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I, Samantha T Michaels M.D., hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

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Selective Intra-Ophthalmic Artery Chemotherapy for Advanced Intraocular Retinoblastoma: CCHMC Early Experience

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Selective Intra-Ophthalmic Artery Chemotherapy for Advanced Intraocular Retinoblastoma:
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Selective Intra-Ophthalmic Artery Chemotherapy for Advanced Intraocular Retinoblastoma: CCHMC Early Experience
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ABSTRACT

Selective intra-ophthalmic artery chemotherapy infusion (SIOAC) has been increasingly used in the management of retinoblastoma with the goal of minimization of therapy related toxicity and ocular salvage. Nineteen eyes in 17 patients with intraocular retinoblastoma received 87 SIOAC treatments between 2008 and 2013. While local reactions were common, mild and self-limited, rarer procedure-related adverse effects included bronchospasm, carboplatin anaphylaxis, transient lower extremity arterial thrombosis and reversible cerebral vasoconstriction. Neutropenia was more common with triple therapy cycles (melphalan, carboplatin and topotecan) when compared with single agent melphalan. Ocular salvage was achieved 11 of 19 eyes. Triple therapy was associated with improved rates of ocular salvage (p-value 0.0056). SIOAC can be effective therapy for intraocular retinoblastoma. Triple therapy seems more effective but also more myelosuppressive than single agent therapy. Larger scale clinical trials are necessary to better define the role of SIOAC.
Acknowledgments:

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Introduction

Retinoblastoma is the most frequently occurring ocular tumor in children. Advances in therapy over the last hundred years have given what was once a nearly uniformly fatal disease an overall survival rate of greater than 97% in developed countries. Therapy may include one or multiple treatment modalities including local ophthalmologic therapy (laser therapy, cryotherapy or plaque radiotherapy), systemic chemotherapy, external beam radiation therapy (EBRT), selective intra-ophthalmic artery chemotherapy (SIOAC), intra-vitreal chemotherapy and/or enucleation. With the dramatic improvement in overall survival, the primary goals of therapy now also include, when possible, maintaining functional vision, minimizing treatment related toxicities and improving cosmetic outcomes. SIOAC delivery is an emerging technique that has, in many cases, allowed for the avoidance of higher risk therapies such as external beam radiation, systemic chemotherapy and enucleation.

The initial chemotherapeutic agent delivered via SIOAC was melphalan. Melphalan is a potent alkylating agent with impressive activity against retinoblastoma. Its use is limited systemically due to bone marrow toxicity. When chemotherapy is delivered directly into the ophthalmic artery, the dose required is approximately one-tenth the dose required systemically and systemic absorption is thought to be minimal [1]. Though single agent melphalan is efficacious for some patients, for many it is insufficient. To improve efficacy of SIOAC, topotecan and carboplatin have been added to melphalan for more advanced tumors [2].

Intra-arterial chemotherapy technique is not without risk. In the early study by Gobin et al, transient occlusion of the superficial femoral artery, bronchospasm, contrast allergy, ocular inflammation (peri-ocular edema and erythema), avascular retinopathy (with total vision loss), cataracts, eyelash loss, and neutropenia were all reported [3]. While subsequent reports have had
similar findings, most report the benefits of the procedure outweigh the risks [4-8]. This paper will report on 87 SIOAC procedures focusing on toxicity and efficacy, noting an evolution of both when transitioning from single agent to triple drug therapy.

Materials and Methods

Cincinnati Children’s Hospital Medical Center Institutional Review Board approval was obtained for a retrospective review of 17 patients with intraocular retinoblastoma consecutively treated with SIOAC between December 2008 and December 2013. Patient records were reviewed for demographic data, International Classification, laterality, prior retinoblastoma therapies, SIOAC procedural data (chemotherapy, concurrent ocular therapy, and adverse events), local ocular adverse events, systemic toxicities and ocular outcomes (response to therapy, relapse, additional therapy required after SIAOC and ocular survival). Statistical analysis was done using two-sided Fisher exact tests.

All patients were treated by a single operator [TA] as previously described [9]. Patients received SIOAC at 3 to 4 week intervals. Patients were routinely monitored with ophthalmologic exam under anesthesia (EUA) with RetCam imaging by a single operator [JA] within 24 hours of the procedure and followed by a pediatric oncologist [JG]. Laboratory evaluations included baseline PT and PTT (normal in all), pre- and mid-cycle assessments of blood counts and renal and liver function tests each cycle. Patients were evaluated for hematologic toxicity as defined by the CTCAEv4.0.

Results

Treatment

Nineteen eyes of 17 patients (9 female) with intraocular retinoblastoma were treated with SIOAC. Patient ages ranged from 5 months to 16 years (median 29 months). Fifteen eyes were
International Classification Group D, 3 eyes Group C and 1 eye Group E. Sixteen of the 19 eyes had extensive vitreal and/or sub-retinal seeding at the time of SIOAC. Ten patients (all with bilateral retinoblastoma) had received retinoblastoma therapy prior to SIOAC: including systemic chemotherapy (carboplatin, etoposide and vincristine in 10 patients) with or without laser therapy (3 patients) and/or cryotherapy (7 patients). Four patients had also received prior EBRT. Seven patients with unilateral disease were chemotherapy naïve at time of SIOAC. Nineteen eyes received 87 technically successful SIOAC procedures for chemotherapy delivery. Patients received an average of 5 cycles (range 2-10). Two patients with bilateral disease received treatment in both eyes, 1 received 6 concurrent cycles and a second patient received 3 cycles OD followed by 2 cycles OS, 6 months apart.

Patients were treated with single agent melphalan or topotecan, or they were treated with combination “triple agent” melphalan, topotecan and carboplatin. Single agent melphalan was used in 41 cycles, single agent topotecan was used in 16 cycles (as part of an institutional protocol IARB1 (NCT 01466855)) and triple agent chemotherapy was used in 30 cycles (Table 1). Three patients initially treated with single agent topotecan were transitioned to single agent melphalan and 2 patients were transitioned from single agent melphalan to triple agent therapy after incomplete tumor response. Eight patients received concurrent cryotherapy and 2 received concurrent laser therapy. One patient received 2 cycles of concurrent sub-Tenon carboplatin.

Adverse Local Reactions

Overall 14 patients had localized erythema including all patients who received concurrent laser or cryotherapy. Twelve patients developed localized eyelid edema (9 of which received concurrent laser or cryotherapy). Seven patients developed ipsilateral eyebrow and/or eyelash loss. Five patients developed skin hyperpigmentation involving the ipsilateral upper face and
forehead. Symptomatic ophthalmitis was seen in only 4 out of 87 cycles (4.8%) and was treated with 3-5 days of oral steroid therapy. All localized reactions resolved completely.

**Adverse Systemic Reactions**

Laboratory data was available for all 87 cycles. Overall grade 3 (absolute neutrophil count ≤ 1000) or grade 4 (absolute neutrophil count ≤ 500) neutropenia occurred in 27 of 87 cycles (31%). Eleven patients (64.7%) experienced grade 3 neutropenia at least once, and 5 of those 11 (29.4%) also experienced grade 4 neutropenia after at least 1 cycle. Grade 3 neutropenia occurred after 15.8% (9/57) of single agent SIOAC cycles and 33.3% (10/30) of triple agent SIOAC cycles; and grade 4 neutropenia occurred after 3.5% (2/57) of single agent SIOAC cycles and 20% (6/30) of triple agent SIOAC cycles. Grade 3 neutropenia occurred in 17% (7/41) of single agent melphalan cycles and 12.5% (2/16) of single agent topotecan cycles. Six of the 11 patients who developed grade 3 neutropenia had received prior intravenous chemotherapy (p-value 0.84). Three of the 5 patients who developed grade 4 neutropenia had received prior intravenous chemotherapy (p-value 0.69) Neutropenia resulted in 2 cycles being delayed a few days beyond the planned 28 days. No patients required platelet or red blood cell transfusion.

There was one episode of uncomplicated febrile neutropenia requiring a short inpatient hospitalization.

Nine patients (53%) during 16 cycles (18.4%) reported nausea and vomiting in the first 24-48 hours after the procedure. No patient required intravenous hydration or inpatient admission for management of nausea and vomiting. Symptoms were controlled with antiemetic therapy and those patients then received antiemetic prophylaxis for subsequent cycles.

Fever developed within the first 48 hours of SIOAC after 5 cycles (5.7%). Blood cultures were drawn in all cases and were negative. Four patients received a single dose of ceftriaxone
and 1 received observation only. One patient was found to have a urinary tract infection and was treated accordingly.

**Procedural Complications**

Bronchospasm occurred in 4 of 87 SIOAC procedures (4.6%); treatment with epinephrine and albuterol provided uniform resolution of symptoms. Minor bleeding at the inguinal insertion site in 3 procedures (3.4%) was responsive to applied pressure, no hematomas developed.

Carboplatin anaphylaxis, transient lower extremity arterial thrombosis, and reversible cerebral vasoconstriction each occurred once. Carboplatin anaphylaxis was noted as severe hypotension and tachycardia, developing immediately after the start of triple agent chemotherapy injection in a patient previously treated with systemic carboplatin. Treatment for chemotherapy related anaphylaxis led to rapid improvement in hemodynamics. The child had achieved a complete remission (CR) in the completed four cycles so no additional therapy was given; however, the child ultimately underwent enucleation for persistent vitreal hemorrhage and complete retinal detachment. Asymptomatic transient right lower extremity arterial thrombosis was noted as angiography showed occlusion of the right external iliac artery with the distal circulation reconstituted by collaterals from the right internal iliac artery. The dorsalis pedis pulse in the right foot returned after removal of the right femoral artery sheath and administration of heparin. A therapeutic course of anticoagulation led to complete resolution of the thrombus without any further thrombotic complications. No additional SIOAC was given due to parental preference and the patient went on to receive additional therapy with intra-vitreal melphalan. A single case of reversible cerebral vasoconstriction, as evidenced by significant systemic hypertension which correlated with constriction of the cortical branches of the right anterior cerebral artery and right middle cerebral artery, was noted. Both the patient’s hypertension and
cerebral vasoconstriction resolved, a post procedure MRA was normal, and she had no further complications during 2 subsequent treatments [9]. Despite having achieved CR, the patient had a local recurrence 4 months after her last SIOAC and underwent enucleation.

**Outcomes**

Eleven of the 19 eyes (57.9%) treated with SIOAC were salvaged. The median follow-up for salvaged eyes is 13 months. Seven eyes required enucleation for disease progression or relapse (6 achieved a complete response prior to relapse, 1 had persistent vitreal disease despite SIOAC). Time to relapse varied from 2 to 14 months (mean 5.8 months) after the last primary treatment SIOAC cycle. One eye was enucleated for persistent vitreal hemorrhage and retinal detachment; however, viable tumor was found in the enucleated eye, similar to the other 7 enucleated eyes. Overall, 3 eyes did not achieve a complete remission with SIOAC combined with local directed therapy. Two eyes had persistent vitreal disease; the remaining eye did not complete a full course of SIOAC due to parental preference to change therapy after external iliac thrombosis (as discussed previously). Among these 3, 2 eyes went on to receive intra-vitreal chemotherapy (both receiving therapy at time of writing) and the third was salvaged with systemic chemotherapy and EBRT. Among the 16 eyes that achieved CR, 9 remain in remission without additional therapy, 6 relapsed after CR, and 1 underwent enucleation for vitreal hemorrhage and persistent retinal detachment. Among the 6 relapsed eyes, 3 received subsequent intra-vitreal melphalan for persistent vitreal disease: 2 achieved durable remission and 1 eye was enucleated. Two patients went on to receive systemic chemotherapy, though only 1 was salvaged with the addition of EBRT. The sixth eye was enucleated at time of relapse after SIOAC without additional therapy.
Of the 6 eyes that received initial SIOAC with triple agent therapy, 5 eyes were salvaged (83.3%). Of the 11 eyes that received initial single-agent SIOAC therapy, 4 eyes (36.4%) were salvaged (p-value 0.1312): without additional rescue therapy 2 eyes were salvaged with transition from single agent therapy to triple therapy. Overall, triple therapy provided improved ocular survival as compared to single agent therapy (p-value 0.0056). Of the 12 eyes that had received prior therapies, 8 eyes were salvaged (66.7%). Of the 7 treatment naïve eyes, 3 eyes (42.9%) were salvaged (p-value 0.3765). When evaluating outcomes by stage at time of treatment, 7 of 13 Group D eyes were salvaged (53.8%), 1 of 3 Group C eyes was salvaged (33.3%) and the single Group E eye was salvaged. Three patients are still receiving retinoblastoma therapy at the time of writing.

Discussion

With improved survival, the goals of retinoblastoma therapy have extended from overall survival to ocular survival, minimization of treatment adverse effects and improved cosmetic outcomes. Treatment modalities have emerged, fallen out of favor and re-emerged not only as new modalities are developed, but as the ones in existence are improved upon. Despite many effective treatment modalities, not all are widely available at many institutions and as such, there is no uniform treatment strategy. Additionally, treatment goals differ among families, with varying emphasis or value in ocular salvage versus the finality and generally favorable clinical journey that accompanies well supported enucleation. The advance of SIOAC has presented yet another option adding to, and also confounding, clinical treatment algorithms and choices. To this end, the cohort presented herein adds to the growing body of literature reporting toxicity and efficacy of SIOAC.
In our series, though many patients experienced a localized mild inflammatory reaction (peri-ocular edema and erythema) symptoms were mild, transient and self-limited. Common ocular events previously reported can include blepharoptosis and transient ocular dysmotility [3, 4, 10], and more significant ophthalmologic outcomes including vasculopathy in the ophthalmic, retinal and choroidal vessels [4]. Shields et. al. evaluated ocular toxicity in 17 eyes after SIOAC [10]. In their cohort eyelid edema, blepharoptosis, cilia loss and orbital congestion with temporary dysmotility were frequently observed but all resolved within 6 months. Occlusive vasculopathy was observed in the ophthalmic artery in 4 patients as demonstrated by central retinal artery obstruction, multifocal branch retinal artery obstruction and or evidence of choroidal atrophy. Despite this, no patients developed neovascularization of the disc or retina, glaucoma, pain or toxicities required enucleation. While occlusive vasculopathy may be more common than previously thought, effects are often subclinical.

Systemically, myelosuppression was frequently observed in our cohort. The initial report of SIAOC for retinoblastoma by Gobin et al. reported grade 3 neutropenia during 8.2% of cycles and grade 4 neutropenia during 3.1% of cycles for patients receiving single agent melphalan with or without topotecan [3]. A later report of triple agent therapy by Marr et al. reported grade 3 hematologic toxicity after 37% of cycles and grade 4 hematologic toxicity after 23% of cycles [11]. Nearly all patients who receive standard retinoblastoma chemotherapy intravenously (carboplatin, etoposide and vincristine) will have grade 3 or 4 neutropenia [12]. Our data confirm that triple agent chemotherapy is more myelosuppressive than single agent melphalan, highlighting an overall increasing systemic effect of such SIOAC. Schaiquevich et al. published preclinical data that revealed a higher systemic area under the curve in children who received melphalan at doses greater than 0.48mg/kg during bilateral tandem infusions, giving them a 50%
probability of grade 3-4 neutropenia [13]. It has also been proposed that patients who had been exposed to systemic chemotherapy prior to SIOAC would have a higher incidence of myelosuppression. In our cohort, prior systemic chemotherapy did not predict myelosuppression from subsequent SIOAC treatments. As the field of SIOAC continues to undergo refinements, it will be important to acknowledge that therapy intensification via SIOAC may increase both local and systemic effects, narrowing the therapeutic benefit of such an approach. More recent studies are reporting improving ocular salvage rates with conventional systemic intravenous therapy for patients with advanced intraocular (Group D) retinoblastoma, possibly approaching those reported from SIOAC-based therapy. Berry et al. reported an ocular salvage rate of 82% at 54.4 months for Group D bilateral retinoblastoma using systemic chemotherapy with local consolidation and low dose intensity modulated radiation therapy for recurrent intraocular disease [14]. Chemoreduction (with dose intense carboplatin) with local therapies alone cured 47% of patients.

Procedural adverse effects from SIOAC are generally rare but can range from mild to effects with more consequence. In our cohort, bronchospasm occurred in only 4.8% of procedures, comparing favorably with prior reports demonstrating an incidence up to 25% [3, 8]. It is possible that prophylactic use of albuterol, routinely used as pre-treatment for SIOAC procedures at our center, may account for differences in rates of bronchospasm. Three patients in our cohort had more severe procedural outcomes including carboplatin anaphylaxis, transient arterial thrombosis and reversible cerebral vasoconstriction. Allergic reactions are more commonly reported with iodinated contrast but do occur with chemotherapy, and in this regimen the most common culprit is carboplatin [15]. While reported in the literature as a potential severe complication, in our series, there were no cases of central vascular infarction (stroke) or
development of metastatic disease [3]. While fever, nausea and vomiting did commonly occur, it is unclear whether this is a consequence of SIOAC or post anesthesia effect.

Eleven eyes (58%) in our cohort were salvaged, though several remain on therapy and thus it is possible that with more time, the salvage rate from this cohort may decrease. Despite the ultimate need for enucleation of 8 eyes, all eyes did show varying degrees of clinical response to SIOAC. Gobin et al reported overall 2-year ocular event free survival of 70% (81.7% for therapy naïve eyes and 58.4% for pre-treated eyes) for patients who had received single agent melphalan with or without topotecan (13 month median follow up) [3]. Marr et al. reported an 88% ocular salvage rate at a mean follow up of 14 months in patients who had received triple agent SIOAC. The Kaplan Meier estimate of ocular survival at 24 months was 75% [2]. The differences in outcomes likely reflect the evolution in technique over time, patient selection and sample size. Smaller cohorts, similar to our institution, have reported similar outcomes [8]. In our cohort, relapse occurred with development of new tumors and/or vitreal seeding 2 to 14 months after the last SIOAC cycle (mean 6.25 months). Vitreous seeds remain a challenge due to poor chemotherapy concentration in the vitreous. Ocular salvage rates are significantly inferior in patients with seeding and new techniques are emerging to increase vitreal concentration of chemotherapy, including intra-vitreal chemotherapy, posterior sub-Tenon carboplatin and topotecan injection and dose escalation of systemic chemotherapy [16, 17]. Our cohort was heavily weighted towards patients with extensive vitreal and/or sub-retinal seeding suggesting that patients with advanced intraocular disease will more likely benefit from triple agent SIOAC rather than single agent therapy. Contrary to the published literature, in our cohort, there was no significant difference in ocular salvage rates of patients who had received prior therapy versus those who had not. This is likely secondary to our limited sample size and variation in therapies
provided. This report also demonstrates the evolution of the therapy and technique from 2008 to 2013. As its safety was elucidated, patients received additional cycles with more aggressive therapy given to patients with more advanced disease. In addition to ocular salvage, functional outcomes must be considered. In our cohort, patients report varying degrees of functional vision after SIOAC; more formal testing will elucidate those visual outcomes.

Conclusion

SIOAC is now a more widely used treatment modality that affords improving ocular salvage rates, minimization of systemic effects and avoidance of other potentially higher risk therapies. Triple drug therapy seems to improve ocular survival compared with single agent melphalan or topotecan, though at a price of increasing myelosuppression. Persistent or recurrent vitreal seeds remain a key challenge to ocular salvage, and hopefully with the advance of intra-vitreal therapy, multi-modal treatment approaches can be optimized to improve outcomes. Larger prospective protocols and standardization of care and outcome measures, including visual function metrics and quality of life, are necessary to advance therapy options for infants, children and their families affected by intraocular retinoblastoma.
References:


Table 1. Standard chemotherapy dosing.

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*IARB1

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