Intravitreous Chemotherapy as Adjuvant Treatment for Vitreous Seeding in Retinoblastoma: A Philippine Tertiary Hospital Experience

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ABSTRACT

Background. Intravitreal chemotherapy has been an effective addition in treating vitreous seeding in retinoblastoma. However, it was only in 2020 that it was used in the Philippines. There is no literature on its use in multiple Filipino retinoblastoma patients.

Objectives. To describe the clinical course of the four patients who are the first to undergo intravitreal chemotherapy for vitreous seeding of retinoblastoma in the Philippine tertiary hospital.

Methods. A case series of four eyes of four patients with retinoblastoma who underwent intravitreous injection of melphalan and topotecan for vitreous seeding at the Department of Ophthalmology and Visual Sciences of a Philippine tertiary hospital.

Results. Two eyes, with International Intraocular Retinoblastoma Classification (IIRC) Group C with vitreous seeding, responded well to intravitreous melphalan and topotecan. One eye had recurrent vitreous seeding despite 10 intravitreal injections. One eye with IIRC Group E, did not respond to intravitreous chemotherapy and was eventually enucleated.

This is the first case series on the local use of intravitreous chemotherapy in the country for vitreous seeding in retinoblastoma. The control of 50% achieved in this case series is lower than in other series due to longer treatment interval from poor follow-up and the presence of advanced disease.

Conclusion. The use of intravitreous melphalan and topotecan can be an effective adjuvant for systemic chemotherapy in controlling vitreous seeding in eyes with IIRC Group C. It is not effective in controlling IIRC Group E disease.

Keywords: intravitreous, melphalan, topotecan, retinoblastoma, vitreous seeding, Philippines

INTRODUCTION

Retinoblastoma is a childhood malignancy of the retinal cells. It is graded based on the size and location of the mass inside the eye and staged based on its ocular and systemic extent. One of the intraocular grading systems is the International Intraocular Retinoblastoma Classification (IIRC) takes into consideration the presence of seeding in the vitreous and retina and is being used in the Philippine tertiary hospital.[1] More retinoblastoma treatment options have also become available leading to a shift in management goal from life-saving to globe-saving as more patients are being diagnosed early even in developing countries.[2,3] The introduction of intravitreous chemotherapy as an adjuvant to intravenous or intraarterial chemotherapy has been reported

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to be effective in controlling vitreous seeds.[4] Kaneko and Suzuki introduced the use of intravitreous melphalan in the 1990s to address vitreous seeding in retinoblastoma which remains poorly responsive to systemic chemotherapy and radiotherapy.[5]

Melphalan, an alkylating agent, was found to be the most effective among a group of drugs tested in vitro against cultured retinoblastoma cells.[6] However, it was also reported to have significant retinal and anterior segment toxicities.[7,8] In 2012, Munier et al. introduced a set of criteria for patient selection, a dosage regimen, and a safe technique in the use of intravitreous melphalan.[4,9] Depending on age, 20 to 30 micrograms (μg) of melphalan given intravitreously every 7 to 10 days were found to be effective in suppressing vitreous seeds while not being toxic to the retina.[4] A triple freeze and thaw technique using cryotherapy was also described to prevent the extraocular spread of the disease thru the needle tract.[9] High globe salvage rates ranging from 81% to 100% were reported in managing vitreous seeding resulting to the use of intravitreous melphalan in becoming the most used intravitreous drug for treating vitreous seeds.[4,8,10,11]

Topotecan, a topoisomerase inhibitor, is another drug being used for intravitreous chemotherapy to control vitreous seeding in retinoblastoma. It is also being used for intravenous and periocular chemotherapy for retinoblastoma.[8] Topotecan has been proven to be effective when used intravitreously at 30 μg every 3 weeks with a reported globe salvage rate of 94%.[8] Its longer shelf life after reconstitution and better safety profile makes it a good alternative for melphalan, especially in low-resource settings.[8]

METHODS

There is limited literature on the use of intravitreous injection of melphalan and topotecan among retinoblastoma patients in the Philippines.[12,13] We present a case series of four eyes of four patients who underwent a total of 20 injections of intravitreous chemotherapy (8 melphalan and 12 topotecan) at a Philippine tertiary hospital since 2020. This case series adhered to the Declaration of Helsinki.

The method of delivery and the dosing used for melphalan and topotecan followed the recommendations available in the literature.[2,6,7] In the Philippine tertiary hospital, the reconstituted melphalan or topotecan is delivered using a 1 milliliter (ml) syringe with a half-inch long gauge 30 needle. The agent is delivered intravitreally after examination under anesthesia. A quadrant far from the vitreous seeding is identified first. Then, using sterile technique, 30 μg melphalan or topotecan in 0.05 ml is injected intravitreally, 3 millimeters from the limbus with the needle bevel up. Depth of needle penetration is guided by the view of the posterior fundus. On withdrawal of the needle, the triple freeze thaw cryotherapy technique is applied to the needle entry point to avoid possible externalization of tumor or seeds. Irrigation of the eye is done with sterile water.

The patient is given tobramycin + dexamethasone eye drops four times a day for one week. Melphalan is given every 7-10 days while topotecan is given every three weeks unless there are other uncontrolled factors leading to the delay in administration. Intravitreous chemotherapy regimen is discontinued when there is either complete disappearance or calcification of vitreous seeds. An additional dose may be given as a security measure once vitreous seeds disappear or are fully calcified. If there is definite progression or no detectable improvement of the vitreous seeds on follow-up, a shift to a different intravitreal drug regimen or treatment option should be considered.

RESULTS

Case 1 is a 5-year-old boy who underwent enucleation of left eye at 2 months old for IIRC Group E. At 5 years old, tumors were discovered in the right eye diagnosed as Group C. Six months after good response to local therapy, vitreous haze with dust vitreous seeds, and peripheral tumor recurrence were seen at the 3-6 o'clock ora serrata prompting five cycles of systemic vincristine, etoposide, and cisplatin (VEC). Gradual decrease in vitreous haze was noted but the seeds and tumor persisted. Then the patient was lost to follow-up for nine months due to the pandemic.

New vitreous seeds and epiretinal seeds were noted at the 4-6 o'clock periphery. An intravitreal 30 μg of melphalan resulted to decrease in vitreous haze after two weeks but new vitreous seed clouds and clumps were seen in the inferonasal area. Due to availability concerns, 30 μg topotecan was given instead, resulting to further decrease in vitreous haze. Four more doses of topotecan resulted in sheets of calcified vitreous seeds at the 5-7 o'clock periphery after 11 weeks. The patient was again lost to follow-up for 3 months. New vitreous seeds were noted again at the 5-7 o'clock periphery (Figure 1A). Two more doses of melphalan were given but still with vitreous seeds inferiorly after four weeks. A 6th dose of topotecan resulted to calcification of vitreous seeds inferiorly after seven weeks (Figure 1B). The peripheral tumor source persisted despite repeated cryotherapy sessions.

Five months after, new vitreous seeds were seen at the 5 o'clock periphery necessitating another dose of melphalan. There was minimal effect after two weeks and a new ciliary body mass was seen at 7 o'clock. The patient was advised to undergo radiotherapy for 25 sessions. In the last follow-up, the patient received a total of 10 injections of intravitreous chemotherapy (4 melphalan and 6 topotecan), with visual acuity in the right eye of 20/20.

Case 2 is a 7-month-old boy who underwent enucleation of the right eye for IIRC Group E and eight cycles of systemic VEC followed by radiotherapy for positive optic nerve resection margin. The left eye, graded Group C, had masses with overlying vitreous seeds. Five of the eight cycles of systemic VEC with local therapy reduced the size of the masses in the left eye but with persistence of vitreous seeds.

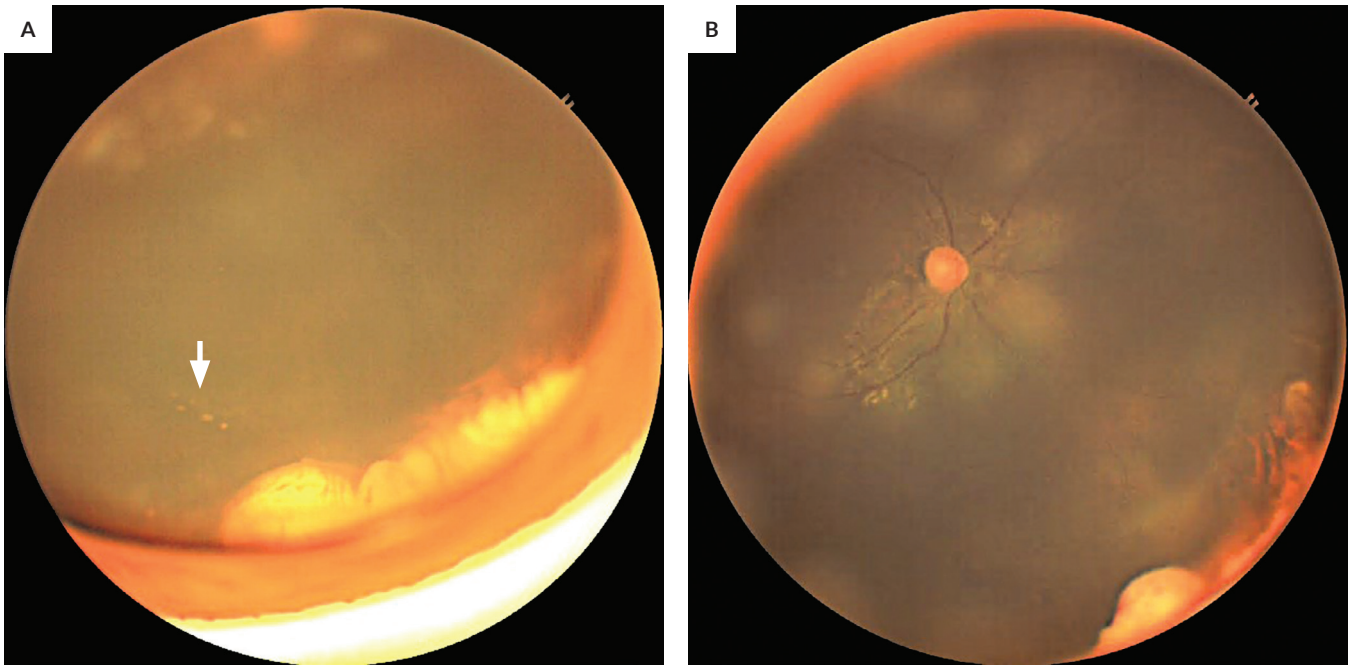

Figure 1. Fundus photographs of the right eye showing **(A)** active vitreous seeds *(white arrow)* over a mass located at the 5-6 o'clock periphery and **(B)** absence of vitreous seed in the same area seven weeks after the 6th dose of intravenous chemotherapy.

Additional vitreous seeds were seen in the inferotemporal periphery after a month. Two doses of 20 µg melphalan were given within a month due to a persistent overlying vitreous seed in a mass. The patient was lost to follow up for three months but the seeds and tumors were found to be controlled. In his last follow-up, 19 months after the 2nd dose of melphalan, visual acuity was at least finger play at 10 feet. He had normal anterior chamber findings and flat retinal scars with no tumor activity and seeds (Figure 2).

Case 3 is a 1-year-old boy who underwent enucleation of the right eye for IIRC Group E and six cycles of systemic chemotherapy for massive choroidal invasion. His left eye was diagnosed with Group C and underwent two monthly sessions of cryotherapy for an active tumor with the 1st and 2nd cycles of systemic VEC. After three months, there were generalized fine vitreous seeds, central subretinal seeds, fluffy vitreous seeds at the inferonasal portion, and an inferior active tumor with overlying vitreous seeds. Thirty micrograms of topotecan were added to the 3rd cycle of systemic VEC resulting in calcified seeds 360° peripherally but still with vitreous seeds inferonasally after three weeks (Figure 3A). Two more doses of topotecan were given with the 4th and 5th cycle of systemic VEC within five weeks. There were increase in vitreous haze and of vitreous seeds, and appearance of a small subretinal seed inferiorly after three weeks.

A 4th dose of topotecan with the 6th cycle of systemic VEC resulted to a significant reduction of vitreous seeds inferiorly but still with small spherical vitreous seeds inferotemporally after six weeks. There were multiple new

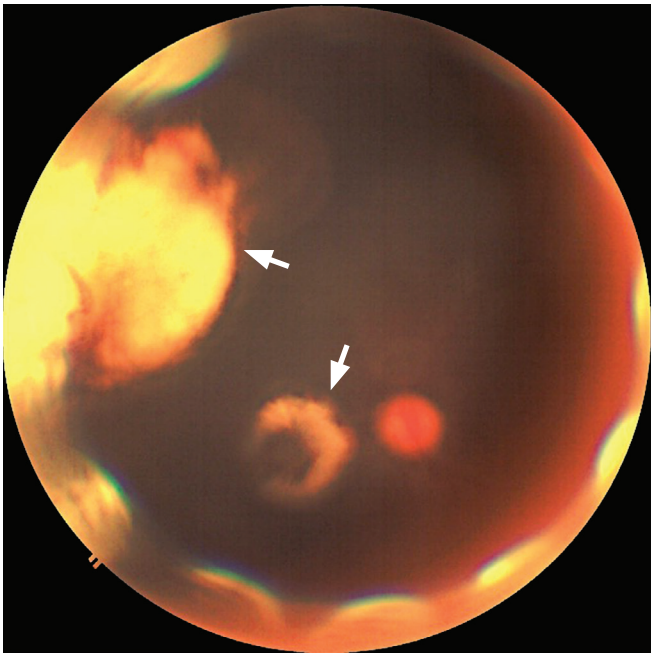

Figure 2. A fundus photograph of the left eye showing flat retinal scars *(white arrows)* nasal to the optic nerve and at the 9-11 o'clock periphery with no active mass or vitreous seed 19 months after two injections of intravitreous chemotherapy.

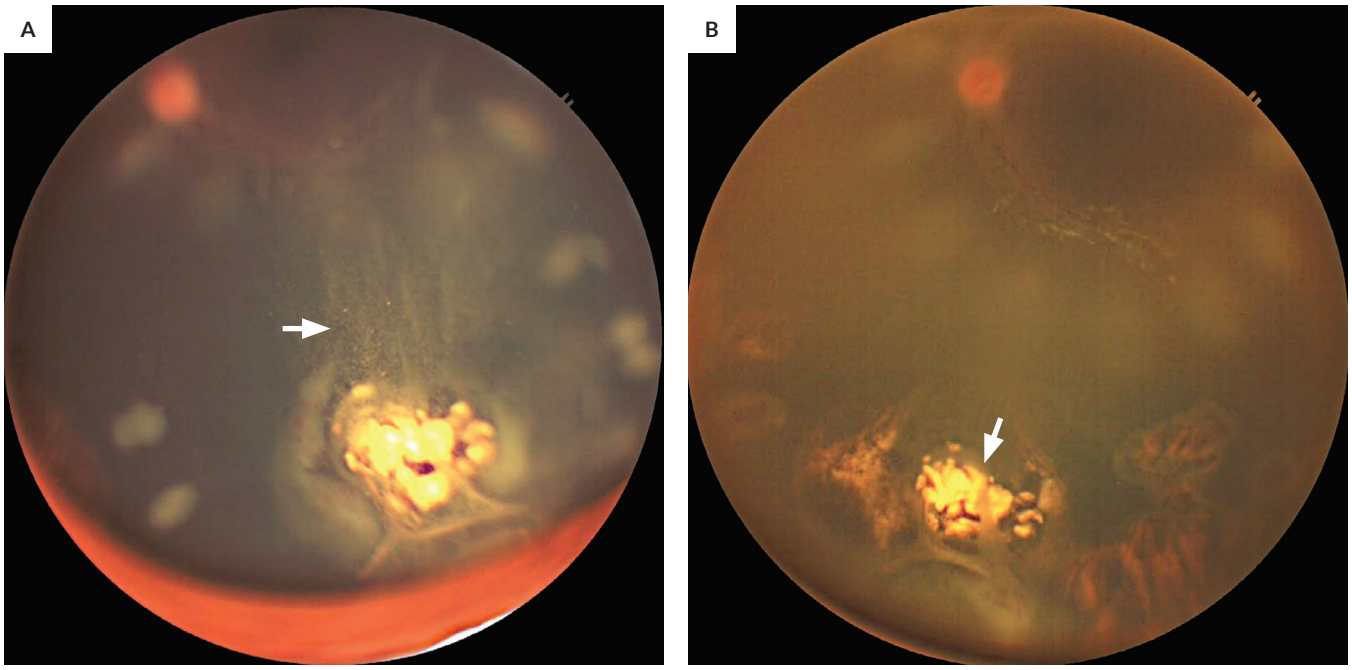

Figure 3. Fundus photographs of the right eye showing **(A)** multiple active vitreous seeds *(white arrow)* over a mass at the 5 o'clock periphery and **(B)** a flat retinal scar *(white arrow)* located peripherally at 5 o'clock without overlying vitreous seeds two months after the 7th injection of intravenous chemotherapy.

tumors noted in the inferotemporal quadrant. Two doses of melphalan were given within two weeks. Seeds were noted in the posterior lens capsule after four weeks. A 3rd dose of melphalan resulted in the resolution of the posterior lens capsule seeds and calcification of all vitreous seeds inferiorly. In his latest follow-up, two months after seven injections of intravitreous chemotherapy (four topotecan and three melphalan), his vision on the left eye was finger play at 20 feet with no active mass and seeds (Figure 3B).

Case 4 is a 2-year-old girl diagnosed with IIRC Group E in the right eye (Figure 4) and Group C in the left eye. Her mother refused enucleation of the right eye and opted for systemic VEC instead. After three cycles of systemic VEC, there was a reduction and calcification of the vitreous seeds. Persistence of vitreous seeding in the right eye prompted two doses of topotecan with the 4th and 5th cycle of systemic VEC resulting in the calcification of vitreous seeds. A Magnetic Resonance Imaging done to evaluate response suggested disease extensions in the distal optic nerve and inferior rectus muscle of the right eye resulting to its immediate enucleation. On histopathology study, no scleral involvement or posterior laminar involvement was seen but there was massive choroidal invasion.

A summary of the four cases is presented in Table 1.

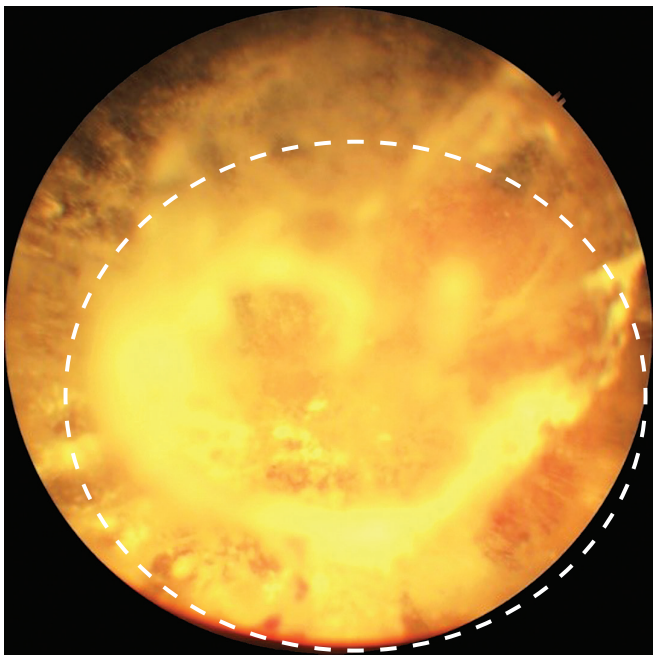

Figure 4. Fundus photograph of the right eye with a hardly seen mass *(white dashed-line circle)* covered with vitreous seed dusts and clouds located inferiorly.

Table 1. Summary of cases

	Case 1	Case 2	Case 3	Case 4
Age at diagnosis of bilateral retinoblastoma	5 years	7 months	1 year	2 years
Baseline IIRC grade of better eye	C	C	C	C
Intravenous chemotherapy	11 cycles (initial 6 + 5)	8 cycles	6 cycles	6 cycles
Number of injections given	10 (4 melphalan and 6 topotecan)	2 (2 melphalan)	7 (4 topotecan and 3 melphalan)	2 (2 topotecan)
External beam radiotherapy	Advised 25 sessions	2 sessions	None	Not applicable
Length of follow-up without activity (months)	0	19	2	Not Applicable
Response of vitreous seeding to intravitreous chemotherapy	With intermittent initial responses but with persistence at last follow-up	Resolved vitreous seedings	Resolved vitreous seedings	Enucleated
Visual acuity	20/20	At least Finger Play at 10 feet	Finger Play at 20 feet	Enucleated

DISCUSSION

This case series is the first to report on the local use of intravitreous chemotherapy in multiple patients for vitreous seeding with follow-up periods of 2-19 months after the last injection was given. Two eyes had controlled vitreous seeding with no recurrence with the use of intravitreous chemotherapy as an adjuvant to systemic VEC. Control is defined as the complete disappearance of vitreous seeds or conversion to fully calcified vitreous seeds. Recurrence is defined as development of new vitreous seeds after initial control was achieved. Two and seven injections were needed for the two eyes to control vitreous seeding, which are within the range of Rao et al.'s series.[8] This is despite the switching between melphalan and topotecan as opposed to the Rao et al.'s where they only used topotecan.[8]

In the Philippine tertiary hospital, intravitreous chemotherapy is offered to patients with vitreous seedings which are not responsive to intravenous chemotherapy, in accordance to the recommendations in literature. The 4th case was offered intravitreous chemotherapy, despite prior literature reporting that it is not effective in advanced cases, as a temporizing procedure while waiting for the guardian to give consent to enucleate. The patient was still included in the series as she underwent intravitreous chemotherapy. The choice of use between melphalan and topotecan is based on the availability of the agent from the supplier and costs, and not on effectiveness. Both agents are already proven effective in controlling vitreous seeding in prior literature and will not be discussed in this paper. The recommendations to inject intravitreous melphalan every 7-10 days and topotecan every three weeks were followed unless the agent is not available thus the shift to another, the patient did not follow-up on time, the patient or guardian tested positive for COVID-19 necessitating the then two-week quarantine, or the patient was not cleared by the pediatrician for surgery. Intravitreous chemotherapy was stopped once the vitreous seedings resolved.

The control of 50% achieved in this case series is lower than in other published series due to longer treatment interval from poor follow-up and the presence of advanced disease in the 4th case.[4,8,10,11] The use of intravitreous chemotherapy for the 4th case, despite its documented low success rate for globe salvage in IIRC Group E, was done to control the seeding, albeit temporarily, while allowing the ophthalmologist to convince the parents for enucleation. Due to the absence of an ultrasound biomicroscopy (UBM) in the operating room, the injection site for the 4th case was determined using indirect ophthalmoscopy. The triple freeze and thaw technique using cryotherapy of the injection site was employed in the intravitreal injection of all four eyes.[9] The failure of intravenous chemotherapy to control the vitreous seeding of the 1st case can be a result of the inability to monitor and control the activity of the seeds on time due to longer treatment interval from poor patient follow-up.

Dosages and injection techniques were based on recommendations from prior literature.[4,8] However, the recommended interval of 7-10 days for melphalan and three weeks for topotecan between injections were difficult to follow due to delays mostly from the patients not being medically cleared for examination under anesthesia and from the challenges brought about by the COVID-19 pandemic.[4,8] Although melphalan has been used more extensively for intravitreous chemotherapy based on the available literature, we freely switched between melphalan and topotecan based on availability.[8] There is preference for topotecan over melphalan for its longer reconstitution life, making it available to more patients, thus more economical.[8]

Chorioretinal toxicity and thinning from melphalan were not monitored due to the unavailability of an electroretinogram and a handheld optical coherence tomography at the institution.[7] Other reported side effects of intravitreous

melphalan injection such as anterior segment toxicity, posterior lens opacity, uveitis, vitritis, vitreous hemorrhage, vascular occlusion, and optic atrophy were not seen in the patients.[10] Other ocular side effects such as anterior chamber reaction, iritis, cataract, retinal pigment, and epithelium changes; and systemic ones like hematoxicity were also not seen with the use of intravitreous topotecan.[8]

CONCLUSION

The use of intravitreous melphalan and topotecan can be an effective adjuvant for systemic chemotherapy in controlling vitreous seeding in eyes with IIRC Group C. It is not effective in controlling IIRC Group E disease.

Statement of Authorship

GJVM, RJDT and PPPA contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising of manuscript, and final approval of the version to be published. MZMT contributed in the acquisition and analysis of data and final approval of the version to be published.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

None.

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