Favorable outcome of alternate intra-arterial and systemic chemotherapy for retinoblastoma

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Favorable outcome of alternate intra-arterial and systemic chemotherapy for retinoblastoma

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ABSTRACT

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Intra-arterial chemotherapy (IAC) is one of the current standard treatment of retinoblastoma, however it cannot exclude the risk of occult micrometastases in the central nervous system in advanced stage retinoblastoma. Alternate fashion of IAC and intravenous chemotherapy (IVC) strategy was developed to increase the eye salvage rate and to reduce the metastatic risk. Between January 2012 and December 2014, 13 eyes of 12 patients with newly diagnosed retinoblastoma received alternate IAC and IVC in Yonsei Cancer Center. Eye salvage rate was assessed by the eye preservation time which was defined as the duration from the diagnosis to the time of enucleation. Total 13 eyes were classified according to the International Classification of Retinoblastoma (ICRB) as group B (n = 1), group C (n = 2), group D (n = 5), or group E (n = 5). IAC was performed three to five times for each eye, total 54 times. Five to fifteen courses of IVC were performed. During the median follow-up period of 30.4 months, overall eye salvage rate was 63.9 ± 14.7%. All patients survived. The treatment was tolerable without significant complications. Primary alternate IAC-IVC was tolerable and effective for retinoblastoma.

Key words: retinoblastoma – chemotherapy – infusions, intra-arterial

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I. INTRODUCTION

With timely diagnosis and proper treatment, retinoblastoma has an excellent cure rate compared to other pediatric solid tumors. Survival rate is known to be as high as 95-97% in the United States and Europe, while the survival rate is 60-80% in many developing countries and <50% in less developed countries[1-3]. In Korea, children who were diagnosed with retinoblastoma between 2001 and 2010 showed a 5-year survival rate of 95.5%[4].

In spite of this, the treatment of retinoblastoma is constantly evolving, and the current goal of the treatment in developed countries is not only survival but also to save the eye, save the vision and minimize complications following therapy. These goals lead to the change in first-line treatment of retinoblastoma from enucleation or external beam radiotherapy (EBRT) to systemic chemotherapy and local treatment[5]. From the early 2000s, intra-arterial chemotherapy (IAC) has been introduced in a similar context. The concept of delivering the chemotherapeutic agent directly to the adjacent vessels of the tumor was introduced decades ago by Reese et al. and, Kiribuchi et al[6,7]. In Japan, several groups: Yamane et al. and, Suzuki et al. used the technique of selecting the internal carotid artery with a micro-balloon catheter in which the balloon occlusion was performed just distal to the ophthalmic artery and melphalan was

infused in 187 and 176 patients, respectively[8,9]. In United States, Abramson and Gobin first used the ophthalmic artery superselective cannulation method for IAC and they reported their experienced with IAC in 95 eyes of 78 patients, while Shields et al. analyzed 70 eyes in 67 patients, 198 sessions of IAC[10-12]. In both reports, IAC was effective in treating advanced stage retinoblastoma. In these studies, IAC was used not only as secondary or salvage therapy but also as primary or solitary therapy.

In the IAC era for eye preservation, advanced stage of retinoblastomas is treated with IAC for eye salvage, however the pathologic examination is not possible unless an enucleation is performed. For advanced stage retinoblastoma has risk of systemic metastasis or recurrence, We thought that IAC was basically local chemotherapy infusion strategy and it could not eradicate the micrometastatic foci in the central nervous system[13,14]. These aspects of IAC, expecially if the eyes are high-risk disease, have been discussed in other studies[15]. Moreover, unless systemic chemotherapy is delivered, eyes with high-risk features develop metastasis in 24%, while the metastatic rate is 4% with adjuvant systemic chemotherapy[16]. Therefore, the need for systemic chemotherapy should be considered for the patients with advanced stage retinoblastoma who were treated with IAC alone.

We have reported our experience with IAC and intravenous chemotherapy (IVC), combined approach for refractory retinoblastoma[5]. IAC was performed in 5 advanced stage (Reese-Ellsworth stage IV-V) patients with 14 sessions of catheterization, all resulting in eye preservation. In this article, we tried alternated IAC-IVC approach for the newly diagnosed patients with retinoblastoma to achieve improved eye salvage rates and to assess feasibility of the alternate treatment.

II. MATERIALS AND METHODS

1. Patients

Among the 40 patients who were diagnosed and treated as retinoblastoma in Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea between January 2012 and December 2014, 26 patients received IAC. Fourteen patients who received IAC as secondary salvage therapy were excluded, and 13 eyes of 12 newly diagnosed patients were evaluated (1 bilateral cases). Patients' demographic data including sex, age at diagnosis (months), symptoms at diagnosis, mutation of the RB1 gene, grouping according to the Reese-Ellsworth (RE) group, International Classification of Retinoblastoma (ICRB), brain magnetic resonance imaging (MRI) were reviewed retrospectively. This study was approved by the ethical committee of Yonsei University College of Medicine, Yonsei University Health System (approval number: 4-2015-0538).

2. Treatment

All patients received both IAC and IVC. IVC consisting of vincristine (1.5mg/m2, day 1), carboplatin (200mg/m2, day 1-2), etoposide (150mg/m2, day 1-2), and cyclosporine (12mg/kg, day 1-2) (CVE) was performed as first choice, and it was repeated every 3 weeks. After repeating 6 to 8 courses of first line chemotherapy, 2nd line chemotherapy including vincristine (1.5mg/m2, day 1), doxorubicin (45mg/m2, day 1), cyclophosphamide (500mg/m2, day 1-3) (VDC) have been tried to the patients who were suspected to have remained viable tumor after the first line therapy. The other regimen was applied to the patients when the disease progresses. High dose chemotherapy, including carboplatin (500mg/m2, day 1-3), etoposide (250mg/m2, day 4-6), and thiotepa (300mg/m2, day 4-6) as a conditioning regimen, with autologous hematopoietic

stem cell transplantation was performed in one patient.

In most cases, IAC was performed alternatively with IVC (alternate IAC-IVC). However, according to the availability of the IAC treatment and patients' condition, systemic chemotherapy alone or IAC alone therapies were performed consecutively during the treatment course. Our technique of IAC has been described in the previous report[5]. Femoral arterial puncture was performed under general anesthesia. Four French angiocatheters were passed through the aorta, and carotid artery subsequently, and then the Marathon flow microcatheter was positioned into the ophthalmic artery during 30 minutes of melphalan infusion. All of the procedures were performed by a trained interventional radiologist. The doses of 3 mg, 4 mg or 5 mg of melphalan were used according to the age of the patient (< 1yr, 3 mg; 1-2 yr, 4 mg; >3 yr, 5 mg). The complications of IAC were closely monitored for one day, and the patient was discharged on the next day after the procedure. All adverse events related to the treatments were assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Focal therapies such as thermotherapy, laser photocoagulation, cryotherapy, and intravitreal chemotherapy (melphalan) injection were also performed in the patients. The ophthalmologist meticulously examined the eye after every one or two courses of chemotherapy under general anesthesia and determined the need for focal therapy.

3. Statistical analysis

Data were presented as median value with range, number (n) with percent, and mean ± standard deviation. The duration of the eye salvage was calculated from the day of diagnosis to the day of enucleation. Eye salvage rate was analyzed using the Kaplan-Meier method, and tested by log-rank test. All statistical analyses were performed using the SPSS statistical software (version 20.0, SPSS Inc., Chicago, IL).

III. RESULTS

Demographic characteristics of the patients are presented in Table 1. Median age of total 12 patients was 18.8 months at diagnosis (range, 11.0 to 35.8 months). Two patients with eye number 5, and 6 had RB1 gene mutation. Total 13 eyes were classified according to the RE system as group 3 (n = 3, 23.1%), group 4 (n = 3, 23.1%), or group 5 (n = 7, 53.8%). The ICRB classified the eyes as group B (n = 1, 7.7%), group C (n = 2, 15.4%), group D (n = 5, 38.5%), or group E (n = 5, 38.5%).

All eyes received alternate IAC-IVC. IVC was usually performed prior to IAC, and only three eyes (eye number 8, 10, and, 12 in Table 2) initially received IAC followed by IVC. Most of the eyes received IVC first for one to five cycles (one cycle, n = 3; two cycles, n = 3; three cycles, n = 2, four cycles, n = 1; five cycles, n = 1), and started IAC in their later treatment course. Eye number 2, 4, and 5 received three or four courses of IVC ahead of IAC. In these patients, IVC courses were given to the patients to assess independent therapeutic effect of IVC rather than IAC before introducing IAC. The evaluation showed insufficient regression of tumor, or progression of seeding. Patient 3 received alternate IAC-IVC at first, meanwhile ceased IAC because of vitreous hemorrhage. The median duration from diagnosis to first IAC was 46 days (range, 9 to 119 days) in all patients. The longest duration for the eye to receive IAC was 119 days in eye number 3-right, and in that case, five courses of IVC were administered before IAC due to failure of procedure to target the ophthalmic artery. The patient had bilateral retinoblastoma, and the other eye received IAC after two courses of IVC. The median age of the patients at first IAC was 22.7 months (range, 12.5 to 36.6 months), and three to five times for each eye, total 54 times of IAC was performed in 13 eyes.

Five to fifteen courses (median, 8 courses) of IVC were performed in the

patients (Table 2). The first-line chemotherapy with CVE was applied to all of the patients. Four patients (5 eyes) received the other chemotherapy regimen consists of VDC. Only one eye (eye number 2) with multiple vitreous seeding received high dose chemotherapy with autologous hematopoietic stem cell rescue. The patient was treated before we started intraviteral chemotherapy.

Local therapy was performed in 12 out of the 13 eyes (92.3%). Transpupillary thermotherapy was the most commonly performed local therapy (total 22 times). Intravitreal melphalan injection was administered in 5 eyes for a total 15 times. Besides, cryotherapy, indirect laser photocoagulation, endolaser coagulation were performed according to the judgement of the ophthalmologist to control the posteriorly located small seedings (Table 2).

Complications related to the treatments are described in Table 3. Neutropenia was the most common complication related to IVC. Patient 7, showed grade 2 rashes and hypertension during cyclosporine infusion and patient 9 had grade 3 rashes. In most patients, IAC was performed without serious side effect. However, three patients developed grade 2 periorbital edema, one patient developed vitreous hemorrhage, and patient 4, showed hypotension and desaturation right after the infusion of melphalan in the selected ophthalmic artery.

There was no death during the median follow-up duration of 30.4 months (range, 8.5 to 43.5 months). Overall eye salvage rate was 63.9 ± 14.7% (Figure 1). Overall eye salvage rate in group D and E (total 10 eyes) was 49.2 ± 18.8%. According to the group, ICRB group B, and C resulted in 100% of salvage rate, 33.3 ± 27.2% in group D, and 60.0 ± 21.9% in group E (p=0.39) (Figure 2).

Four out of the thirteen eyes (30.7%) were enucleated due to progression of vitreous and subretinal seeding in two eyes (eye number 1 and, 5), and vitreous hemorrhage with high intraocular pressure, and retinal detachment in two eye (eye number 7 and, 9). Histopathologic evaluation of the enucleated eyes

revealed residual tumor in three cases except the eye number 9, and eye number 1 showed choroid involvement, hence the patient received adjuvant chemotherapy after enucleation. Two eyes were classified as ICRB group E, and two eyes were classified as ICRB group D.

Table 1. Patients characteristics

Eye number	Sex	Age at diagnosis (months)	Symptom at diagnosis	RB1 gene mutation	RE group	ICRB staging
1	Male	22.2	Leukocoria	No	5	D
2	Male	34.1	Leukocoria	No	5	D
3-right	Male	18.8	Leukocoria	No	4	C
3-left					5	E
4	Female	18.5	Leukocoria	No	3	C
5	Male	18.8	Leukocoria	Yes[1]	5	E
6	Female	18.6	Leukocoria	Yes[2]	3	B
7	Male	27.1	Visual disturbance	Not checked	5	E
8	Male	14.9	Leukocoria	No	5	E
9	Female	11.0	Leukocoria	No	3	D
10	Female	30.1	Leukocoria	No	5	E
11	Female	29.9	Leukocoria	No	4	D
12	Male	35.8	Leukocoria	Not checked	4	D

[1]intron6 c.607+G>T.

[2]exon18 c.1735C>T.

RE: Reese-Ellsworth, ICRB: Internatinal Classification of Retinoblastoma.

Table 2. Treatment summary and outcome

Eye number	IAC times	CTx times before first IAC	CTx regimen	Number of courses of systemic CTx	Age at first IAC (months)	First IAC from diagnosis (days)	Local therapy	Eye salvage duration (months)
1	3	2	CVE, VDC	15 (12+3)[1]	24.0	56	ILP, cryotherapy, endolaser[2]	10.8[3]
2	5	3	CVE, VDC, CTE	12	36.6	76	TTT	41.8
3-right	4	5	CVE, VDC	12	22.7	119	TTT	40.3
3-left	5	2	CVE, VDC	12	20.2	44	TTT	40.3
4	5	4	CVE	8	21.6	95	TTT	41.8
5	5	3	CVE	8	20.9	62	TTT, endolaser photocoagulation	9.6[3]
6	3	2	CVE, VDC	9	20.5	57	TTT, Ivtr melphalan	31.3
7	3	1	CVE	6	28.3	37	TTT	7.6[3]
8	3	0	CVE	5	15.3	13		22.8
9	3	1	CVE, VDC	11	12.5	46	Ivtr melphalan	17.3[3]
10	5	0	CVE	7	30.6	14	Ivtr melphalan, ILP, cryotherapy	16.6
11	5	1	CVE	6	30.9	29	Ivtr melphalan	10.6
12	5	0	CVE	6	36.1	9	Ivtr melphalan	9.4

[1]three adjuvant cycles of chemotherapy after enucleation.

[2]endolaser for cataract treatment.

[3]enucleation.

IAC: Intra-arterial chemotherapy, CTx: chemotherapy, CVE: cisplatin, vincristine, etoposide with cyclosporine, TTT: transpupillary thermotherapy, VDC: vincristine, doxorubicin, cyclophosphamide, ILP: indirect laser photocoagulation, CTE: carboplatin, thiotepa, etoposide, Ivtr: intravitreal.

Table 3. Adverse events related to treatment

Complications	Grade 2	Grade 3	Grade 4
Systemic chemotherapy related			
neutropenia	4 (30.8)	2 (15.4)	7 (53.8)
neutropenic fever	0	7 (53.8)	0
pneumonia	0	1 (7.7)	0
vomiting	2 (15.4)	2 (15.4)	0
rash	1 (7.7)	1 (7.7)	0
hypertension	1 (7.7)	0	0
Intra-arterial chemotherapy related			
perorbital edema	3 (23.1)	0	0
vitreal hemorrhage	0	2 (15.4)	0
cardio-respiratory reflex reaction	0	0	1 (7.7)
nonspecific focal brain lesion	1 (7.7)	0	0

presented as number (%).

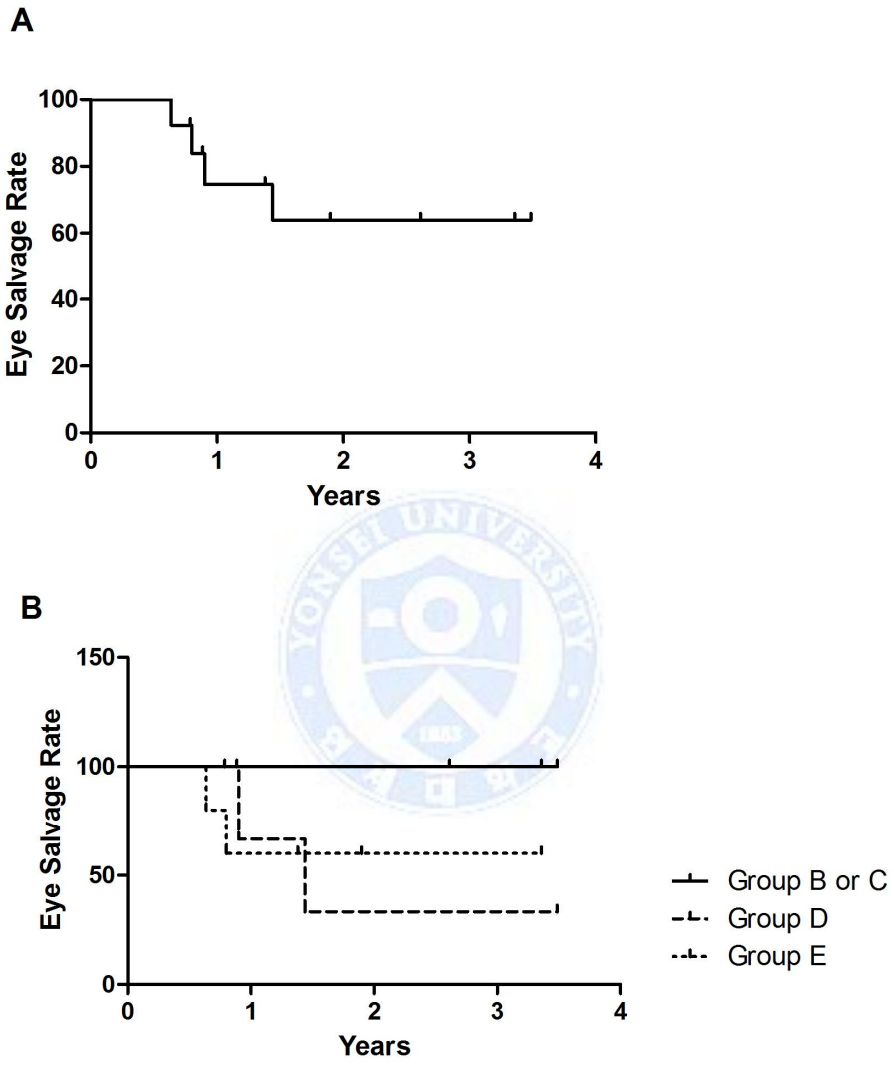

Figure 1. Eye salvage rate of retinoblastoma using alternate intra-arterial and intravenous chemotherapy approach

1A. Overall eye salvage rate

1B. Overall eye salvage rate per International Classification of Retinoblastoma group (B or C vs. D vs. E)

IV. DISCUSSION

Alternate IAC-IVC approach showed promising result of eye preservation (overall eye salvage rate, 63.9 ± 14.7%). Advanced stage of retinoblastomas were salvaged adequately. There were no significant toxicities associated with IAC or IVC. Histopathologic examination of enucleated eyes showed high risk pathologic features in one eye, and this indicated the need for adding IVC to IAC.

Reese introduced intra-arterial triethylene melamine injection via the carotid artery with radiotherapy, and this was the first attempt at IAC for retinoblastoma[6]. After decades, in Japanese groups, selective IAC of retinoblastoma by temporary occlusion of the internal carotid artery was generally successful with respect to tolerability[8,9]. However, there were some limitations because the chemotherapeutic agents may flow into other cerebral arteries. Moreover, they combined multimodal approaches such as systemic chemotherapy, local treatment and even external beam radiotherapy, hence, the sole role of IAC was not evidently proved in their valuable works. Superselective ophthalmic artery chemotherapy was introduced by Abramson from the Memorial Sloan Kettering Cancer Center in 2008[12]. They avoided the balloon occlusion method and a technically well selected ophthalmic artery was used. Chemotherapeutic agents were infused over 30 minutes in a pulsatile fashion, and the procedure was well tolerated. Their several subsequent reports proved the beneficial effect of IAC in treatment of refractory or primary retinoblastoma treatment. Since then many institutions adopted IAC as the major modality for treating retinoblastoma.

We introduced alternate treatment fashion with IAC and IVC, which is assumed to be the best in reducing metastasis rate and increasing the eye salvage rate. Because IAC is one of the local chemotherapeutic infusion

methods, it cannot eradicate the potential metastatic foci in the brain. IAC only approach can impose the metastasis risk in advanced stage retinoblastoma. Moreover, current trend of retinoblastoma treatment is to preserve eye globes and eye sights, hence the exact pathologic confirmation is impossible during current treatment approaches. Ophthalmologic examination alone may not exclude all of the high risk pathologic features. We experienced no metastasis nor deaths from retinoblastoma with this alternative approach. The high-risk pathologic features are known to increase the risk of metastasis in retinoblastoma, and indicate the necessity of adjuvant systemic chemotherapy[13,14,17,18]. These features include anterior chamber seeding, choroidal involvement, tumor beyond the lamina cribrosa, intraocular hemorrhage, scleral and extrascleral extension, and tumor at the cut end of the optic nerve. Presence of these high-risk pathologic features are correlated with the clinical staging system of group D or E retinoblastoma. Group D retinoblastoma has high risk features in 17% of patients, and group E retinoblastoma has high risk features in 24% of patients[19]. In this context, all of the advanced ICRB stage retinoblastoma have possibility of micrometastases, yet it is difficult to know before we obtain the pathology by enucleation. Our treatment approach is unique because we tried both treatment concurrently, IAC for intraocular lesion and IVC for possible micrometastases. Because advanced stage has more risk of micrometastases, this approach may benefit more in the advanced stages.

We experienced no metastasis nor deaths from retinoblastoma with this alternative approach. However most metastasis occur several years after the last treatment. Hence, more data and long-term follow-up of at least ten years after our alternate approach are needed to prove its definite role in preventing metastasis and, increasing survival.

Various complications of systemic chemotherapy including hearing

impairment, second malignancies, and other hematologic and, infectious complications in patients with retinoblastoma are well known[20]. Compared with other centers where systemic chemotherapy is performed, we have performed more number of courses of chemotherapy, median 8 courses[5,21]. Nonetheless, systemic chemotherapy was tolerable without severe complications, and neutropenia and neutropenic fever were the most common complications after systemic chemotherapy.

Generally, IAC is a tolerable procedure in most patients. Local periocular edema and conjunctival injection can occur; however, these can be managed well[22,23]. Three of our patients also experienced eyelid edema. In recent reports, choroidal ischemia, intraocular vascular complications, and hyperpigmentation of the retinal pigment epithelium were documented but their negative effects on the eye survival rate and visual acuity should be followed up and evaluated further[11,22]. We did not observe vascular changes; however, close monitor is needed. There was no hematologic toxicity over grade 2 during IAC. The most serious acute complication of IAC is hemodynamic instability[24]. We noted this complication in one patient. This phenomenon is thought to be related to increased vagal tone, and the time sequence of the event was similar to that in the other report[24]. Although the patient was recovered completely, we discontinued IAC. One patient who had received five courses of previous IAC, showed T2 hyperintense lesion in the left frontal cortex incidentally on MRI; however she had no clinical symptoms and the lesion disappeared spontaneously after three months. This finding is thought to be due to a nonspecific focal ischemic lesion after cerebral angiography.

Shields CL presented their experience in the chemotherapy era, and they showed that ICRB group D patients had an eye salvage rate of 47%[25]. With systemic chemotherapy combined with local therapy or radiotherapy, only 25~38% of eyes in high RE stage patients could be salvaged in other articles[26,27].

However, recent reports of IAC show an eye-opening progress. Gobin and Abramson reported their 4 year experience of treating 95 eyes in 78 patients[10]. They used melphalan and added topotecan, carboplatin, or methotrexate depending upon the retinoblastoma stage and the status of the eye. Even in the RE group V eyes, the naïve eyes were preserved at a rate of 70%. None of the 12 eyes of the RE group I~IV were enucleated[20]. Shields CL reported their 5-year experience at Wills Eye Hospital, 100% eye preservation rate in ICRB stage B and, C patients, 94% in stage D and 36% in group E patients[11]. In our study, the salvage rate was 63.9% among all eyes. Even in the group D or E patients, we could preserve the eyes in 49.2%. This success rate is comparable with that in work performed at other institutions'[10,11,22,23]. Instead of combining of 2 or 3 drugs during IAC, we reduced the IAC interval after systemic chemotherapy from 3 weeks to 2 weeks to intensify the treatment, and this effect on eye preservation should be studied further. In this aspect, for treating advanced stage retinoblastoma, we can have two options in performing IAC; one option is increasing the dose intensity and the other option is adding more drugs.

There are limitations to this study: most patients followed the protocol of alternate IAC-IVC regimen; however, the time of starting IAC after diagnosis and the number of courses of systemic chemotherapy before and after IAC were varied among patients. This makes difficult to evaluate the treatment response and, efficacy of IAC or IVC separately. And, from September 2013, intraviteral chemotherapy has been introduced to the patients, however, the application of new treatment method was not considered. Several data were collected retrospectively, and this might have caused a bias. A larger number of patients are needed to indicate a more reliable role of combination therapy, and longer follow-up duration is needed to determine the long-term effect of this regimen.

V. CONCLUSION

In conclusion, in spite of several limitations, primary IAC combined with systemic chemotherapy was tolerable and effective in patients with retinoblastoma. Combined alternative IAC and systemic chemotherapy is a promising option for advanced stage retinoblastoma.

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ABSTRACT (IN KOREAN)

망막모세포종 환자를 대상으로 한 동맥 항암 및 전신 항암 병용 요법의 효과

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눈동맥 항암은 망막모세포종의 표준치료로 자리 잡아가고 있으나 전신 전이나 재발을 막는데에 얼마나 효과적인지에 대해서는 아직 확립 되지않았다. 따라서 전신 항암치료와 눈동맥 항암을 병용하는 요법의 장점이 있을 것으로 생각되고 있다. 2012년 1월부터 2014년 12월까지 연세대학교 의과대학 세브란스 병원에서 망막모세포종으로 진단된 환자 중 눈동맥 항암, 전신 항암 병용요법을 시행한 12명 (13안구)을 대상으로 치료의 효과를 분석하였다. International Classification of Retinoblastoma (ICRB) 분류에 따라 그룹 B (n = 1), 그룹 C (n = 2), 그룹 D (n = 5), 혹은 그룹 E (n = 5) 환자를 나누었으며 눈 적출까지 안구의 생존율을 비교하였다. 중간 값 30.4 개월 간의 추적 관찰 기간 동안 안구의 생존율은 63.9 ± 14.7% 였으며 사망한 환자 및 심각한 부작용을 보인 환자는 없었다. 눈동맥 항암 및 전신 항암의 병용 요법이 망막모세포종의 효과적인 치료적 방법 중 하나가 될 수 있을 것으로 생각한다.

핵심되는 말: 망막모세포종, 항암 치료, 동맥 내 주입