Analysis of the short-term curative effect of 356 cases of intraocular retinoblastoma in children

Mei Jin | Junyang Zhao | Dawei Zhang | Chengyue Zhang | Wen Zhao | Xisi Wang | Qian Zhao | Chao Duan
Yan Su | Huimin Hong | Xiaoli Ma

1Beijing Key Laboratory of Pediatric Hematology Oncology, National Key Discipline of Pediatrics (Capital Medical University), Key Laboratory of Major Diseases in Children, Ministry of Education, Department of Hematology Oncology Center, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China
2Department of Ophthalmology, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China

Correspondence
Xiaoli Ma, Department of Hematology Oncology Center, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing 100045, China.
Email: mxl1123@vip.sina.com

Funding source
AI YOU Foundation (AYEK201801); Scientific Research Program of the National Health and Family Planning Commission of China (201402014); Capital’s Funds for Health Improvement and Research (2018-2-2-95).

Received: 27 August, 2018
Accepted: 22 December, 2018

ABSTRACT

Importance: Retinoblastoma (Rb) is the most common primary malignant intraocular cancer in children. Systemic chemotherapy combined with local therapy is safe and effective for intraocular Rb.
Objective: To summarize the short-term outcomes of patients with Rb to provide evidence for optimizing treatment protocols and improving therapeutic safety and efficacy.
Methods: The clinical data of 356 patients (486 eyes) with intraocular Rb admitted to our center from December 2009 to April 2017 were retrospectively analyzed. The measures included drug toxicity, eye-preservation rate, and survival rate, with an emphasis on safety and short-term efficacy. The date of last follow-up was 30 November, 2017.
Results: The patients comprised 226 unilateral Rb and 130 bilateral Rb. Enucleation before chemotherapy was performed in 72 patients. Among the 174 patients with unilateral Rb, enucleation after chemotherapy was performed in 80 patients (46.0%), and the eye was not enucleated in 89 (51.1%); 68 eyes were preserved (68/114, 59.6%) in Group D and 20 eyes (20/59, 33.8%) in Group E. Among the 220 eyes in patients with bilateral Rb, enucleation after chemotherapy was performed for 35 eyes; the eye-preservation rate was 91.7% in Group C, 79.1% in Group D, and 52.1% in Group E. All patients developed grade II to IV myelosuppression after chemotherapy, among whom 18 patients (5%) requiring transfusion. Fourteen patients (3.9%) died of intracranial metastasis following self-elected discontinuation of treatment (n = 7). Patients were followed up for a median of 47 (range, 1–96) months. The expected 5-year overall survival rate was 95.3% (96.7% for unilateral Rb and 92.9% for bilateral Rb, P = 0.074).
Interpretation: The VEC (vincristine, etoposide, and carboplatin) regimen with local treatment was safe for intraocular Rb. Intracranial metastasis remains the most common cause of Rb-related death.

KEYWORDS
Chemotherapy, Enucleation, Intraocular retinoblastoma, Local therapy

DOI: 10.1002/ped4.12095

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INTRODUCTION

Retinoblastoma (Rb) is a rare malignant tumor and is the most common primary malignant intraocular cancer in children. The incidence of Rb is 1 in 15,000 to 20,000 live births worldwide, and about 9000 new cases are diagnosed each year.\(^1\) Modern diagnostic and treatment techniques for Rb have been actively adopted in Beijing Children’s Hospital affiliated to Capital Medical University, Beijing, China. Since 2009, the departments of ophthalmology and oncology in our center have applied a multidisciplinary approach based on systemic chemotherapy and local treatment to save the lives of patients with Rb and preserve their eyes and sight. In this article, we summarize the short-term outcomes of patients with intraocular Rb who were treated in our center from 6 November, 2009 to 1 April, 2017 to provide evidence for optimizing treatment protocols and improving therapeutic safety and efficacy.

METHODS

Patients

We retrospectively analyzed the clinical data of pediatric patients with Rb who were admitted to our center from December 2009 to April 2017 and received at least one cycle of chemotherapy. All children enrolled in this study received a fundus examination under general anesthesia and were then divided into Groups A, B, C, D, and E based on their disease stage, which was determined according to the International Intraocular Retinoblastoma Classification (IIRC).\(^2\) All patients underwent a fundus examination (RetCam; Natus Medical Inc., Pleasanton, CA, USA) performed by an experienced ophthalmologist for fundus staging. Orbital computed tomography and eye magnetic resonance imaging (MRI) were also performed. Bone marrow cytology and cerebrospinal fluid tests were performed for children in Group E. The last date of follow-up was 30 November, 2017.

Chemotherapy regimen

The Beijing Children’s Hospital Rb-2009 Protocol (based on the Canadian Rb-2003 Protocol) was applied.\(^3\) Different treatment strategies were offered after the patients were clinically diagnosed with Rb. For patients with bilateral Rb or with stage D or E unilateral Rb who refused enucleation, a combination of vincristine, etoposide, and carboplatin (VEC) was applied as follows: vincristine, 0.05 mg/kg/d, day 1; carboplatin, 26 mg/kg/d, day 1; and etoposide, 5 mg/kg/d, days 1 and 2. The interval between cycles was 21 to 28 days. Some patients with unilateral Rb who underwent enucleation at the time of the initial diagnosis also had high-risk histopathologic features: posterior uveal infiltration, involvement of the choroidal appendages and optic nerve, involvement of the postlamellar optic nerve (clean cut end), scleral involvement, an anterior chamber implant, ciliary body infiltration, or iris permeation. In these patients, six cycles of VEC chemotherapy were offered 4 weeks after enucleation, but a carboplatin dose was 18.6 mg/kg/d instead of 26 mg/kg/d. For patients with tumor thrombi in the iris vessels, the carboplatin dose was increased to 26 mg/kg/d.

Local treatment

Local treatment was performed under general anesthesia by experienced ophthalmologists in the operating room. The most common methods were laser treatment and cryotherapy. Laser treatment was applied from the equatorial region to the posterior pole. Such treatment is feasible for tiny tumors (diameter of < 3 mm, thickness of < 2 mm) located within the retina and does not affect the optic nerve or macula. Cryotherapy is mainly used for the treatment of small tumors in the equatorial region and its peripheral areas, especially for recurrence by tumor implantation beneath the retina near the serrated edge. The efficacy and risk of transfer were assessed under ophthalmoscopy.

Eye-preservation treatment

For patients undergoing eye-preservation treatment, two cycles of chemotherapy were conducted before deciding whether the eye(s) should be preserved or enucleated. The interval between cycles was 21 to 28 days. Liver and kidney function, hearing, and routine blood cell parameters were monitored. Pure tone audiometry (PTA) was performed in patients over 5 years old. Auditory brainstem responses (ABR) was perform in patients under 5 years old. Toxicities related to chemotherapy were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The indicators for enucleation were thickening of the optic nerve posterior to the eyeball on imaging examination; failure to visualize the optic disc on fundus examination, suggesting tumor invasion of the papilla; obvious vitreous implantation; tumor enlargement during chemotherapy; the inability to observe tumor growth because of intraocular hemorrhage; and/or no obvious improvement in a stage D or E tumor despite chemotherapy and topical treatment.

Follow-up

Children younger than 1 year were followed up every 4 weeks in the first year after drug withdrawal, every 2 months in the second year, and every 3 months in the third year. Children older than 1 year were followed up every 8 weeks in the first year after drug withdrawal, every 3 months in the second year, and every 6 months in the third year. Children with bilateral Rb were monitored with cranial and orbital MRI examination once a year.
Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). The relationship between age at disease onset and unilateral/bilateral Rb was analyzed with an independent-sample t-test. Based on the follow-up results, univariate survival analysis was performed with the Kaplan–Meier method. A value of \( P < 0.05 \) was considered statistically significant.

RESULTS

Clinical data

The 356 patients in this study comprised 193 males and 163 females with a median age of 18.5 months (range, 1–84 months); 226 patients had unilateral Rb and 130 had bilateral Rb (Table 1). In total, 486 eyes were affected. The mean age at disease onset was 25.6 months in the patients with bilateral Rb and 14.5 months in those with unilateral Rb (Figure 1). Thus, the age at disease onset was significantly younger in patients with bilateral than unilateral Rb \( (P < 0.01) \). The mean interval to treatment was 4.18 ± 2.04 months.

| Clinical features | Numbers | Percentage (%) |
|-------------------|---------|----------------|
| Gender            |         |                |
| Male              | 193     | 54.2           |
| Female            | 163     | 45.8           |
| Unilateral Rb (IIRC stage) |         |                |
| A                 | 0       | 0              |
| B                 | 0       | 0              |
| C                 | 1       | 0.4            |
| D                 | 127     | 56.2           |
| E                 | 98      | 43.4           |
| Bilateral Rb (IIRC stage) |       |                |
| A                 | 7       | 2.7            |
| B                 | 36      | 13.8           |
| C                 | 32      | 12.3           |
| D                 | 121     | 46.6           |
| E                 | 64      | 24.6           |

Rb, retinoblastoma; IIRC, International Intraocular Retinoblastoma Classification

![Diagram of treatment outcomes](7904275719782617152209262780.png)

**FIGURE 1** Treatment outcomes of 356 patients with retinoblastoma.
Treatments

All 356 children (486 eyes) received treatment in our center. Eyes were enucleated in 185 patients (52.0%) and successfully preserved in 157 patients (44.1%). The eye-preservation rate in patients with unilateral Rb was 39.4% and 52.3% in patients with bilateral Rb ($P < 0.05$). Fourteen patients (3.9%) died, among whom 2 underwent direct enucleation (2.8%), 1 underwent enucleation following chemotherapy, and 11 received eye-preservation treatments, that were 12 patients (4.2%) ($P = 0.744$), eye-preservation treatments did not increase mortality in Rb patients. Enucleation before chemotherapy was performed for 72 eyes, and eye-preservation treatments were conducted in 284 patients. Among 174 patients with unilateral Rb, enucleation following chemotherapy was performed in 80 patients (46.0%), and eyes were not enucleated in 89 patients (51.1%); 5 patients died (2.9%). The eye-preservation rate was 59.6% in Group D and 33.8% in Group E. Among 220 eyes of patients with bilateral Rb, enucleation following chemotherapy was performed for 35 eyes; the eye-preservation rate was 100% in Groups A and B, 91.7% in Group C, 79.1% in Group D, and 52.1% in Group E; 7 patients (6.4%) died. In patients with either unilateral or bilateral Rb, the enucleation rate was significantly correlated with the IIRC stage ($P = 0.01$ and $P < 0.01$, respectively).

Treatment outcomes

Of all 356 children, 284 received a mean of $4.18 \pm 2.04$ cycles of eye-preservation chemotherapy. During the 1- to 96-month follow-up (median, 47 months), the expected 5-year overall survival (OS) rate was 95.3% (96.7% for patients with unilateral Rb and 92.9% for patients with bilateral Rb, $P = 0.074$) (Figure 2). After application of the VEC protocol, chemotherapy-induced myelotoxicity was closely monitored during the follow-up period in the outpatient department. Although all of the children had grade II to IV bone marrow suppression, none developed severe infection throughout follow-up. Transfusion of suspended red blood cells or platelet concentrates was required in 18 patients (5%) with grade IV bone marrow suppression. Reversible grade I-II hearing loss was found. No irreversible grade IV hearing loss was reported.

Fourteen patients died in our current series. Among them, 2 patients had received chemotherapy after enucleation and 12 had received eye-preservation treatments. Eight patients were in Group E and six were in Group D. The causes of death were intracranial metastasis ($n = 7$, 50%), early abandonment of treatment ($n = 3$, 21%), complications after chemotherapy without follow-up ($n = 2$, 12%), surgical complications ($n = 1$, 7%), and tumor progression ($n = 1$, 7%). The median interval from disease confirmation to death was 16 months (range, 1–51 months), and the mean number of chemotherapy cycles was $2.85 \pm 1.78$ (Table 2).

DISCUSSION

Rb has a higher cure rate than other solid tumors in children because of timely diagnosis and proper treatment. Although the OS rate of Rb reaches 95% to 97% in developed countries, it ranges from 60% to 80% in many developing countries and is only 50% in the least-developed countries.¹ The eye-preservation rate is 30% to 60% in patients with Group C to E intraocular Rb and 57% in patients with bilateral Rb Group D by intravenous chemotherapy.² In the current series, the 5-year OS rate was 95.3%. Among patients with unilateral Rb, the eye-preservation rate was 59.6% in patients with Group D Rb and 33.8% in those with Group E Rb; in contrast, among patients with bilateral Rb, the eye-preservation rate was 79.1% in patients with Group D Rb and 52.1% in those...
with Group E Rb. Notably, the proportion of patients with Group E Rb was high in our series, which is mainly due to the inadequate screening and late identification of this disease in China.

All children in this series were treated with high-dose carboplatin and therefore faced the risk of hearing loss; however, no irreversible grade IV hearing impairment was observed during the short-term follow-up. Jehanne et al. performed a long-term follow-up of the hearing of 175 children with Rb who had received chemotherapy with carboplatin and found that only 2 children developed grade IV hearing impairment requiring a hearing aid and only 1 had ototoxicity during chemotherapy. The others developed hearing impairment during the long-term follow-up, among whom the longest interval was 7 years after the withdrawal of carboplatin. Therefore, long-term hearing tests are needed to avoid affecting the quality of life of children with Rb.

Because the survival rate of patients with intraocular Rb is high, many international centers have attempted to reduce or simplify the intraocular chemotherapy. The goal is to minimize exposure to excessive chemotherapy and radiotherapy and thus reduce long-term side effects, prevent the occurrence of a second tumor, and improve patients’ quality of life. Rodriguez-Galindo et al. from St. Jude Children’s Research Hospital reported that patients with intraocular Rb received primary treatment with eight courses of vincristine and carboplatin (VC), and focal treatments were delayed until documentation of disease progression. Disease in all eyes responded to chemotherapy and progressed in only two patients. Event Free Survival was as effective as VEC. In another study, the authors treated 20 patients (36 eyes) with the same method, and 33 eyes (92%) progressed after completion of 8 cycles of chemotherapy. Thus, they proposed that early combination with focal therapy is needed for the VC protocol.

In a study by Chantada et al., the VC regimen combined with local therapy was offered to 26 patients with Reese–Ellsworth class I to III Rb; enucleation was avoided in 90% of patients, and 2 patients needed etoposide for eye preservation. Based on the above findings, the Children’s Oncology Group recommended that patients with Group B Rb should be treated with the VC regimen in combination with local therapy.

Fourteen patients in our current series died during a median follow-up of 16 months. Half (50%) of them died of intracranial metastasis. Disease in all eyes responded to chemotherapy and progressed in only two patients. Event Free Survival was as effective as VEC. In another study, the authors treated 20 patients (36 eyes) with the same method, and 33 eyes (92%) progressed after completion of 8 cycles of chemotherapy. Thus, they proposed that early combination with focal therapy is needed for the VC protocol. In a study by Chantada et al., the VC regimen combined with local therapy was offered to 26 patients with Reese–Ellsworth class I to III Rb; enucleation was avoided in 90% of patients, and 2 patients needed etoposide for eye preservation. Based on the above findings, the Children’s Oncology Group recommended that patients with Group B Rb should be treated with the VC regimen in combination with local therapy.

### Table 2: Causes of death among 14 patients with retinoblastoma

| Case | Gender | Age at diagnosis (months) | IIRC stage | Follow-up duration (months) | Chemotherapy cycle times | Causes of death |
|------|--------|-------------------------|------------|-----------------------------|--------------------------|-----------------|
| 1    | Male   | 59                      | 0          | E                           | 16                       | Intracranial metastasis after relapse |
| 2    | Female | 12                      | C          | E                           | 16                       | Intracranial metastasis after drug withdrawal |
| 3    | Male   | 23                      | D          | 0                           | 6                        | Three chemotherapy cycles before enucleation, and no further chemotherapy was offered after enucleation. Intracranial metastasis |
| 4    | Male   | 35                      | D          | 0                           | 11                       | Parents refused to continue the treatment due to economic difficulty |
| 5    | Male   | 20                      | D          | 0                           | 24                       | Parents refused to continue the treatment due to economic difficulty |
| 6    | Male   | 4                       | D          | C                           | 2                        | Abandonment of treatment due to poor treatment effectiveness |
| 7    | Female | 14                      | D          | D                           | 15                       | Chemotherapy; drug withdrawal after vitrectomy. Intracranial metastasis |
| 8    | Female | 25                      | D          | D                           | 29                       | Chemotherapy; drug withdrawal after vitrectomy. Intracranial metastasis |
| 9    | Female | 10                      | E          | 0                           | 18                       | One chemotherapy cycle before enucleation, and no further chemotherapy was offered after enucleation. Intracranial metastasis |
| 10   | Female | 31                      | E          | 0                           | 51                       | Intracranial metastasis |
| 11   | Female | 19                      | E          | C                           | 4                        | Organ failure after enucleation |
| 12   | Female | 2                       | E          | D                           | 27                       | Tumor progression after drug withdrawal |
| 13   | Male   | 3                       | E          | D                           | 1                        | Went home after chemotherapy without follow-up; died of lung infection after choking on milk |
| 14   | Female | 13                      | E          | D                           | 19                       | Intracranial metastasis after drug withdrawal |

*Enucleation was performed first. IIRC, International Intraocular Retinoblastoma Classification*

TABLE 2 Causes of death among 14 patients with retinoblastoma
effectively reflect the intracranial condition of children with Rb. Systemic chemotherapy can effectively prevent and reduce the risk of metastasis. Imaging examinations are equally important. Cranial MRI is performed within the first 5 years after the disease is confirmed, especially for patients with bilateral Rb or high risk.

Early abandonment of treatment and returning to a local hospital following chemotherapy are also major causes of death, highlighting the importance of a multidisciplinary approach and health education. Effective management and adequate awareness-raising activities can avoid delays in diagnosis, encourage active treatment, and strengthen follow-up visits to effectively control complications and further lower the case-fatality rate.

Systemic chemotherapy combined with local therapy is safe and effective for intraocular Rb. The expected 5-year OS in our current series was 95.3%, and no second tumor was found during the follow-up. Education for pediatric patients and their families is still very important, and the treatment should not be abandoned. Intracranial metastasis remains the most common cause of death in patients with Rb, and Cranial MRI is performed within the first 5 years after the disease is confirmed. In addition, medical management is still very important after chemotherapy because it can effectively prevent chemotherapy-induced complications and improve the safety of chemotherapy.

CONFLICT OF INTEREST

There are no conflicts of interest.

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