent reports showed that it may be active also as second-line therapy [14-16]. The use of IAO sparked intense controversies among the major retinoblastoma treatment groups [17, 18] and even though it has been performed in developing countries[18], its indications in that setting may be controversial. However, because of the lack of effective options for the salvage of eyes failing chemoreduction and EBRT, our group decided that it was justified to introduce IAO as a pilot program for salvage therapy in 2010. The results of this treatment and its comparison with our previous schedule including periocular chemotherapy followed by systemic chemotherapy in terms of efficacy and toxicity are the basis of this report.

PATIENTS AND METHODS

Children with bilateral retinoblastoma who received standard intravenous chemoreduction with 3 agents including carboplatin, etoposide and vincristine [10] and subsequently needed EBRT for tumor control and relapsed after both modalities are the subject of this report. Those patients in whom local therapy, (cryotherapy, laser or plaque radiotherapy) could be administered as the sole treatment of relapse were not included. Extraocular dissemination was ruled out by head and orbit MRI or CT scan, but no bone marrow or cerebrospinal fluid examination was done routinely. Written informed consent was obtained from all cases and the study was done in accordance with the Declaration of Helsinki.

Two treatment modalities were evaluated:

1) Sequential periocular chemotherapy followed by intravenous chemotherapy: This modality was used from November 2005 to May 2009 and children received periocular topotecan at a dose ranging from 0.5 to 2 mg as described in detail in a previous publication [7] or carboplatin at 20 mg according to a previously reported technique[19]. In this cohort, if the disease could not be controlled by local therapy after periocular chemotherapy but at least disease stabilization was achieved, intravenous chemotherapy including topotecan alone at a dose of 2 mg/m2/day (days 1 to 5) or combined with cyclophosphamide 250 mg/m2/day (days 1 to 5) was offered. In the latter the dose of topotecan was 0.75 mg/m2/day (days 1 to 5).
2) Intra-arterial chemotherapy: This modality was used from July 2010 onwards and children received melphalan (dose adjusted by age)[14] alone or after topotecan (1 mg) or the combination of topotecan (1 mg) and carboplatin (30 mg). The drug was chosen according to availability. The technique for IAO was based on previously reported data from Abramson et al with no modifications [13]. No other chemotherapy was attempted after IAO and cases with progressive disease were enucleated. No bilateral infusions were done.

In both cases, focal therapy was done after effective chemoreduction and chemotherapy was stopped when responding tumors were judged to be inactive or controllable by local therapy by the treating ophthalmology group. Each drug administration was done 3 to 4 weeks apart and each patient was examined under anesthesia every 3 to 4 weeks.

A retrospective chart review was done and the main outcome measures of this study were tumor control and eye retention rates at 1 year and patient survival. A comparison between the toxicity of both treatments was also done. Actuarial enucleation-free survival was calculated by the Kaplan-Meier method from the day salvage therapy started to the day of enucleation or day of last visit. Differences between treatment groups were calculated with the log rank test. The Mann-Whitney test was used for comparing continuous variables. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 3.

RESULTS

A total of 18 eyes from 15 patients were included. Clinical and demographic characteristics of children included in both treatment strategies are shown in Table I.

Treatment and response

Periocular group: Seven patients (10 eyes) were included in this group. Nine eyes received a median of 2 (range 1 to 3) applications of periocular topotecan and 1 received an application of periocular carboplatin as salvage therapy. Five eyes were enucleated because of progressive disease soon after periocular chemotherapy and the remaining five eyes had at least stable disease. One of them that received periocular topotecan was given further focal therapy and was saved (follow-up of 59 months). The remaining 4 eyes (3 patients) were given sequential intravenous chemotherapy for treatment with the combination of topotecan and cyclophosphamide for 4 cycles and all of them were ultimately enucleated after this treatment. Pathological examination of enucleated eyes showed no major pathology risk factors except for one case with intra-scleral involvement who received adjuvant chemotherapy and another eye with postlaminar optic nerve involvement but no adjuvant chemotherapy was given. No extraocular relapse or second malignancy occurred and all patients are alive with a median follow up of 74 months (range 65 to 97 months) from disease diagnosis.

Intra-arterial group: Eight patients (8 eyes) received this treatment. Catheterization of the ophthalmic artery was successful in all cases. The median number of cycles was 4, range 2 to 9. The drugs used included melphalan alone (n=3) or after topotecan and carboplatin (n=4). For these eyes, the combination of topotecan and carboplatin was given initially, followed by single agent melphalan as it became available in our setting. In the remaining eye, no melphalan was given and the child received only topotecan and carboplatin. All eyes responded to treatment and were given local therapy with laser ablation in 5, and Iodine^{125} plaque radiotherapy in 3. Two eyes were enucleated because of relapse at 5

and 14 months after IAO, the remaining ones were saved with a follow-up (median follow up time is 21.5 months, range 18 to 24). One patient is blind because of bilateral enucleation. One of the enucleated eyes had received single agent melphalan and the other the combination of carboplatin and topotecan. Pathology examination showed no pathology risk factor in one case and intra-scleral invasion in the remaining one and adjuvant chemotherapy was given. No extraocular relapse or second malignancy occurred and all patients are alive with a median follow up of 30 months (range 24 to 84) from disease diagnosis.

The probability of ocular survival at 12 months was 0.1 (95% confidence interval 0.06 to 0.35) for the periocular group and 0.87 (95% confidence interval 0.42 to 0.97) for the intra-arterial group (Figure 1) ($p<0.01$)

Toxicity

There were no toxic deaths in any group. No child had a second malignancy.

Periocular group: There was no episode of neutropenia following periocular chemotherapy. Six eyes from 6 patients had orbital edema and no other ocular or systemic complications were recorded at this phase of therapy. However, 5 episodes of grade 4 neutropenia occurred after systemic chemotherapy administered sequentially. Three of these episodes resulted in patient admission to the inpatient facility because of sepsis in one case and urinary tract infection and fever without localizing signs in the remaining two. No children needed transfusion support. No other grade 3 or higher toxicity was recorded.

Intra-arterial group: No neurological or thrombotic event occurred. Two patients had orbital edema, resolving spontaneously. In one child, it was associated to retinal vasculitis and resolved with steroids. One child had optic nerve edema with decreased visual acuity that resolved with steroid therapy. There was no episode of grade 4 neutropenia or fever and neutropenia in this group and no patient had to be admitted because treatment complications. No transfusion was necessary. No grade 3 or higher toxicity occurred in any organ.

DISCUSSION

In this first reported series of patients treated with IAO from a developing country, we found that this modality may save eyes failing chemoreduction, focal therapy and EBRT and it is significantly more effective and less toxic than our previous schema of periocular chemotherapy followed by sequential systemic chemotherapy.

The treatment of eyes that relapsed or progressed after 3-drug chemoreduction with standard carboplatin, etoposide and vincristine typically involved EBRT when cases are not amenable to focal therapy if attempts to preserve the eye are to be undertaken[1]. Relapse may involve the tumor, vitreous or subretinal seeds or a combination of them and a proportion of these eyes can be saved. However, when the disease further progresses or relapses after EBRT, the results are dismal and there are few options for treatment. Attempts to save these eyes are only justified in single remaining eyes after enucleation of the fellow eye or when both eyes are similarly affected and useful vision is possible. These are heavily pretreated patients in whom potentially carcinogenetic therapy has been already administered and treatment should balance the likelihood of preserving the eye without increasing the risk of extraocular dissemination while trying to minimize the long term side effects of the treatments administered. In this context, our approach from 2005 to 2009 was to explore innovative therapies by including these patients in investigational trials that included the use of periocular chemotherapy using mostly topotecan, which would be a non-cross resistant agent with a low likelihood of inducing secondary malignancies. Responding patients, based on our previous experience with intravenous topotecan where an encouraging response rate was found[5], were offered sequential treatment with intravenous topotecan combined with cyclophosphamide in an attempt to deliver a higher dose of effective chemotherapy by administering the drug over 5 consecutive days. Cyclophosphamide was added in an attempt to provide exposure to an active agent[20], not used for initial treatment that could have an additive effect with topotecan as seen in other related malignancies[21]. This therapy was not effective as salvage of these eyes since only 1 out of

10 eyes was preserved and disease progressed within the first year of therapy in most cases. However, after the introduction of IAO, encouraging clinical data on ocular preservation were reported [13]and preclinical studies from our group showed an 8-fold increase in vitreous exposure of IAO compared to periocular topotecan[22]. So we started our pilot IAO program by treating these patients with the hope that increased chemotherapy levels would improve tumor control. IAO achieved a notable activity by inducing tumor responses in all cases which made it possible to administer focal therapy resulting in eye preservation in 6 of 8 cases. Our results, though encouraging should not be taken as definitive since follow up is still short and the patient population is limited. However, in our previous experience, tumor progression occurred within the first year in all cases and all the eyes treated with IAO have more than 1 year follow up. However, the possibility of late relapses should not be underestimated. This modality was reported previously for a limited number of eyes failing chemoreduction and EBRT[14, 15]. Thus, the New York group reported that when IAO is used a secondary treatment, the eye preservation rate was 58.4% at 2 years, including a cohort of 15 eyes that had received chemoreduction with 3 agents and EBRT that was comparable to our population[14]. In their analysis, most of the patients that relapsed or progressed did so within the first year. Median follow-up of their cohort was 13 months. Muen et al reported a series of 15 eyes in 14 patients treated with IAO melphalan, including 3 patients comparable to our population with a median follow-up of 8 months for their entire cohort[15]. Their results were also encouraging since 2 of their 3 eyes could be preserved. Shields at al reported 4 eyes treated with IAO for secondary therapy but none of their cases had received EBRT before IAO[23].

A limitation of our study and from other published reports is the lack of consistency of the drugs and dosages used. This was our first experience with IAO and melphalan was not readily available for this treatment in Argentina. Thus, topotecan was favored as the initial drug in the first cohort, but as melphalan became available, we introduced it for this indication following the published dosages[14]. Based on our preclinical work, and considering that these patients would need a high exposure to the drug because our poor results with periocular and intravenous topotecan was disappointing, we used a dose of

1 mg of topotecan which is higher than that used by the New York group that recommends up to 0.4 mg. We did not perform electroretinograms as surrogate for retinal drug toxicity which was found by the New York group as a potential marker of topotecan retinal toxicity, so it is not possible to evaluate this phenomenon in our population. No clinical evidence of permanent retinal toxicity was found in our cohort, however more detailed studies including electroretinograms or other modalities may be necessary. However, it would be difficult to estimate the role of each of the multiple treatments in the occurrence of ocular toxicity in these heavily pretreated eyes. Systemic toxicity was also minimal regardless of the regimen used, which concurs with all previous reports [13-15, 24, 25]. Ocular toxicity was also comparable between both groups. Self-limiting orbital edema was noted in our cohort of both periocular administration and IAO. Functional outcome is also satisfactory with IAO since all 5 patients with their single remaining eye treated with this modality retain useful vision. Systemic toxicity was also very low in both cohorts for periocular and IAO, but since periocular chemotherapy was followed by sequential systemic chemotherapy, that cohort had a significantly higher systemic toxicity, including grade IV neutropenia, which lead to life-threatening infections requiring hospitalization in about half of them. Thus, the toxicity profile clearly favors IAO in this population. Another concern of eye preservation of heavily pretreated and potentially chemoresistant tumors is the possibility of extraocular relapse[26]. None of our patients developed extraocular relapse in either cohort, however, 2 patients had high risk pathology features warranting adjuvant therapy (1 in each cohort). The pathology features of enucleated eyes after failure of IAO reported features consistent with thrombotic events but no increased risk of optic nerve or choroidal invasion compared to other modalities[27, 28]. Another limitation of our study is its retrospective design, so even though all cases relapsing after chemoreduction and EBRT were included, there may be differences in their likelihood of salvage depending on the tumors features. Our results in these heavily pretreated eyes failed to show any distinctive feature.

IAO has been applied for many years for the treatment of retinoblastoma in Japan and that group reported their long term results showing that IAO did not increase the risk of secondary malignancies, which were

mostly associated to EBRT in their cohort[29]. Given its feasibility, high efficacy and low toxicity profile in our setting, our group introduced this treatment for rescue therapy in patients failing systemic chemoreduction before attempting EBRT, which has been unequivocally associated to long term side effects. Its use for the conservative treatment of advanced (Reese-Ellsworth Vb) unilateral retinoblastoma is not routinely recommended for patients in our group because of our high prevalence of pathology risk factors in initially enucleated eyes requiring adjuvant therapy[30]. If IAO were given to these patients at high risk of extraocular relapse that potentially harbor minimally disseminated disease, extraocular relapse may occur because of insufficient systemic chemoprophylaxis. In addition, despite reported previously in developing countries[31] IAO is a costly procedure needing high compliance with follow-up evaluations which may not always be possible in that setting. However, the higher cost associated to the procedure may be compensated by the high efficacy and the low toxicity profile since in our small cohort. Because of the lower doses utilized in IAO, the overall cost of chemotherapy drugs is also significantly lower for children receiving IAO.

There are few effective alternatives to IAO for this population. Encouraging results were recently reported from Switzerland with the use of intravitreal melphalan[8] resulting in preservation of 20 of 23 eyes with a median follow up of 22 months in a patient cohort of patients failing standard systemic chemoreduction and focal therapy but not receiving EBRT[8]. These results are comparable with our report, albeit our group of patients received EBRT for salvage before and they are therefore at higher risk of failure. Two of our patients had received intravitreal melphalan before IAO with no response. However, the dose that we used was lower than that reported by the Swiss group. In any case, both options are not mutually exclusive and selected patients may benefit from both modalities.

To conclude, IAO chemotherapy administration was not only feasible in these high risk patients in our setting, but it was also associated to a better eye preservation rate and lower toxicity compared to sequential periocular and intravenous chemotherapy. Based on these results, our group is introducing this therapy earlier in patient management.

References

1. Chan MP, Hungerford JL, Kingston JE, Plowman PN. Salvage external beam radiotherapy after failed primary chemotherapy for bilateral retinoblastoma: rate of eye and vision preservation. Br J Ophthalmol 2009; 93: 891-894.
2. Abramson DH, Ellsworth RM, Rosenblatt M et al. Retreatment of retinoblastoma with external beam irradiation. Arch Ophthalmol 1982; 100: 1257-1260.
3. Gombos DS, Cauchi PA, Hungerford JL et al. Vitreous relapse following primary chemotherapy for retinoblastoma: is adjuvant diode laser a risk factor? Br J Ophthalmol 2006; 90: 1168-1172.
4. Dunkel IJ, Chantada GL, Fandino AC, Abramson DH. Lack of activity of oral etoposide for relapsed intraocular retinoblastoma. Ophthalmic Genet 2004; 25: 25-29.
5. Chantada GL, Fandino AC, Casak SJ et al. Activity of topotecan in retinoblastoma. Ophthalmic Genet 2004; 25: 37-43.
6. Leahey AM. Chemotherapy protocols. New Delhi: Jaypee Brothers Medical Publisher 2012.
7. Chantada GL, Fandino AC, Carcaboso AM et al. A phase I study of periocular topotecan in children with intraocular retinoblastoma. Invest Ophthalmol Vis Sci 2009; 50: 1492-1496.
8. Munier FL, Gaillard MC, Balmer A et al. Intravitreal chemotherapy for vitreous disease in retinoblastoma revisited: from prohibition to conditional indications. Br J Ophthalmol 2012.
9. Abramson DH. Second nonocular cancers in retinoblastoma: a unified hypothesis. The Franceschetti Lecture. Ophthalmic Genet 1999; 20: 193-204.
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. 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.
12. Marr BP, Dunkel IJ, Linker A, Abramson DH. Periocular carboplatin for retinoblastoma: long-term report (12 years) on efficacy and toxicity. Br J Ophthalmol 2012; 96: 881-883.
13. Abramson DH, Dunkel IJ, Brodie SE et al. A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. Ophthalmology 2008; 115: 1398-1404, 1404 e1391.
14. 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.
15. Muen WJ, Kingston JE, Robertson F et al. Efficacy and complications of super-selective intra-ophthalmic artery melphalan for the treatment of refractory retinoblastoma. Ophthalmology 2012; 119: 611-616.
16. Venturi C, Bracco S, Cerase A et al. Superselective ophthalmic artery infusion of melphalan for intraocular retinoblastoma: preliminary results from 140 treatments. Acta Ophthalmol 2012.
17. Levin MH, Gombos DS, O'Brien JM. Intra-arterial chemotherapy for advanced retinoblastoma: is the time right for a prospective clinical trial? Arch Ophthalmol 2011; 129: 1487-1489.
18. Abramson DH. Chemosurgery for retinoblastoma: what we know after 5 years. Arch Ophthalmol 2011; 129: 1492-1494.
19. Abramson DH, Frank CM, Dunkel IJ. A phase I/II study of subconjunctival carboplatin for intraocular retinoblastoma. Ophthalmology 1999; 106: 1947-1950.
20. Pratt CB, Kun LE. Response of orbital and central nervous system metastases of retinoblastoma following treatment with cyclophosphamide/doxorubicin. Pediatr Hematol Oncol 1987; 4: 125-130.
21. London WB, Frantz CN, Campbell LA et al. Phase II randomized comparison of topotecan plus cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: a Children's Oncology Group study. J Clin Oncol 2010; 28: 3808-3815.

22. Schaiquevich P, Buitrago E, Ceciliano A et al. Pharmacokinetic analysis of topotecan after superselective ophthalmic artery infusion and periocular administration in a porcine model. Retina 2012; 32: 387-395.
23. Shields CL, Bianciotto CG, Jabbour P et al. Intra-arterial chemotherapy for retinoblastoma: report No. 1, control of retinal tumors, subretinal seeds, and vitreous seeds. Arch Ophthalmol 2011; 129: 1399-1406.
24. Shields CL, Bianciotto CG, Jabbour P et al. Intra-arterial chemotherapy for retinoblastoma: report No. 2, treatment complications. Arch Ophthalmol 2011; 129: 1407-1415.
25. Vajzovic LM, Murray TG, Aziz-Sultan MA et al. Supraselective intra-arterial chemotherapy: evaluation of treatment-related complications in advanced retinoblastoma. Clin Ophthalmol 2011; 5: 171-176.
26. Chantada GL, Dunkel IJ, Antoneli CB et al. Risk factors for extraocular relapse following enucleation after failure of chemoreduction in retinoblastoma. Pediatr Blood Cancer 2007; 49: 256-260.
27. Vajzovic LM, Murray TG, Aziz-Sultan MA et al. Clinicopathologic review of enucleated eyes after intra-arterial chemotherapy with melphalan for advanced retinoblastoma. Arch Ophthalmol 2010; 128: 1619-1623.
28. Eagle RC, Jr., Shields CL, Bianciotto C et al. Histopathologic observations after intra-arterial chemotherapy for retinoblastoma. Arch Ophthalmol 2011; 129: 1416-1421.
29. Suzuki S, Yamane T, Mohri M, Kaneko A. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. Ophthalmology 2011; 118: 2081-2087.
30. 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.
31. Trinavarat A, Chiewvit P, Buaboonnam J et al. Selective Ophthalmic Arterial Infusion of Chemotherapeutic Drugs for Recurrent Retinoblastoma. J Pediatr Hematol Oncol 2012.