

Chemoreduction Followed by Local Therapy and Adjuvant Chemotherapy for Advanced Intraocular Retinoblastoma: A Pilot Study in a Single Center

Intraocular (IO) retinoblastoma (RB) has traditionally been treated with enucleation (ENU) or external beam radiotherapy (EBRT). Recently, clinical trials are in progress to cure RB without ENU or EBRT in order to salvage the globe and to avoid unacceptable side effects of EBRT. We performed a pilot study to treat patients with advanced Reese-Ellsworth (RE) stage IO RB with initial chemotherapy (CRx) followed by local therapy (LT) and adjuvant CRx. Ten eyes (8 RE group V, 2 RE group IV) from 9 patients were enrolled from March 2001 to November 2001. All tumors responded to CRx. In 5 of 10 eyes, the RB was enough to be treated with LT after chemoreduction. One patient who underwent LT is waiting for ENU due to post-cryotherapy complication. For a median follow-up of 13 months (8-16 mo), 4 eyes that received LT and adjuvant CRx were relapse-free. A patient with bilateral RB who failed to be a candidate for LT was rescued with high-dose CRx and hematopoietic stem cell transplantation. Consequently, by treating patients according to our strategy, we were able to salvage 6 out of 10 eyes without ENU or EBRT. These results suggest that chemoreduction followed by LT and adjuvant CRx might offer the opportunity to salvage the globe and vision even in patients with advanced stage IO RB.

Key Words : *Retinoblastoma; Chemoreduction; Local Therapy; Chemotherapy; Adjuvant*

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INTRODUCTION

Retinoblastoma (RB) is the most common intraocular (IO) malignancy in children and it occurs almost exclusively in young children less than 5 yr. The incidence is 1 in 15,000 to 30,000 live births in the United States (1). Though the accurate incidence of RB in Korea is not known, it is estimated to be about 20 to 40 per year according to the annual report of the Korean Central Cancer Registry Program based on registered data from 131 hospitals.

More than 80% of children with RB are cured with various treatment modalities including enucleation (ENU), external beam radiotherapy (EBRT), local therapy (LT), and chemotherapy (CRx) (2). ENU has been the standard curative method for advanced unilateral IO RB or for the more severely affected eye in a bilateral disease (3, 4). Despite the excellent survival of IO RB with simple ENU, it inevitably brings loss of the globe and vision of the affected eye. EBRT can be used as a primary treatment modality or adjuvant therapy after ENU (5, 6). But it can cause many serious late complications including cosmetic deformity and second malignancy (6-8). For these reasons, there has been a substantial decrease in the frequen-

cy of ENU or EBRT over the recent decades, a great portion of which is attributable to the advance in CRx and local treatment modalities (9-17). However, there is still some debate over the benefit of chemoreduction in advanced stage IO RB and most published reports do not have the concept of adjuvant CRx after LT. Therefore, we designed this pilot study to investigate whether chemoreduction could reduce the size of advanced IO RB enough to be treated by local modality, and to investigate if adjuvant CRx might have a role in preventing relapse.

MATERIALS AND METHODS

Patients

Nine consecutive patients (10 eyes) with advanced IO RB were enrolled in Samsung Medical Center from March 2001 to November 2001. Diagnosis was confirmed by typical clinical presentation (leukocoria and/or strabismus) and ophthalmologic examination. Ultrasonography of globes, neuroimaging studies (CT or MRI), cerebrospinal fluid cytology, bone scan,

and bone marrow examination were done to define the tumor size and extent. IO RBs were grouped according to the Reese-Ellsworth (RE) classification. Tumor size was recorded as 'tumor base \times tumor thickness' in millimeters. In the case where the tumor was too large and almost filled the whole globe, the size of each dimension was recorded as 'over 20.00 mm' and regarded as 20.00 mm for the convenience of later comparison with that of post-chemoreduction.

Treatment

All 9 patients were initially treated with systemic CRx, named 'VEC', including vincristine (1.5 mg/m² i.v. on day 0), etoposide (150 mg/m² i.v. on day 0 and 1), and carboplatin (560 mg/m² i.v. on day 0). Informed consent was obtained on every occasion before treatment. After 3 cycles of 3-week interval CRx, the affected eye was thoroughly examined to evaluate for objective reduction in tumor volume. Tumor response was estimated as the percent reduction in tumor base and thickness.

If objective reduction in tumor volume was achieved after 3 cycles of CRx, the same regimen was repeated for additional 3 cycles. After total 6 cycles of reduction CRx, the tumor was reevaluated to decide on the next mode of therapy. In cases where the tumor was reduced enough, we applied LT followed by additional 3 cycles of adjuvant CRx. In cases where the tumor was reduced but insufficient for LT, we added a few cycles of the same regimen or more intensive CRx such as 'CCG (Children's Cancer Group) 321P2' (cisplatin 60 mg/m² i.v. on day 0, adriamycin 30 mg/m² i.v. on day 2, etoposide 100 mg/m² i.v. on day 2 and 5, and cyclophosphamide 30 mg/kg i.v. on day 3 and 4) and 'ICE' (ifosfamide 1,200 mg/m²

i.v. on day 0 to 4, carboplatin 400 mg/m² i.v. on day 0 and 1, and etoposide 100 mg/m² i.v. on day 0 to 4) to increase the tumor response. In our institution, only cryotherapy and photocoagulation were available as LT modalities. EBRT was excluded as a therapeutic tool in our protocol because of its numerous late complications including cosmetic deformity and second malignancy.

After completion of treatment, patients were followed-up by an ophthalmologist with an interval of less than 2 months to monitor local recurrence.

Evaluation of treatment outcome and toxicities

Probability of event was estimated by the Kaplan-Meier method. Event was defined as ENU (or decision to remove the globe) or EBRT.

Toxicities of CRx were recorded according to the common toxicity criteria of National Cancer Institute of U.S.A..

RESULTS

Treatment outcomes

Table 1 summarizes patient characteristics and treatment outcomes. Of 10 affected eyes in 9 patients (6 males and 3 females), 2 eyes were RE group IV and the other 8 eyes were RE group V. One patient with bilateral RB was classified as RE group IV and RE group V in each eye. None of the cases had an extraocular disease. All 10 eyes showed objective reduction in tumor volume after CRx (Fig. 1, 2) but only 5 eyes showed sufficient reduction of tumor volume for LT. There

Table 1. Patient characteristics and treatment outcome

| Patient No. | Sex | Age (mo) | Affected Eye | RE Group | CRx Regimen | Regimen Change | CRx Cycles* | Size (base \times thickness in millimeters) | | Local Therapy | Enucleation | Final Vision (Affected Eye) | Follow-up (mo) |
|-------------|-----|----------|--------------|----------|------------------|--------------------------------|-------------|---|---------------------|---------------|------------------|-----------------------------|----------------|
| | | | | | | | | Initial | After CRx | | | | |
| 1 | M | 69 | L | V | VEC [†] | - | 9 | 20.00 \times 20.00 | 4.69 \times 1.65 | Yes | Yes [‡] | No | 16 |
| 2 | F | 14 | R | V | VEC | - | 6 | 16.32 \times 9.95 | 6.03 \times 2.50 | Yes | No | Yes | 16 |
| 3 | M | 10 | R | IV | VEC | - | 6 | 10.61 \times 5.05 | 9.99 \times 3.37 | Yes | No | Yes | 14 |
| 4 | M | 21 | R | IV | VEC | CCG 321P2 [‡] | 13 | 17.28 \times 7.23 | 14.42 \times 2.82 | No | No [‡] | Yes | 13 |
| | | | L | V | | | 13 | 16.30 \times 12.39 | 10.95 \times 1.86 | No | No [‡] | Yes | 13 |
| 5 | M | 16 | R | V | VEC | CCG 321P2 | 11 | 15.80 \times 20.00 | 11.74 \times 2.94 | No | Yes | No | 13 |
| 6 | F | 17 | L | V | VEC | CCG 321P2 →ICE [§] | 7 | 17.68 \times 11.10 | 17.20 \times 8.77 | No | No ^{**} | No | Lost |
| | | | | | | | | | | | | | |
| 7 | M | 32 | R | V | VEC | - | 6 | 20.00 \times 20.00 | 16.65 \times 3.75 | No | Yes | No | 10 |
| 8 | F | 34 | R | V | VEC | - | 6 | 15.81 \times 14.07 | 9.95 \times 3.50 | Yes | No | Yes | 9 |
| 9 | M | 24 | R | V | VEC | - | 6 | 15.51 \times 13.36 | 10.12 \times 3.91 | Yes | No | Yes | 8 |

RE, Reese-Ellsworth; CRx, chemotherapy.

*Total number of reduction chemotherapy. [†]Vincristine (1.5 mg/m² i.v. on day 0), etoposide (150 mg/m² i.v. on day 0, 1), carboplatin (560 mg/m² i.v. on day 0). [‡]Cisplatin (60 mg/m² i.v. on day 0), adriamycin (30 mg/m² i.v. on day 2), VP-16 (100 mg/m² i.v. on day 2, 5), cyclophosphamide (30 mg/kg i.v. on day 3, 4). [§]Ifosfamide (1,200 mg/m² i.v. on day 0, 1, 2, 3, 4), carboplatin (400 mg/m² i.v. on day 0, 1), VP-16 (100 mg/m² i.v. on day 0, 1, 2, 3, 4).

[‡]We decided to enucleate the globe due to extensive retinal detachment after cryotherapy. [‡]A patient with bilateral disease is waiting for high-dose chemotherapy and stem cell rescue due to lack of accessibility to either eye by local therapy. ^{**}Refused enucleation and lost to follow-up against medical advice.

was a median 29.3% (range, 2.7-76.6%) decrease in tumor base and 75.0% (range, 21.0-91.8%) decrease in tumor thickness. No tumor was sufficiently reduced enough to be a candidate for photocoagulation, so only cryotherapy was used as LT because plaque radiotherapy was unavailable. Among the 5 patients (5 eyes) that entered into LT, one patient (Table 1, Patient No. 1) had received additional 3 cycles (total 9 cycles) of reduction CRx due to persistent retinal detachment, but we decided to enucleate the globe due to extensive retinal detachment that developed after cryotherapy. Ultimately, 4 of 10 eyes with RE group IV or V achieved disease control by chemoreduction and LT followed by adjuvant CRx and we were able to preserve the globe and vision. Of the 5 eyes in which the tumor volume was not reduced enough for LT, 2 eyes were enucleated and one eye was lost to follow-up against medical

advice. The other 2 eyes in a patient with bilateral disease were rescued with high-dose CRx and hematopoietic stem cell transplantation because we could not access to either eye by LT in spite of remarkable reduction in tumor volume and gain of vision in both eyes. No patient received EBRT. Accordingly, we could avoid ENU and EBRT and could preserve useful vision in 6 out of 10 eyes in our cohort. Patients were followed for a median of 13 months (range, 8-16 months). When we define 'event' as ENU (or decision to enucleate) or EBRT, the Kaplan-Meier estimate revealed 48.6% probability of event at 16 months after chemoreduction (Fig. 3).

Of the 4 patients (5 eyes) who were not candidates for LT, CRx regimen was changed in 3 patients (4 eyes)-due to persistent retinal detachment in one patient with bilateral disease (Table 1, Patient No. 4), poor response in the second case

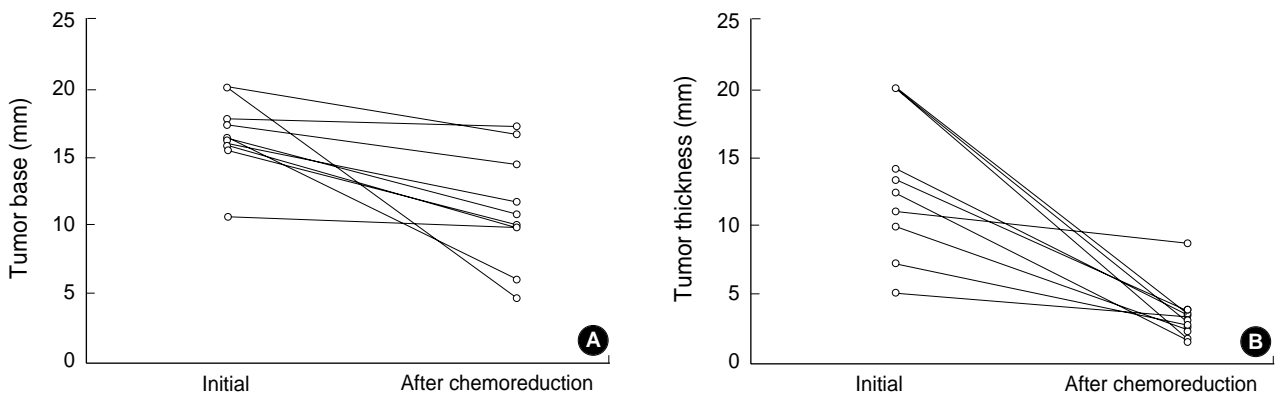


Fig. 1. Reduction of tumor size in base and thickness after chemotherapy. All 10 affected eyes responded to chemotherapy with variable sensitivity. Tumor thickness seemed to be more dramatically reduced than tumor base after chemotherapy.

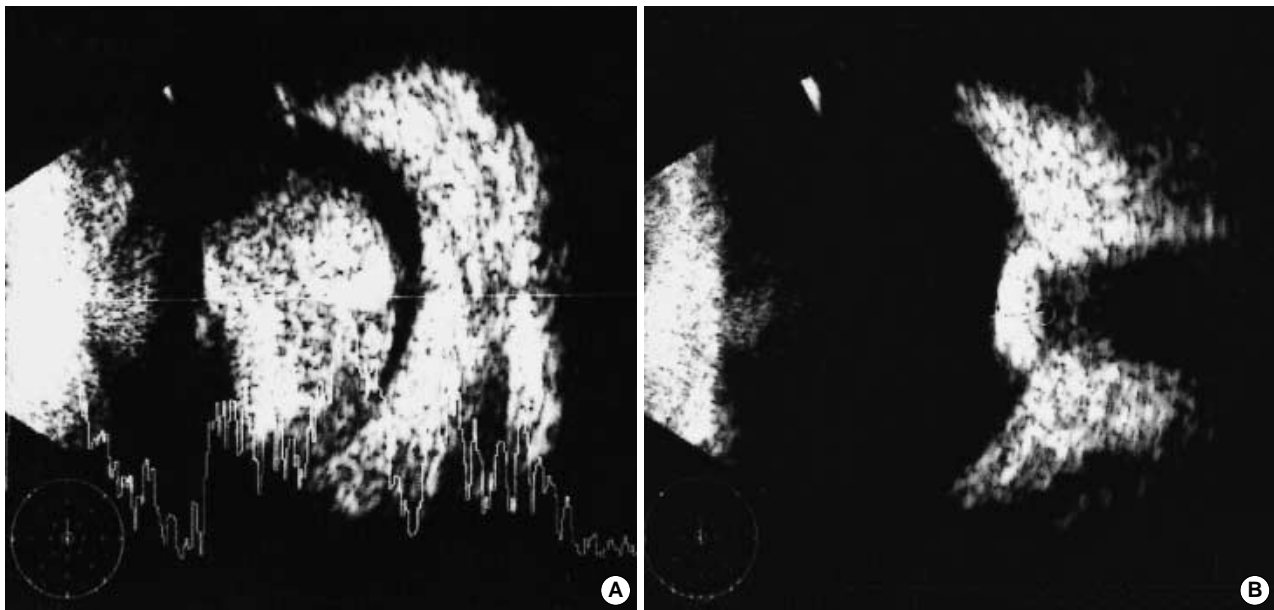


Fig. 2. Ultrasonographic finding of the globe in a patient with right intraocular retinoblastoma. Initial large intraocular mass (A) was dramatically reduced in size (B) after 6 cycles of VEC (vincristine, etoposide, and carboplatin) chemotherapy.

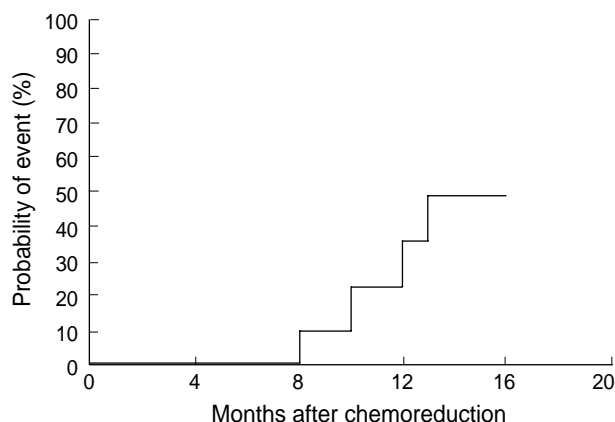


Fig. 3. Kaplan-Meier estimate of the probability of event. Event was defined as enucleation (or decision to enucleate) or external beam radiotherapy. Though patients had advanced stage intraocular retinoblastoma, none received external beam radiotherapy and less than a half (48.6%) of the affected eyes were expected to be ultimately enucleated according to our chemoreduction strategy. All salvaged eyes had useful visions as well.

(Table 1, Patient No. 6), and lastly because the mass was too near the optic disc to treat with LT (Table 1, Patient No. 5). One patient who had received CRx as scheduled was finally enucleated because the tumor showed insufficient response and the initial total retinal detachment persisted even after 6 cycles of CRx

Toxicities of CRx

Table 2 summarizes the toxicities of CRx. There were no treatment-related mortalities or serious life-threatening complications attributable to CRx. Grade 4 leukopenia or thrombocytopenia was observed in some patients. All patients who received more intensive CRx for the reasons previously described were subject to grade 4 leukopenia but none of those who received 'VEC' CRx suffered from severe leukopenia. Five of 9 patients were subject to grade 4 thrombocytopenia but there was no life-threatening bleeding episode. Three patients required admission due to infectious complications, which resolved completely after a short duration of intravenous antibiotics.

DISCUSSION

Prior to entering this study, we had three important points in mind in treating IO RB. First, we wanted to avoid ENU that had been the most common treatment method of IO RB because it might cause later psychotic problems in addition to visual loss. Second, we decided not to use EBRT even in cases where LT was impossible because of its serious complications including cosmetic deformity, which occurs in about 90% of patients, and other various late effects such as second

Table 2. Toxicities of chemotherapy

| | VEC* (n=6) | Intensive† (n=3) |
|-------------------------------------|------------|------------------|
| Grade 4 leukopenia | 0/6 | 3/3 |
| Grade 4 thrombocytopenia | 3/6 | 2/3 |
| Mean no. of RBC transfusion (range) | 2.2 (1-4) | 1.7 (0-3) |
| Mean no. of PLT transfusion (range) | 2.5 (0-7) | 4 (1-7) |
| Infection requiring admission | 2/6 | 1/3 |
| Treatment-related mortality | 0/6 | 0/3 |

*Patients who received only VEC chemotherapy. †Patients who were treated with more intensive regimen later.

malignancy that would deteriorate the patient's quality of life. Third, we intended to make efforts to prevent recurrence or metastasis because the prognosis of recurrent or metastatic RB is generally poor with conventional treatment (18, 19). We thought that CRx might increase the chance of globe salvage potential and might reduce the probability of relapse as well.

ENU is a relatively simple way of treatment and yields a high cure rate. But as published by Ross *et al.*, many patients are more likely to show delays in visuomotor integration (20). EBRT has been used as a method for saving the globe because RB is generally a radiosensitive tumor. But little has been known about the visual outcome after EBRT and it accompanies many radiation-induced complications including cosmetic deformity, cataract, retinopathy, glaucoma, vitreous hemorrhage, optic neuropathy, keratopathy, and second malignancy in the field of irradiation eventually leading to the loss of vision (6).

In this background, we thought chemoreduction strategy would give the patient an opportunity to live with his or her 'own eye(s)' and preserve useful vision in some patients. Until now, the indications for chemoreduction in IO RB are not clearly established. According to Friedman *et al.*, small tumors of RE group I to III were best treated with chemoreduction strategy to avoid ENU and EBRT (13). However, they concluded that more effective therapy is required for RE group IV and V. On the other hand, Gunduz *et al.* suggested that advanced IO RB could also be treated well with chemoreduction followed by various local treatment modalities such as photocoagulation, cryotherapy, and plaque radiotherapy (12). However, tumors may recur after LT. Because there are no reports that emphasize the role of adjuvant CRx after LT to prevent RB from relapse, we expect that our results would uncover the role of additional adjuvant CRx in these patients after long-term follow-up.

Of the local therapeutic modalities, plaque radiotherapy can control relatively larger tumors up to 16 mm (21). However, it is not available and most patients with RB are diagnosed at an advanced IO stage in Korea. Therefore, the role of CRx is much more important because the tumor size is a critical issue for the success of cryotherapy or photocoagulation. Adjuvant CRx is considered beneficial in this situation of limited local therapeutic tools. Of the 5 eyes successfully treated with local cryotherapy, 4 eyes did not show any sign of relapse. The other one eye was eventually enucleated not due to recurrence but due to retinal detachment as a complication of cryotherapy. Long-

term follow-up is needed to uncover the benefits of adjuvant CRx in this situation.

This pilot study demonstrates that successful treatment of IO RB is feasible with CRx, even in advanced group, if combined with LT and adjuvant CRx. Though a proportion of patients were not successfully treated with this protocol, at least disease-progression was not observed in our patients. Our study is limited due to the short follow-up period. However, Gallie et al., who used 2 or 6 cycles of chemoreduction for IO RB, demonstrated that relapse-free survival reached plateau at 1 yr after chemoreduction (9). We used a minimum of 6 cycles of chemoreduction, which is a bit longer than in other published reports. This was based on the concept that though tumors respond dramatically during the first 2 or 3 cycles of CRx and less thereafter, prolonged CRx might further reduce the number of viable tumor cells even in cases where there was no further reduction in tumor size, leading to reduced chance of tumor recurrence after off-therapy. Adjuvant CRx after LT can also be regarded as a portion of prolonged CRx in this concept. Shields et al. used 6 cycles of chemoreduction before LT and concluded that patients with RE group V required EBRT in 47% and ENU in 53% with a median follow-up of 28 months (15). This result seems somewhat worse than that in our patients considering that no patients received EBRT in our patients. They used the same CRx regimen, or VEC, but their interval between CRx was longer (4 weeks) than ours (3 weeks) and they applied maximum 6 cycles of CRx compared with minimum 6 cycles in our institution. Though our follow-up duration is relatively short, we suppose that our prolonged and compact CRx strategy might bring out superior results after long-term follow-up.

We changed CRx to more intensive ones in 3 patients (4 eyes) who showed relatively insufficient responses after a minimum of 3 cycles of standard CRx, but all 3 patients failed to enter into LT. This suggests that early reduction potential is important in foretelling the prognosis of globe salvage. On the basis of the results in our pilot study, we are conducting another pilot study using more intensive CRx regimen for the initial treatment to see if more intensive CRx would bring out greater reduction in tumor volume as well as in tumor necrosis leading to increased chance of globe salvage. The pathology of 2 globes ultimately enucleated revealed still viable tumor cells. It is yet unknown whether more intensive CRx would lead to greater tumor necrosis as well as greater reduction in tumor volume. The results of intensive CRx in advanced IO RB will be presented later.

In conclusion, we suggest that chemoreduction might be an effective treatment strategy even in advanced IO RB provided that proper LT and adjuvant CRx are combined. Long-term follow-up might reveal the potential benefits of CRx such as preventing metastatic or trilateral RB as well as preventing relapse.

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