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Feasibility and results of an intraarterial chemotherapy program for the conservative treatment of retinoblastoma in Argentina

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Abstract

Background: The feasibility and results of intraarterial chemotherapy, also termed ophthalmic artery chemosurgery (OAC), for retinoblastoma in less developed countries have seldom been reported.

Procedure: A retrospective evaluation of a program of OAC in Argentina from 2010 to 2015.

Results: Ninety-seven eyes from 81 patients (61 bilateral) were analyzed. In 35 eyes, OAC was given as primary therapy and in 62 it was used for the treatment of tumors with partial response or those relapsing after systemic chemoreduction with focal therapy or external-beam radiotherapy. Twenty-two primarily treated eyes had group D and 13 groups B/C. A total of 400 procedures were carried out. Chemotherapy used included combinations of melphalan, carboplatin, and topotecan. There was no mortality associated with OAC. Toxicity included fever and neutropenia in five (1.25%), hypotension and bradycardia during anesthesia in two and femoral thrombosis in one, eyelid edema in nine, and neutropenia or thrombocytopenia in 28 cycles. With a median follow-up of 48.7 months (range 12–79), the 3-year probability of event-free survival (pEFS) (enucleation and/or radiotherapy were considered events) was comparable for patients who received first-line therapy and those treated at relapse (0.65 vs. 0.63, $P = 0.5$). In the former, the pEFS was 0.91 and 0.43 for groups B/C and D, respectively ($P = 0.01$). Two patients died of extraocular dissemination after refusal of enucleation.

Conclusions: OAC was feasible with low toxicity. pEFS improved in all groups compared to the previous experience with systemic chemotherapy reducing the use of radiotherapy. The overall mortality associated with OAC is comparable to our previous experience with systemic chemoreduction.

KEYWORDS

carboplatin, chemoreduction, conservative therapy, intraarterial chemotherapy, melphalan, retinoblastoma, topotecan

1 | INTRODUCTION

Intraarterial chemotherapy, also termed ophthalmic artery chemosurgery (OAC), has become a successful option for the conservative treatment of eyes with advanced retinoblastoma.[1–9] Systemic chemotherapy including carboplatin-based regimens, such as

Abbreviations: CEV, carboplatin–etoposide–vincristine; EBRT, external-beam radiotherapy; OAC, ophthalmic artery chemosurgery; pEFS, probability of event-free survival

carboplatin–etoposide–vincristine (CEV) and focal therapies, was previously used for chemoreduction in the conservative therapy of retinoblastoma to avoid the use of external-beam radiotherapy (EBRT).[10,11] Its results in cases of more advanced disease were not satisfactory. In our previous experience, up to 68% of patients of all groups still received EBRT.[12] EBRT is associated with increased risk of secondary malignancies resulting in higher morbidity and mortality later in life.[13] A relatively high proportion of patients needed transfusions, intravenous catheters, and admissions for severe infections as a consequence of the toxicity of systemic chemotherapy.[14,15] Fatal secondary leukemias associated with etoposide occurred occasionally.[16,17] These uncommon but severe cases of early morbidity and mortality associated with systemic chemotherapy and potentially fatal events associated with the use of EBRT are of great concern in these children with almost 100% chance of surviving their primary tumor. Hence, strategies such as OAC were developed not only to improve ocular survival rate but also to avoid EBRT, especially in cases of eyes with advanced disease.

Even though OAC has been used in at least 35 countries,[18] few studies have been reported from less developed countries.[19,20] In that setting, the risk to benefit ratio of some treatments may differ because of increased toxicity, limited resources, and treatment compliance issues, making it important to report local experiences to guide clinical decisions.[18,21]

Hence, our aim was to report our experience in the implementation of a large OAC program in Argentina with the main objective of evaluating its feasibility and complications and results in eyeball preservation avoiding EBRT.

2 | METHODS

A program for OAC was developed involving the following activities: Before launching the program, the group visited the Memorial Sloan Kettering Cancer Center for intensive learning of the technique.[22] Because of the lack of available equipment at the Hospital Garrahan, an agreement with another center (Clinica y Maternidad Suizo Argentina) was signed, so that OAC procedures would be performed there, but patients would be evaluated at the Hospital Garrahan. Access to this treatment was not restricted by the insurance status of the patients. In this phase, patients with relapsed intraocular retinoblastoma (n = 8)[23] failing systemic chemoreduction and EBRT and facing imminent enucleation were candidates for OAC.

After these actions, an implementation phase (March 2011 to December 2015) followed. A guideline for the use of OAC was written. Since the supply of melphalan was not constant during the period of this report, the use of specific chemotherapy regimens was not protocolized and depended on the availability of melphalan in many instances. The chemotherapy agents used included combinations of topotecan with carboplatin or melphalan for the treatment of tumors in unilaterally affected eyes. In cases with single remaining eyes, all three drugs were more commonly used. For bilateral tandem treatments, the worse eye usually received melphalan and topotecan, and the less-affected eye received carboplatin. In cases with bilateral group D eyes, these drugs were usually switched in each cycle. The overall treatment strategy in our whole patient cohort is detailed in Supplementary Figure S1. All group E eyes with a few exceptions, most unilateral group D eyes, and selected group D eyes in patients with bilateral disease were enucleated initially. Patients with bilateral retinoblastoma and massive buphthalmus in one eye received preenucleation systemic chemotherapy, as previously reported.[12] In these cases, as well as those initially enucleated with pathology risk factors, systemic chemotherapy was given for both prevention of extraocular relapse and tumor chemoreduction of the preserved eye. In these cases, OAC was offered after the failure of systemic chemotherapy. OAC was consistently offered to patients failing systemic chemoreduction and it was used as frontline therapy for patients with bilateral retinoblastoma with at least one group D eye. Patients presenting with bilateral group B-C eyes were offered initial systemic chemoreduction, and OAC was used for salvage therapy if needed. Patients younger than 6 months, with at least one group D eye, were offered "bridge" systemic chemotherapy until they reached the target age and weight (6 months or 6 kg).[24] They received single-agent intravenous carboplatin if they were younger than 3 months, followed by CEV from the age of 3 months to 5–6 months until they achieved a weight of at least 6 kg so they could be treated with OAC. Since the use of OAC was dictated by the presence of at least one group D eye, these children were analyzed in the primary treatment group. Drugs and dosages used are outlined in Table 1.

TABLE 1 Chemotherapy doses used for intraarterial chemotherapy. Occasional cases received a higher dose because of poor filling of the ophthalmic artery

	Age			
Drug (mg)	6–12 months	1–3 years	>3 years	Maximum dose/patient
Melphalan	3	4	5	0.5 mg/kg
Topotecan	1	1	1	1 mg
Carboplatin	40	50	50	15 mg/kg

Patients were examined under anesthesia 3–4 weeks after each OAC procedure, and this treatment was given within a week of this examination until they showed complete inactivity. For definitive tumor control, focal consolidation treatments with laser therapy and cryotherapy were used as soon as tumors became reduced with OAC and plaque brachytherapy was used for larger tumors usually after achieving the maximal response and completing treatment with OAC.

Prior to the OAC procedure, all children received heparin at 50–75 UI/kg. The catheterization of the ophthalmic artery was performed under general anesthesia as follows: First, the femoral artery was punctured to place a 3 F introducer sheath (Balt, Montmorency, France). Angiography with iopramide was then performed to verify the arterial flow of the cerebral hemisphere. Then, a 1.2–1.5 F microcatheter (Magic, Balt) with a microguide Mirage and Hybrid 0.008 inch (Medtronic, Irvine CA; Balt) was inserted and placed in the ostium of the ophthalmic artery. Occasionally, a 4 F guiding catheter (Cordis JR 4 F, Miami Lakes, FL) was needed. Occasional variations of this

procedure, namely catheterization of the anastomotic branch of the middle meningeal artery or the use of guide catheters (4 F; Cook, Bloomington, IN) were used in cases with anomalous anatomy. Balloon obstruction was not used in any case. A second iopramide angiogram was done in order to confirm microcatheter flow toward the ocular globe and minimal or absent backflow to the internal carotid artery. Chemotherapy was done in a pulsatile fashion, as reported previously.[3] Catheter position was checked during infusion, usually between infusions of each of these drugs. Intravitreous injection of melphalan (20 μg) was given to selected patients with vitreous seeding, as previously reported,[25] for a total of four weekly doses.

In the initial phase, patients were admitted overnight; but afterward, they were discharged after 6–8 hr of the procedure if no toxicity was seen. A complete blood count was obtained about 10 days after the procedure, along with a clinical evaluation. An ocular examination under anesthesia was done after 3–4 weeks of each OAC procedure.

All patients treated by our group whose ophthalmological and oncological treatment and follow-up were done at the Hospital Garrahan were evaluated for this report. Patients with relapsed or refractory tumors treated at other centers were evaluable only if ophthalmological treatment and follow-up were done by our group. Therefore, 17 patients coming only for OAC, from other institutions, were not analyzed. This study was performed in accordance with the Declaration of Helsinki. This strategy was considered implementational and institutional review board approval was waived for this report. A thorough discussion of the risks and benefits of this treatment was undertaken with each family and written informed consent was obtained in all cases. Follow-up was updated to April 2017. Toxicity was scored with the Common Toxicity Criteria for Adverse Events Version 4.0.

Extraocular relapse, death of any cause, enucleation, and/or use of EBRT (in eyes that were not previously irradiated) were considered events. Probability of event-free survival (pEFS) was calculated with the Kaplan–Meier method and differences between groups were evaluated with the log-rank test.

3 | RESULTS

3.1 | Patient characteristics

A total of 97 eyes treated with OAC in 81 patients were evaluated (61 bilateral). There were 12 patients with a family history of retinoblastoma and three patients had 13q14 syndrome. Median age at the treatment of OAC was 11.8 months (range 4–54).

3.2 | OAC treatment

A total of 400 procedures were carried out and catheterization was successful in 99%. The median number of OAC procedures per patient and per eye was four (range 1–14). In one patient, vasospasm was observed at first treatment, which made it necessary to cancel the procedure. In 313 cycles (78.2%), the ophthalmic artery was accessed via the internal carotid and 87 (21.8%), from the external carotid. The median duration of fluoroscopy (data available in 326 cycles) was 4.4 min per cycle (range 1.1–20). The median dose–area product was 135 cGy/cm^2 (range 23–775) per OAC treatment. In 17 eyes (17.5%), tumors relapsed or new tumors appeared after the first round of OAC treatments, needing a second round. In all these cases, a melphalan-containing regimen was used for the second round.

TABLE 2 Comparative description of evaluable eyes treated with ophthalmic artery chemosurgery (OAC) as primary therapy and those treated as secondary therapy

	Eyes treated with OAC as primary therapy (n = 35)	Eyes treated with OAC after partial response or relapse with other therapies (n = 62)
Age at OAC in months (median, range)	11.4 (4–52)	14.6 (3–81)
Prior chemotherapy, n (%)	12 (34%)	62 (100%)
Prior EBRT	0	12 (20%)
Number of OAC cycles (median, range)	5 (1–8)	4 (1–14)
Tandem infusions, n (%)	8 (23%)	6 (9.6%)
Eyes relapsing after the first round of OAC and receiving a second round, n (%)	4 (11%)	13 (21%)
Melphalan/nonmelphalan containing regimens	25/10	52/10
Enucleation, n (%)	11 (31%)	20 (32%)
Intravitreous chemotherapy, n (%)	1 (2.8%)	2 (3.2%)
EBRT for treatment of relapse after OAC, n (%)	1 (2.8%)	6 (9.6%)
Severe choroidal/retinal toxicity, n (%)	1 (2.8%)	2 (3.2%)

Thirty-five eyes were treated primarily with OAC (12 of them had received "bridge" systemic chemotherapy with a median of 4 [range 1–6] cycles of systemic chemotherapy treatment). Grouping of eyes treated initially with OAC or bridge therapy were B = 5, C = 8, D = 22. There were two cases with unilateral disease (group D) whose parents refused initial enucleation and only one cycle of OAC was given in order to bide time for the psychosocial team to work with the families to accept enucleation. In one of these patients, pathological examination of the enucleated eye revealed 95% necrosis with 5% viable tumor cells in the retinal tumor and no extraretinal invasion. The remaining case had massive choroidal invasion. Both cases are alive and disease free after enucleation. These cases are not analyzed for ocular survival because the treatment intent was enucleation.

Sixty-two eyes were treated after failing a previous treatment that included systemic chemoreduction including CEV chemotherapy in 58 or a higher intensity regimen for the treatment of concomitant pathology risk factors in four. Twelve cases had received EBRT. One patient with bilateral retinoblastoma continued therapy elsewhere and, therefore was not analyzed for ocular survival. Intravitreous chemotherapy was used in three eyes for the treatment of vitreous seeds that persisted after OAC. The characteristics of both groups are detailed in Table 2.

3.3 | Toxicity

There were no deaths associated with OAC. Hematopoietic toxicity was observed in 24 cycles (6%) with grade 3–4 neutropenia, and in five (1.3%) cases, the child needed to be admitted for fever but with no documented infection. Eight of these episodes (33%) occurred after tandem infusions, and in 21 cases (88%), chemotherapy included melphalan alone or in combination. Grade 3 thrombocytopenia was found in eight cycles (2%) but no child needed transfusions. Additionally, two patients needed hospitalization (one for varicella-zoster infection and one because of viral respiratory infection). Three patients had episodes of bronchospasm after OAC, which were managed with aerosolized bronchodilators.

Grade 2 eyelid edema or localized forehead erythema or focal alopecia occurred in twelve (12%) eyes during treatment. In two, there were more severe symptoms needing systemic steroids that were associated with grade 2, cranial nerve III palsy. In one of these cases receiving OAC for primary therapy, this event occurred after the sixth cycle and orbital swelling resolved after 3 weeks. Cranial nerve palsy improved gradually over 2 months. No further treatment was given since the tumor completely regressed, and the eye is preserved with a follow-up of 53 months. In the remaining case receiving tandem therapy for the treatment of relapsed bilateral tumors, this event occurred after the first cycle and resolved gradually over 3–4 weeks. In this case, further systemic chemotherapy and eventually a second course of OAC to the contralateral eye were needed for disease control. Both eyes are preserved with a follow-up of 40 months. Both these eyes had severe retinal and choroidal vascular occlusions leading to irreversible visual loss, which was also evident in an additional eye in another patient. In one case, grade 2 cranial nerve III palsy occurred without orbital swelling, and one patient had ptosis. All these toxicities were reversible. OAC treatment was discontinued because of toxicity in two additional patients. One had grade 3 thrombosis of the femoral artery after the first cycle that resolved with anticoagulant therapy, and the other child had grade 4 bronchospasm and hypotension during the procedure, which resolved with supportive care. There was an additional episode of grade 4 episode of bronchospasm and hypotension but OAC was resumed after 2 weeks without recurrence of the complication.

3.4 | Outcome

Both enucleation and EBRT were avoided in 61 of 97 eyes (63%). Median visual acuity of preserved eyes at last visit was 0.3 (range 0–1) log minimum angle of resolution (MAR). An accurate estimation of visual acuity was not possible in two cases because of cataracts following EBRT, nystagmus with poor fixation in one child, and poor cooperation in four children. Thirty-four eyes were enucleated and the pathology of enucleated eyes revealed high-risk features in three cases (two had been treated at relapse and the remaining one with group D had been treated with primary OAC) and received adjuvant chemotherapy.[26] One had minimally disseminated disease in the bone marrow that became not detectable after adjuvant therapy.[27] No extraocular relapse occurred in any of these patients. Two patients with bilateral retinoblastoma died of extraocular dissemination in the context of refusal of timely enucleation. One was treated with OAC after failing systemic chemoreduction and EBRT in another country and the remaining one was treated primarily with OAC in our center because the family refused initial enucleation. In both cases, the families did not accept enucleation when it was recommended by the medical team and had orbital progression with contiguous CNS involvement eventually leading to death at 22 and 38 months from diagnosis.

With a median follow-up of 48.7 months (range 12–79), the pEFS at 3 years was comparable for patients treated with the first-line therapy (0.65; 95% confidence interval [CI] 0.44–0.8) to that of those treated at relapse or progression (0.63; 95% CI 0.49–0.74; $P = 0.5$). Eight eyes received EBRT following OAC and six of them were enucleated. The pEFS for eyes patients treated with melphalan-containing regimens was 0.64 (95% CI 0.51–0.74) and 0.62 (95% CI 0.79–0.67) for carboplatin and topotecan ($P = 0.3$), respectively. The pEFS in different groups is shown in Figure 1.

One child treated with systemic chemotherapy, EBRT, and secondary OAC had a second malignancy (molecularly confirmed bone Ewing sarcoma outside the radiation field) and has survived event free for 26 months after the diagnosis of the second malignancy. One child with unilateral retinoblastoma and no germline mutation of the Rb1 gene, who was treated with OAC as primary therapy, had a craniopharyngioma and survived with 12 months follow-up after surgical resection. No case had trilateral retinoblastoma.

4 | DISCUSSION

Our report shows that a program for OAC in Argentina was feasible and showed similar complications as those reported from referral institutions in developed countries. In addition, globe salvages avoiding EBRT were the best obtained by our group so far. Our study had a high number of patients, treated with a consistent strategy and inclusion criteria. However, due to lack of availability of some chemotherapy agents, a formal prospective study could not be done. This would theoretically allow for determination of the best drug combination, treatment duration, and the impact of variation in the technique stratified by disease extension.

As opposed to the model of OAC proposed by most referral centers from developed countries, where patients with unilateral retinoblastoma are the main target population for this treatment, our series, like others in less developed countries, includes a higher number of bilateral cases (Supplementary Table S1).[8,28,29] Most patients with unilateral retinoblastoma are still enucleated initially in our center (Supplementary Figure S1).

Launching an innovative program in our setting raises the concern that a potentially higher toxicity rate could occur, limiting its success.[19] However, the adverse events were comparable to experience from developed countries (Supplementary Table S1).[1,30,31] There was no death associated with the procedure, no stroke, and no other life-threatening complication. Hematopoietic toxicity occurred in 6% of cycles, with fever and neutropenia requiring hospitalization in only 1.3% of cycles. Hematopoietic toxicity is conceivably higher with

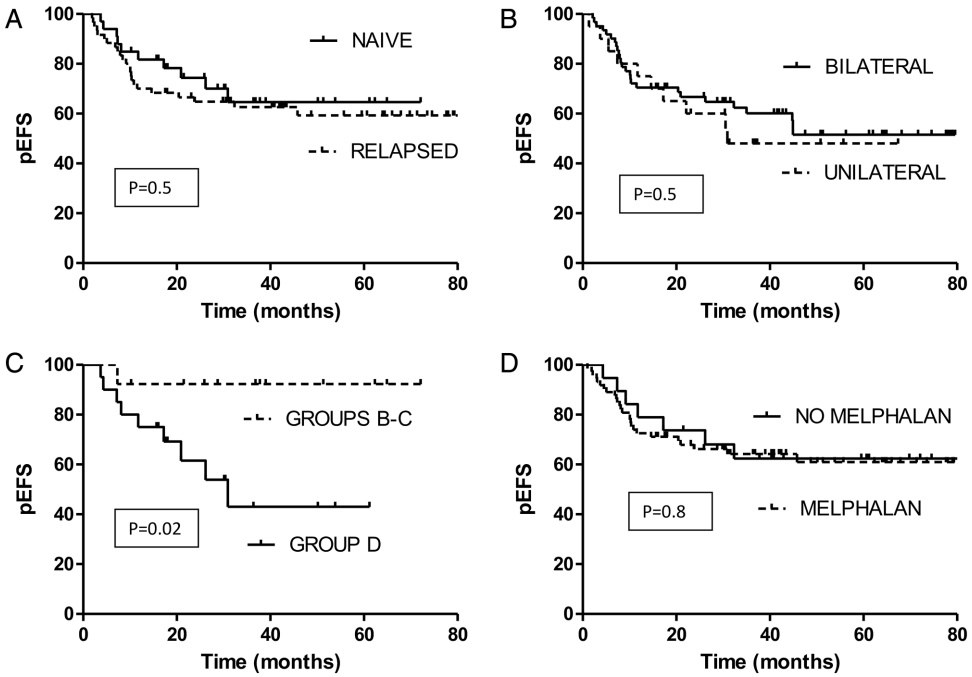

FIGURE 1 Probability of event-free survival (pEFS) according to (A) prior therapy, (B) laterality, (C) eye grouping, and (D) chemotherapy regimen

systemic chemoreduction and it depends on the regimen used and the setting where the child is treated, with a rate reaching up to 80% of the patients.[32] Systemic exposure to chemotherapy is reduced by OAC compared to systemic chemotherapy, but it is still observed albeit with lower plasma drug levels.[33] Our observed rate of admissions from fever and neutropenia fell from 6.8% of cycles when systemic chemoreduction was used, to 1.3% in the current series.[12] In addition, in our previous experience with systemic chemoreduction, two children died of therapy-related acute myeloid leukemia within 2 years from diagnosis,[12] while none had this complication in this series so far. We had three eyes (3%) with vision loss caused by OAC, which is comparable to figures from other programs (Supplementary Table S1).[30,34]

Compared to our previous experience, OAC was more effective for globe preservation and avoidance of EBRT.[35] Fifty percent of the eyes failing systemic chemoreduction and EBRT were saved, compared to 10% before the advent of OAC.[23] In addition, 92% of the initially treated eyes (group B-C eyes) could be retained avoiding EBRT, which compares favorably to our previous experience with systemic chemoreduction, where this figure was 73%.[12] However, this is a comparison with historical data where many factors such as the status of the contralateral eye had an influence on the use of EBRT. In group D eyes, OAC resulted in an ocular preservation rate comparable to our previous experience with systemic chemoreduction,[12] but it allowed to reduce the use of EBRT.[36] It may be argued that groups in developed countries have reported comparable outcomes with avoidance of EBRT with the use of intensive systemic chemoreduction.[32] The use of EBRT is still high in developing countries and it would probably be lower with the use of systemic plus intravitreal chemotherapy; however, there still are multiple sources of biases in the reported studies mostly based on patient selection. Visual outcomes are seldom reported for eyes treated with OAC or intravitreous chemotherapy. Even though visual acuity, on average, in our population was encouraging compared to patients treated with unilateral retinoblastoma,[37] an evaluation reporting visual outcomes in greater detail should be undertaken to arrive at definitive conclusions. Our results in group D eyes need to be improved despite the advances seen with the use of OAC. Using different classifications, Shields et al. reported that 23% of their group D eyes were enucleated after primary treatment with OAC[38] and Abramson et al. reported that only 15% of their group D eyes were enucleated.[34]

Patients receive non-therapeutic radiation during OAC administration. Even though the dose is substantially lower than that needed for tumor control, the potential for inducing radiation-related neoplasms is not known. Our series is consistent with others by limiting the time of exposure and the amount of radiation received per patient.[34]

One of the major critiques of OAC is that it could potentially increase the risk of metastatic disease since a putative protective systemic chemotherapy effect would be lost.[39,40] Metastatic disease was reported in at least 13 cases in published series.[40] Patient selection and timely enucleation when conservative therapy fails are probably key factors to prevent the occurrence of metastatic dissemination. We had no case of distant metastatic dissemination, but our series included two patients (2.5%) who had extraocular dissemination to the CNS because of parental refusal of timely enucleation. This figure is comparable to our previous experience with systemic chemotherapy (2.3%).[12]

We did not restrict our study only to melphalan, since its provision was not constant during the course of the study and we needed alternatives. Hence, we used topotecan and carboplatin, which have additive antitumor activity.[41] We tended not to use single agents and used drug combinations in order to avoid chemotherapy resistance. Nevertheless, in tandem infusions, we used single agent carboplatin[42] for the less affected eye. In order to avoid drug resistance, we switched the drug combinations after each cycle so the eye would be exposed to all

three drugs. However, we could not assess any differences in the efficacy of any regimen; therefore, the most effective chemotherapy and less toxic combination for this treatment are still to be identified. However, despite the limitations of our data, which were based upon drug availability and not tumor-specific features, our results suggest that regimens without melphalan might have comparable efficacy.

Vitreous seeds are an obstacle in curing retinoblastoma. Intravitreous chemotherapy has improved results in these patients.[43] In this series, our patients were treated before the widespread use of intravitreous therapy, so that we may measure the impact of OAC with greater precision; therefore, it is likely that results in group D eyes would improve with the use of intravitreal chemotherapy.[38]

In summary, in our setting, OAC is an effective and safe modality for the treatment of retinoblastoma with a low rate of severe ocular and systemic toxicity, reducing the number of enucleated eyes and the need for EBRT.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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