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ONCOLOGY

Combined intravitreal melphalan and intravenous/intra-arterial chemotherapy for retinoblastoma with vitreous seeds

Ji Hwan Lee[1] · Jung Woo Han[2] · Seung Min Hahn[2] · Chuhl Joo Lyu[2] · Dong Joon Kim[3] · Sung Chul Lee[1]

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Abstract
Purpose We aimed to evaluate the therapeutic effect and complications of combined intravitreal melphalan and intravenous/intra-arterial chemotherapy as a primary approach for retinoblastoma with vitreous seeds.
Methods In this retrospective case series, eight eyes from eight retinoblastoma patients with vitreous seeds were included. All eyes received 20–30 μg of intravitreal melphalan accompanied by intravenous and intra-arterial chemotherapy. Triple freeze-thaw cryotherapy was performed when withdrawing the needle from the eye to prevent tumor dissemination.
Results Tumors and vitreous seeds regressed in all eyes. The mean number of intravitreal melphalan injections was 3.25 (median 3.50, range 2–4). Globe salvage was attained in seven of eight eyes (87.5 %). Enucleation was performed in one case, in which the pathologic section showed no residual tumor and tumor-free resection margins. Serous retinal detachment was observed in four eyes (50 %), and vitreous hemorrhage developed in two (25 %). Retinal pigment epithelium atrophy or mottling was found in three eyes (37.5 %). There were no cases of extraocular tumor extension or remote metastasis.
Conclusions Combined intravitreal melphalan and intravenous/intra-arterial chemotherapy was effective for tumor and vitreous seeding control, but vision-threatening complications such as vitreous hemorrhage or serous retinal detachment occurred in half the cases.

Keywords Combined modality therapy · Intravitreal injections · Melphalan · Neoplasm seeding · Retinoblastoma

✉ Sung Chul Lee
sunglee@yuhs.ac

[1] Department of Ophthalmology, The Institute of Vision Research, Yonsei University College of Medicine, Seoul, Korea

[2] Department of Pediatric Hematology and Oncology, Yonsei University College of Medicine, Seoul, Korea

[3] Department of Radiology, Yonsei University College of Medicine, Seoul, Korea

Introduction

Other than enucleation or external beam radiotherapy, there are several treatment options for retinoblastoma, including intravenous, intra-arterial, and intravitreal chemotherapies. Based on the International Classification of Retinoblastoma (ICRB), treatment success with intravenous chemotherapy was achieved in 90–100 % of eyes classified as group A, B, or C, whereas in those with group C and D eyes, the treatment was successful in 47 % and 25 % of patients, respectively [1, 2]. Intra-arterial chemotherapy has been reported to be more effective in the management of advanced diseases [3, 4]. According to Shields et al., the globe salvage rates were 100 % and 33 % in group D and E eyes, respectively [3]. Another study showed that the 2-year probability of ocular salvage was 64 % for eyes with vitreous seeding alone. These results, however, imply that tumors with vitreous seeds are the most challenging aspect in the management of retinoblastoma.

In recent years, intravitreal chemotherapy has been evaluated for its efficacy and possible complications [5–9]. There are several reports on the role of intravitreal chemotherapy for persistent or recurrent vitreous seeding from retinoblastoma [5–7]. In the present study, we evaluated the therapeutic effect and complications associated with combined intravitreal melphalan and intravenous/intra-arterial chemotherapy as a

primary treatment approach for retinoblastoma with vitreous seeds.

Methods

Patients

We retrospectively reviewed the medical records of retinoblastoma patients with vitreous seeding who were treated between October 2013 and December 2014. In all patients, ≥ 6 cycles of systemic chemotherapy preceded intravitreal chemotherapy not only to treat retinoblastoma with vitreous seeds, but also to prevent metastasis including trilateral retinoblastoma. Systemic chemotherapy was composed of vincristine (1.5 mg/m^2), carboplatin (200 mg/m^2), etoposide (150 mg/m^2), and cyclosporine (12 mg/m^2). This study was approved by the Institutional Review Board of Severance Hospital.

Intravitreal melphalan injection

Melphalan was administered by intravitreal injection under general anesthesia. Intravitreal melphalan (20–30 μg/0.05 mL) was prepared in the operating room under sterile conditions. Intravitreal injection was performed via the pars plana at 2–3 mm from the limbus, depending on patient age. The injection site was carefully chosen to avoid direct contact with any vitreous seeds. Three cycles of freeze-thaw were applied when withdrawing the needle, according to the method described by Shields et al. [7] Forceps-induced jiggling was performed to disperse the medication in the vitreous cavity.

Intra-arterial chemotherapy

Intra-arterial chemotherapy was performed by a skilled interventional radiologist. After puncturing the femoral artery, a catheter was inserted in the ostium of the ophthalmic artery via the aorta, common carotid artery, and internal carotid artery. Melphalan (3–7.5 mg/kg per injection) was infused directly into the ophthalmic artery for 30 min.

Patient examination

Patient examination was performed under general anesthesia with a 2–4 week interval. Intravitreal injection was continued until vitreous seeds were controlled. If the vitreous seeds were not under control, then intra-arterial melphalan was administered after the examination. Treatment success was defined as regression of vitreous seeds, which included decreased vitreous seed size or number, loss of contractility, and loss of glistering. Failure was defined as vitreous nonresponse, increased vitreous seed size, or the development of new vitreous seeds. The patients were followed up with magnetic resonance imaging (MRI) of brain/orbit, chest and abdominal X-ray, and positron emission tomography–computed tomography (PET-CT) regularly for systemic monitoring.

Results

Eight eyes of eight patients treated with intravitreal melphalan and intravenous/intra-arterial chemotherapy and followed up at least 6 months were included in this study. The demographic characteristics of patients are summarized in Table 1. According to the ICRB criteria, tumor-harboring eyes were classified as group C (n=2, 25 %), group D (n=5, 62.5 %), and group E (n=1, 12.5 %). The mean number of intravitreal injections per patient was 3.25 (median 3.50, range 2–4).

Regression of vitreous seeds and tumor control was achieved in all eyes (Table 2, Fig. 1). Four injections were necessary for vitreous seed and tumor control in four eyes (50 %). There were no cases in which complete control of vitreous seeds and tumor was achieved with a single injection.

Globe salvage was attained in seven of eight eyes (87.5 %). Enucleation was performed in one eye (Case 2) due to persistent serous retinal detachment. However, the pathology report showed no residual retinoblastoma with extensive calcification, and the resection margins around the circumferential and optic nerves were tumor-free.

Complications included serous retinal detachment in four eyes (50 %) and vitreous hemorrhage in two (25 %). Serous retinal detachment and vitreous hemorrhage developed in the same eye in two cases (Cases 5 and 6). Atrophy of the retinal pigment epithelium (RPE) occurred in three cases (37.5 %). No other complication such as hypotony or phthisis bulbi was observed, and there were no cases of extraocular tumor extension or remote metastasis.

Table 1 Characteristics of patients with retinoblastoma and vitreous seeds who underwent combined intravitreal melphalan and intravenous/intra-arterial chemotherapy

Findings at diagnosis	Number of patients
Age (mean), months	28
Sex	
Male	1
Female	7
Heredity	
Sporadic	8
Familial	0
Laterality	
Unilateral	8
Bilateral	0
Follow-up period (mean), months	12

Table 2 Treatment outcomes of patients who underwent combined intravitreal melphalan and intravenous/intra-arterial chemotherapy

Case No.	ICRB group	Previous treatment	Combined treatment	Dose, μg	No. of injections	Outcome, vitreous seeds	Outcome, tumor	Complications
1	C	IV (8)	IV (1), IAC (3)	20	4	Regression	Regression	None
2	D	IV (13), IAC (1)	IAC (6)	20	4	Regression	Regression	Serous RD
3	E	NA	IV (6), IAC (5)	20	4	Regression	Regression	None
4	D	IV (6)	IAC (3)	20	2	Regression	Regression	Serous RD
5	D	IV (13), proton (22)	IAC (4)	30	3	Persistence	Persistence	VH, serous RD
6	C	IV (6)	IV (3), IAC (3)	30	4	Regression	Regression	VH, serous RD, RPE atrophy
7	D	IV (7), IVC (2)	IAC (3)	30	2	Regression	Regression	RPE mottling
8	D	NA	IAC (4) IV (6)	20	3	Regression	Partial Regression	RPE mottling

ICRB International classification of retinoblastoma, *IV* Intravenous chemotherapy, *IAC* Intra-arterial chemotherapy, *IVC* Intravitreal chemotherapy, *RD* Retinal detachment, *VH* Vitreous hemorrhage, *RPE* Retinal pigment epithelium, *NA* Not applicable. The numbers in the parenthesis represent the cycles of treatment

Discussion

Combined intravitreal melphalan and intravenous/intra-arterial chemotherapy was effective for tumor and vitreous seed control in all cases, but vision-threatening complications such as vitreous hemorrhage or serous retinal detachment occurred in half the cases.

In the present study, vitreous seeds and tumors regressed in all eyes with a mean of 3.25 injections. Ghassemi et al. reported that vitreous seeds were completely controlled in all cases with combined intravitreal melphalan and topotecan injection, and that tumor control was achieved with a single injection in three out of nine cases (33 %) [10]. In another study, complete control of vitreous seeds was observed early in the course of therapy, usually after the second injection [7]. In the present study, there were no cases of complete tumor or vitreous seed control following a single injection, and we found that vitreous seed control was usually achieved after the third injection.

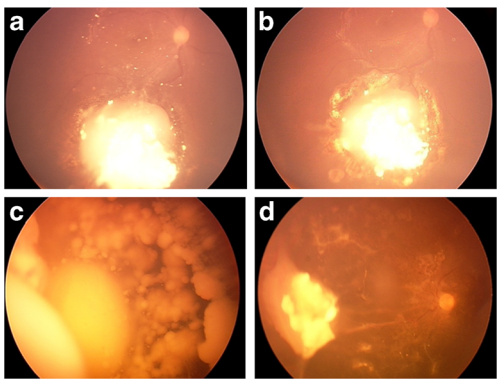

Fig 1 In Case 1, tumor and vitreous seeds regression was noted at 12-month follow-up. Before (**a**) and after (**b**) combined intravitreal and intravenous/intra-arterial chemotherapy. In Case 3, tumor and vitreous seeds (**c**) regressed at 9-month follow-up (**d**)

The globe salvage rate was 87.5 % (seven of eight eyes), which was similar to that noted in a previous report (100 %; 11 cases) [7]. In one case (Case 2), enucleation was performed due to persisting serous retinal detachment during combined treatment with intravitreal melphalan and intra-arterial chemotherapy. The pathologic report, however, showed no residual retinoblastoma with extensive calcification and the resection margins were also free from tumor at both the circumferential and optic nerve. This case implies that persisting serous retinal detachment during treatment does not necessarily mean failure of treatment; thus, a close observation rather than an early enucleation would be advisable.

The rate of serous retinal detachments during treatment (50 %) was much higher than that seen in previous reports administering intravitreal monotherapy (0–8.7 %) [5–7] or intra-arterial chemotherapy (7–17.6 %) [11, 12]. When compared with monotherapy, combined treatment with both intravitreal and intra-arterial chemotherapy might reduce the absorption of subretinal fluid by the RPE. RPE mottling or atrophic changes following intra-arterial melphalan administration have been observed previously in several reports [11, 12]. These RPE changes progress slowly, suggesting that slow-onset atrophy could be caused by chemotherapy toxicity [11]. We speculate that combined treatment could cause a more abrupt necrosis of tumor cells, which might also increase the incidence of serous retinal detachment.

Vitrectomy was performed in two eyes because of persistent vitreous hemorrhage and serous retinal detachment. The location of sclerotomy site was carefully chosen, and surgical manipulation was performed meticulously to minimize a contact with vitreous seeds or tumor mass. The sclerotomy wounds were closed using three cycles of cryotherapy similar

to the method described by Shields et al. [7] In case 6, the intraoperative findings showed a few diffuse RPE atrophy lesions and a tractional membrane with focal retinal detachment. A calcified tumor mass with serous retinal detachment was also observed, but the pathologic report was negative for malignancy. Tamponade was not performed because serous retinal detachment was confined to the periphery of the tumor. In other case (case 5), the intraoperative findings revealed a calcified tumor mass with fibrous traction and total serous retinal detachment. We did perform a tumor biopsy, which was also negative for malignancy. Subretinal fluid drainage and silicone oil injection was performed. In case 2, enucleation was performed because of persistent serous retinal detachment during treatment. The pathologic report showed no residual retinoblastoma with extensive calcification and the resection margins were also free from tumor. From the experience of these cases, we hypothesized that serous retinal detachment would not necessarily mean the treatment failure using combined intravitreal and intravenous/intra-arterial chemotherapy. Surgical intervention for retinal reattachment could be considered, but it would be better to avoid an early enucleation in patients with serous detachment.

We did not find any sign of tumor dissemination with 25 injections as noted in previous reports [5, 7]. We did not perform injections at the site of tumor, but near the site of tumor to avoid direct contact with the tumor or any vitreous seeds. Three cycles of freeze-thaw were used during injection to prevent tumor dissemination through the tract into subconjunctival or extraocular space. There was no serious adverse effect as hypotony or phthisis bulbi.

There are some limitations in the present study. The treatment results should be considered as the combined effect of intravitreal melphalan and intravenous/intra-arterial chemotherapy. The therapeutic effect was evaluated on the tumor lesion and vitreous seeds, but we did not include the effect on subretinal seeds. The mean follow-up period was 12 months, and a longer period would be needed to confirm the long-term safety and efficacy of the combined treatment.

In conclusion, combined intravitreal melphalan and intravenous/intra-arterial chemotherapy was effective for the control of retinoblastoma with vitreous seeds, but vision-threatening complications were not uncommon.

Compliance with ethical standards

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Conflicts of interest The authors declare that they have no conflict of interest. All authors certify that we have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval For this type of study formal consent is not required.

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