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ORIGINAL ARTICLE

Intra-arterial chemotherapy combined with VEC intravenous chemotherapy in the treatment of advanced retinoblastoma

Kuifeng Xu*, Junqi Liu*, Chaojun Zhang

Department of Ophthalmology, Chongqing Bright Eye Hospital, Chongqing, China.

*These authors contributed equally to this work

Summary

Purpose: *To explore the efficacy and safety of intra-arterial chemotherapy (IAC) combined with vincristine + etoposide + carboplatin (VEC) intravenous chemotherapy (IVC) in the treatment of advanced retinoblastoma (RB).*

Methods: *A total of 86 child patients (98 eyes) newly diagnosed with advanced RB (stage D and E), among whom 42 cases (49 eyes) underwent IVC and IAC combined with local ocular treatment (IVC+IAC group), and 44 cases (49 eyes) were treated with IAC combined with local ocular treatment (IAC group). At 4 weeks after treatment, the maximum diameter and thickness of the tumor were evaluated, the expression levels of serum markers [vascular endothelial growth factor (VEGF), neurone specific enolase (NSE), Livin and Survivin] were assessed.*

Results: *The maximum diameter and thickness of the tumor significantly declined in patients after treatment compared with those before treatment. The maximum diameter and thickness of the tumor in IVC+IAC group were significantly smaller than those in IAC group after treatment. In the two groups, the eye salvage rate was 85.7% (42/49) and 79.6% (39/49), respectively. The recurrence rate was 12.2% and 18.4%, respectively, and the metastasis and mortality rate were all 2.0%. The levels of serum VEGF, NSE, Livin and Survivin were obviously decreased in both groups after treatment compared with those before treatment, while they were significantly lower in IVC+IAC group than those in IAC group after treatment.*

Conclusion: *Compared with IAC alone, VEC IVC combined with IAC can significantly reduce the tumor volume, and remarkably lower the levels of serum therapeutic markers, without increasing the incidence of adverse reactions in the treatment of advanced RB, which is worthy of clinical popularization and application.*

Key words: *retinoblastoma, intra-arterial chemotherapy, intravenous chemotherapy, efficacy, metastasis, recurrence*

Introduction

Retinoblastoma (RB) is the most common malignant tumor in the eyeballs of infants and young children, and its morbidity rate is about 1/18000-1/16000 of live births. About 5% of blindness in children is due to RB, and the age of onset is mostly under 3 years old. RB can seriously harm the visual acuity of child patients, and intracranial and systemic metastases of tumor may occur if there is no prompt treatment, ultimately threatening the life and causing death of child patients [1,2].

At the beginning of the 20th century, epoch-making progress has been made by intravenous chemotherapy (IVC) in the treatment of RB, which markedly enhances the survival rate and eye salvage rate of RB patients. However, IVC has severe systemic adverse reactions like hearing impairment and renal damage [3]. Intra-arterial chemotherapy (IAC) can raise the local drug concentration and reduce the systemic toxic side effects. However, it is a kind of local chemotherapy, so IAC cannot ef-

Corresponding author: Chaojun Zhang, MM. Department of Ophthalmology, Chongqing Bright Eye Hospital, No. 210, Zhongshan First Rd, Yuzhong District, Chongqing, China.
Tel: +86 013883164678, Email: zcj13883164678@sina.com
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fectively eliminate potential metastatic tumor cells in high-risk patients [4,5]. Studies have shown that there are pathological high-risk factors in 15-17% and 24-50% of patients with advanced RB in stage D and E, and the metastasis rate in these patients is 24%, which declines to 4% after adjuvant IVC [6-9].

In the present study, the clinical data of 86 child patients (98 eyes) with advanced RB in our hospital were retrospectively analyzed, and the efficacy and safety were compared between vincristine + etoposide + carboplatin (VEC) IVC combined with IAC and IAC alone in the treatment of RB, hoping to provide a more scientific basis for the development of effective therapeutic regimens.

Methods

General data

A total of 86 child patients (98 eyes) with advanced RB (stage D and E) treated with IAC in our hospital from March 2013 to March 2017 were selected. Inclusion criteria: child patients diagnosed with newly-onset RB, namely RB patients without a history of treatment such as external beam radiotherapy before treatment in our department. Exclusion criteria: child patients with intracranial or systemic metastasis of tumor, those with abnormalities in the hepatic and renal function, blood routine or coagulation function through laboratory examination, or those with congenital heart disease or hearing impairment. According to different treatment methods, the patients were divided into IVC+IAC group (42 cases, 49 eyes, treated with IVC and IAC combined with local treatment) and IAC group (44 cases, 49 eyes, treated with IAC combined with local treatment). After admission, the changes in the tumor were observed via ocular ultrasound and RetCam fundus photography, and if necessary, orbital magnetic resonance imaging was performed to determine whether there was invasion of optic nerves. There were 51 males and 35 females with an average age at onset of 15.9±1.3 months, including 75 eyes in stage D and 23 eyes in stage E according to the Intraocular International Retinoblastoma Classification (IIRC) Criteria [10]. The baseline clinical data were comparable between the two groups (p>0.05) (Table 1). All patients enrolled adhered to the Declaration of Helsinki and signed the informed consent. This study was approved by the Ethics Committee of Chongqing Bright Eye Hospital.

Treatment methods

In IAC group, IAC combined with local treatment was performed at an interval of 3-4 weeks, and the treatment times were determined based on the results of each fundus examination. During operation, melphalan + carboplatin (20 mg) were applied for infusion chemotherapy in the first and third IAC, and melphalan + topotecan (0.5-1 mg) were applied for infusion chemotherapy in the second and fourth IAC. The dose of melphalan did not exceed 0.5 mg/kg, and it was appropriately adjusted according to the patient's reaction and the changes in tumor after the previous IAC.

The patients received intravenous combined anesthesia in a horizontal position. Before operation, 0.05% oxymetazoline hydrochloride nasal solution was sprayed into the nose on the affected side and applied on the forehead, so as to reduce the blood supply from the nasal and frontal arterioles to the ophthalmic artery. After routine disinfection, the femoral artery was successfully punctured using the Seldinger technique, the 4F pediatric vascular sheath was placed and heparin (75 IU/kg) was injected for systemic heparinization. Under the guidance of X-ray fluoroscopy, the 4F Cobra super-slip catheter was selectively inserted into the common carotid artery, followed by common carotid artery angiography. After ophthalmic artery development, the roadmap was produced, super-selective catheterization was performed for the ophthalmic artery, and contrast agent was slowly infused for ophthalmic artery perfusion imaging. No ob-

Table 1. Demographics and general clinical data of all studied patients

Parameters	*IVC+IAC group n=42 cases (49 eyes)*	*IAC group n=44 cases (49 eyes)*	*p value*
Onset age (years)	16.2±1.3	15.8±1.2	0.117
Gender (male/female)	27/15	24/20	0.388
Body weight (kg)	11.4±1.9	10.9±1.4	0.141
Onset eye			0.545
One eye	35	39	
Two eyes	7	5	
IIRC stage (%)			0.634
D	36 (50.8)	39 (61.0)	
E	13 (49.2)	10 (39.0)	
Family history (%)			0.356
Yes	8 (72.9)	4 (81.4)	
No	41 (27.1)	45 (18.6)	

IVC: intravenous chemotherapy; IAC: intra-arterial chemotherapy; IIRC: Intraocular international retinoblastoma classification

vious internal carotid regurgitation and the good development indicated the successful catheterization, and the position of microcatheter was fixed. The diluted drugs were perfused through the microcatheter at about 1 mL/min for 30 min or so. Then the catheter was withdrawn and the artery sheath was removed, and the puncture point was pressed for 5-10 min to stop bleeding, followed by pressure dressing with elastic bandage.

In IVC+IAC group, IVC was performed first using the VEC regimen (18.6 mg/kg carboplatin, 5 mg/kg etoposide and 0.05 mg/kg vincristine). When the patient's body weight <10 kg, the dose of etoposide was adjusted to 3.3 mg/kg. IVC was performed once a week, and it should be terminated if the progression of disease, namely the continuous expansion of tumor and increased vitreous or subretinal tumor implantation, was still found via fundus examination every time before chemotherapy, followed by prevention of tumor progression through enucleation, etc. After IVC for 3-6 weeks, IAC puncture injection was performed.

Observation indexes

All patients underwent comprehensive systemic examination and local ocular examination at 4 weeks after operation every 3 months. The maximum diameter of tumor (the longest diameter of the equatorial plane of eyeball) and thickness of tumor (anteroposterior diameter) at 1 month after IAC were measured using ultrasonography. Whether the tumor shrank and whether there was calcification or scar were observed via fundus examination. The complete disappearance of tumor into scar tissues or complete calcification in patients indicated the successful eyeball salvage.

Fasting blood was drawn from patients before and after treatment, and the changes in expression levels of serum markers [vascular endothelial growth factor (VEGF), neurone specific enolase (NSE), Livin and Survivin] were detected via enzyme-linked immunosorbent assay (ELISA). The general conditions and adverse reactions were observed after operation, mainly including local complications (eyelid swelling, eyelid ptosis, enophthalmos, ophthalmic artery spasm, strabismus, cataract and vitreous hemorrhage) and systemic complications (fever, myelosuppression and gastrointestinal reactions).

All patients were followed up till April 1, 2019 after operation, and the eye salvage rate, recurrence rate, metastasis rate and mortality rate were recorded. The initial event was the last IAC, and the stop event was the enucleation or death of patients.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for the intergroup comparison. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of clinical efficacy between the two groups

In IVC+IAC group, IVC was performed for a total of 87 times (2.1 times/eye on average), and IAC was performed for a total of 157 times (3.2 times/eye on average). The success rate of catheterization was 100%. In IAC group, IAC was performed for a total of 171 times (3.5 times/eye on average), and there was 1 case of failed catheterization due to ophthalmic artery spasm, with a success rate of 99.4%. In IVC+IAC group, 17 (34.7%) affected eyes were treated with laser therapy (2.5 times/eye on average), and 8 (16.3%) affected eyes were treated with cryotherapy once. In IAC group, 23 (46.9%) affected eyes underwent laser therapy (2.8 times/eye on average), and 10 (20.4%) affected eyes underwent cryotherapy (2.1 times/eye). In IVC+IAC group and IAC group, after treatment, the tumor shrank in different degrees in 46 eyes and 39 eyes, with an effective rate of 93.9% and 79.6%, and the vision was also recovered in different degrees in 26 eyes (53.1%) and 22 eyes (44.9%), respectively. The maximum diameter and thickness of the tumor overtly declined in patients after treatment compared with those before treatment, and the differences were statistically significant (p<0.001, p<0.001). The maximum diameter and thickness of the tumor in IVC+IAC group were obviously smaller than those in IAC group after treatment (p<0.001, p<0.001) (Table 2).

Table 2. Comparison of tumor size before and after treatment of the studied children in two different groups

Parameters	*IVC+IAC group n=42 cases (49 eyes)*	*IAC group n=42 cases (49 eyes)*	*p value*
Tumor diameter (mm)			
Pretreatment	11.17±1.14	11.02±1.88	0.634
Posttreatment	3.89±0.15	4.11±0.20	0.001
Tumor thickness (mm)			
Pretreatment	6.36±0.26	6.28±0.33	0.186
Posttreatment	2.23±0.10	2.36±0.21	0.001

IVC: intravenous chemotherapy, IAC: intra-arterial chemotherapy

In IVC+IAC group, 40 eyes were successfully retained, with an eye salvage rate of 85.7% (42/49), and 7 eyeballs were removed, including 3 eyeballs in stage D and 4 eyeballs in stage E. In IAC group, 37 eyes were successfully retained, with an eye salvage rate of 79.6% (39/49), and 10 eyeballs were removed, including 7 eyeballs in stage D and 3 eyeballs in stage E. It can be seen that there was no statistically significant difference in the eye salvage rate between the two groups (p=0.595).

In IVC+IAC group, RB relapsed in 6 affected eyes, with a recurrence rate of 12.2%, including 4 eyes in stage D and 2 eyes in stage E. One eye in stage D was accompanied by hemorrhage and secondary retinal detachment, and 1 case in stage E died after failed treatment due to central nervous system metastasis, with both metastasis rate and mortality rate of 2.0%. In IAC group, RB relapsed in 9 affected eyes, with a recurrence rate of 18.4%, including 3 eyes in stage E and 6 eyes in stage D. Three affected eyes were accompanied by enophthalmus, and one case died after failed treatment due to multiple metastases in distant organs, with both metastasis rate and mortality rate of 2.0%. The recurrence rate showed no statistically significant difference between the two groups (p=0.576).

Comparison of levels of VEGF, NSE, Livin and Survivin between the two groups before and after treatment

Before and after treatment, the levels of serum VEGF were 360.41±37.70 pg/mL and 211.25±21.33 pg/mL in IVC+IAC group, and 349.85±27.19 pg/mL and 224.87±17.65 pg/mL in IAC group, respectively. The levels of serum NSE were 26.03±4.22 μg/L and 8.76±2.65 μg/L in IVC+IAC group, and 26.89±4.34 μg/L and 11.48±2.58 μg/L in IAC group, respectively. The levels of serum Livin were (409.32±30.27) ng/L and 194.88±15.67 ng/L in IVC+IAC group, and 404.90±21.37 ng/L and 204.63±16.79 ng/L in IAC group, respectively. The levels of serum Survivin were 27.16±3.51 ng/L and 16.79±1.55 ng/L in IVC+IAC group, and 26.63±2.82 ng/L and 17.54±1.29 ng/L in IAC group, respectively. It can be seen that there were no statistically significant differences in the levels of serum VEGF, NSE, Livin and Survivin between the two groups before treatment (p=0.139, p=0.355, p=0.435, p=0.441), and they were comparable. The levels of serum VEGF, NSE, Livin and Survivin were significantly decreased in both groups after treatment compared with those before treatment (p<0.001), while they were obviously lower in IVC+IAC group than those in IAC group after treatment (p=0.002, p<0.001, p=0.007, p=0.017) (Figure 1).

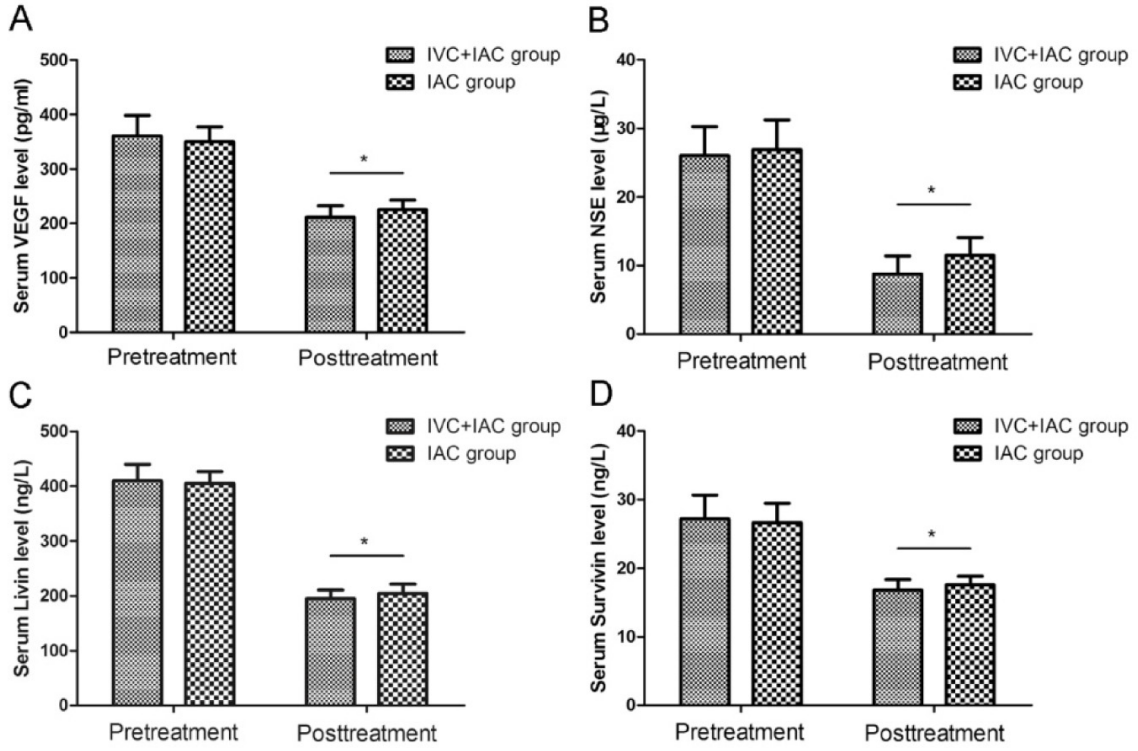

Figure 1. Comparison of serum VEGF, NSE, Livin, Survivin levels of patients in the two studied groups (*p<0.05). The difference of pretreatment serum VEGF **(A)**, NSE **(B)**, Livin **(C)** and Survivin **(D)** levels of patients in IVC+IAC group and IAC group had no significant difference (p=0.139, p=0.355, p=0.435, p=0.441). After treatment, serum VEGF **(A)**, NSE **(B)**, Livin **(C)** and Survivin **(D)** levels decreased dramatically in both groups. Posttreatment serum VEGF **(A)**, NSE **(B)**, Livin **(C)** and Survivin **(D)** levels of patients in IVC+IAC group was significantly lower than that of IAC group (p=0.002, p<0.001, p=0.007, p=0.017).

Table 3. Comparison of adverse reactions of patients in the two studied groups

	IVC+IAC group n=42 cases (49 eyes) n (%)	*IAC group n=44 cases (49 eyes) n (%)*	*p value*
Bone marrow suppression	7 (15.9)	2 (4.5)	0.086
Fever	8 (19.0)	5 (11.4)	0.377
Gastrointestinal reaction	14 (33.3)	9 (20.5)	0.226
Eyelid swelling	13 (26.5)	18 (36.7)	0.385
Ptosis	15 (30.6)	17 (34.7)	0.830
Ophthalmic artery spasm	3 (6.1)	2 (4.1)	1.000
Enophthalmos	15 (30.6)	21 (42.9)	0.295
Cataract	4 (8.2)	1 (2.0)	0.362
Vitreous hemorrhage	1 (2.0)	2 (4.1)	1.000
Strabismus	0 (0)	1 (2.0)	1.000

IVC: intravenous chemotherapy, IAC: intra-arterial chemotherapy

Adverse reactions and complications

Varying degrees of systemic adverse reactions occurred in both groups during treatment, mainly including myelosuppression, fever and gastrointestinal reactions, and they were all alleviated after symptomatic treatment. In the two groups, there were 7 cases and 2 cases of myelosuppression, 8 cases and 5 cases of fever, and 14 cases and 9 cases of gastrointestinal reactions, respectively, displaying no statistically significant differences ($p>0.05$). Short-term complications of the periorbital tissues were mostly recovered within 2 weeks. Ophthalmic artery spasm occurred in 3 eyes and 2 eyes, respectively, which was eliminated after appropriate treatment. One eye had strabismus (oculomotor paralysis) in IAC group. No statistically significant differences were found in the incidence of such complications as eyelid swelling, eyelid ptosis, cataract, vitreous hemorrhage and enophthalmos ($p>0.05$) (Table 3).

Discussion

IVC-based comprehensive therapy is the main method for eye salvage treatment for RB child patients, but it has a poor therapeutic effect on child patients in stage D and E, and the tumor is prone to relapse [11]. As a new technology developed in recent years, IAC enables chemotherapeutic drugs to be directly perfused into the feeding artery of tumor, so that the drug concentration in the intraocular lesions reaches 10 times that via intravenous administration, and the drug concentration in peripheral blood and tissues is low, thereby enhancing the killing effect of chemotherapeutic drugs on tumor cells, and remarkably reducing systemic adverse reactions [12]. The success rate of eye salvage treatment for advanced tumor with IAC is superior to that with systemic chemotherapy, but there is still tumor recurrence after treatment, mostly within 1 year after tumor control [13,14]. Therefore, researchers begin to explore the combination of IVC and IAC for the treatment of RB.

In 2013, Shields et al studied the treatment of advanced RB child patients with IVC combined with IAC, and found that the eye salvage rate is 67% and 50%, respectively, in stage D and E, in which, however, the patients enrolled included those receiving failed IVC, so the true efficacy of IVC combined with IAC cannot be well confirmed [14]. In 2016, Hahn et al from Korea reported 13 affected eyes treated with IVC combined with IAC, and the eye salvage rate was 33.3% and 60.0%, respectively, in stage D and E [15]. However, the order of IVC and IAC and the times of IVC performed for each case were different, making it harder to further analyze the role of IVC and IAC in treatment. In 2016, Abramson et al studied IAC in the treatment of affected eyes in RB in stage D, and found that the eye salvage rate of IAC as first-line treatment was higher than that of IAC as second-line treatment, possibly because there is cross resistance between IAC and IVC [16]. However, Chen et al found through multivariate analysis of RB interventional therapy that the efficacy of interventional therapy as second-line treatment is only related to the history of IVC failure, which is not affected by sequential therapy [17]. In this study, 86 child patients with newly-onset RB were enrolled. The results showed that the maximum diameter and thickness of the tumor in IVC+IAC group were distinctly smaller than those in IAC group after treatment ($p<0.001$), indicating that the killing effect of IVC combined with IAC on RB is superior to that of IAC alone. Moreover, the eye salvage rate in IVC+IAC group [85.7% (42/49)] was higher than

that in IAC group [79.6% (39/49)], but there was no statistically significant difference (p=0.595).

The research results of Shields et al revealed that the recurrence rate of RB after IAC is 19%. Tuncer et al reported that the recurrence rate of high-risk RB after IAC is 29% [18,19]. Studies have also found that the recurrence rate of high-risk RB after IVC alone is up to 53-75% [20,21]. In this study, the recurrence rate in IVC+IAC group (12.2%) was lower than that in IAC group (18.4%), and the metastasis rate and mortality rate were all 2.0%, showing no statistically significant differences between the two groups. It could not be clearly proved that IVC combined with IAC was able to reduce the metastasis rate and recurrence rate of RB, and the possible reasons included the small sample size and late tumor stage.

When distant or central nervous system metastasis occurs in RB, its prognosis is often undesired. Before the application of high-dose chemotherapy and autologous stem cell transplantation, the survival rate of patients with distant metastasis was close to 0 [22]. Gündüz et al [23] followed up 18 patients with distant or central nervous system metastasis for 2 years on average, and they found that only 4 cases survived. Moreover, Leal et al [24] performed radiotherapy and chemotherapy for 81 patients with metastatic RB, and the survival rate was only 4.94%. Recently, Youself et al conducted the meta-analysis for 12 clinical studies and found that the metastasis rate of RB treated with IAC was 2.1%, and RB metastasis mostly occurred within the first year after treatment [25]. In this study, it was observed during follow-up that there was 1 case of metastasis in both IAC group and IVC+IAC group, with a metastasis rate of 2.0%.

NSE is abnormally increased in the serum of RB patients, which is a highly sensitive index of RB child patients, and which is closely related to the severity of disease, indicating the proneness of tumor to nervous system metastasis [26]. In addition, Livin and Survivin are also highly-recognized valuable monitoring indexes for RB, which have a potent anti-apoptosis effect, as well as an association with tumor invasion and migration [27]. In this study, the levels of serum VEGF, NSE, Livin and Survivin were obviously lower in IVC+IAC group than those in IAC group after treatment (p=0.002, p<0.001, p=0.007, p=0.017), suggesting that IVC combined with IAC is more advantageous in improving the serological indexes of disease control in RB child patients. Besides, no statistically significant differences were found in the incidence of adverse reactions between the two groups after treatment (p>0.05), demonstrating that IVC combined with IAC is well tolerated by child patients, and combination therapy does not increase the incidence of complications.

The conclusions made in this study remain to be further verified through more rigorous and comprehensive larger-sample multi-center randomized controlled trials, hoping to provide a stronger basis for the selection of therapeutic regimen for child patients with advanced RB.

Conclusions

Compared with IAC alone, VEC IVC combined with IAC can significantly reduce the tumor volume, and significantly lower the levels of serum therapeutic markers, without increasing the incidence of adverse reactions in the treatment of advanced RB, which is worthy of clinical popularization and application.

Conflict of interests

The authors declare no conflict of interests.

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