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Original Article

A comparison on the effects of conventional therapy and intra-arterial chemotherapy on the serological indicators in the treatment of advanced intraocular retinoblastoma

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Abstract: Objective: This study aimed to analyze the effects of conventional therapy and intra-arterial chemotherapy on the serological indicators in the treatment of advanced intraocular retinoblastoma. Methods: 120 children (160 eyes) who were admitted to our hospital and diagnosed with advanced intraocular retinoblastoma were selected as objects of study for this retrospective analysis and divided into two groups according to the treatment methods, including 60 children (80 eyes) in the control group who received conventional therapy and 60 children (80 eyes) in the observation group who received intra-arterial chemotherapy, so as to compare the clinical effects, tumor thickness, the maximum tumor diameter, and the changes in the relevant serological indicators before and after treatment in the two groups. Results: (1) The total effective rate was 75.00% in the observation group and 46.67% in the control group (X^2=10.108, P<0.05). (2) The tumor thickness and maximum tumor diameter in the observation group were lower than they were in the control group at 4 weeks, 8 weeks, and 12 weeks after the treatment (P<0.05). (3) The survivin, livin, and NSE levels in the observation group were lower than they were in the control group at 4 weeks, 8 weeks, and 12 weeks after the treatment (P<0.05). Conclusion: The total effective rate of intra-arterial chemotherapy was clear in the treatment of advanced intraocular retinoblastoma. Intra-arterial chemotherapy was able to effectively improve the levels of the serological indicators and reduce tumor thickness and the maximum tumor diameter.

Keywords: Intraocular, advanced retinoblastoma, conventional therapy, intra-arterial chemotherapy, serological indicators, effect

Introduction

Retinoblastoma, characterized by a hereditary inclination and a familial nature, is a common malignant tumor among children with a high clinical incidence [1, 2]. In some children, the primary tumor originates from the cranium, so its site is generally located on the conarium and sella turcica, and this retinoblastoma is called trilateral retinoblastoma.

Retinoblastoma, with a high degree of malignancy, may directly cause the death of children through systemic tumor spread or intracranial tumor spread [3, 4]. At the present stage, the clinical treatment methods of this disease commonly include local external radiotherapy, local treatment, systemic chemotherapy, and ophthalmectomy, etc. [5]. In order to guarantee the children safety, the eyeball is generally enucleated or the orbital contents are directly removed in the early treatment of this disease, which may cause orbital cranial dysplasia and a permanent disability and thus seriously affects the physical and psychological health of children [6, 7]. Meanwhile, as for the children with bilateral retinoblastoma, both eyeballs shall be enucleated, which cannot be accepted by most families. With the deepening of clinical research, it has been found that children with retinoblastoma are very sensitive to chemotherapy, so intra-arterial chemotherapy is an effective method for the treatment of advanced intraocular retinoblastoma [8, 9]. Compared

with systemic chemotherapy, this type of chemotherapy can increase the concentration of local chemotherapeutics by 10-30 times or so, but the concentration of chemotherapeutics in the peripheral blood is very low [10, 11]. In this study, a retrospective analysis was conducted based on the clinical data collected from the 60 children (80 eyes) who were admitted to our hospital to discuss the clinical effects of intra-arterial chemotherapy on the treatment of advanced intraocular retinoblastoma.

This study mainly focuses on the clinical effects of intra-arterial chemotherapy and its influence on the serological indicators in the treatment of advanced intraocular retinoblastoma by comparing two groups of children who were treated with conventional therapy and intra-arterial chemotherapy respectively so as to provide more effective and safe methods for the treatment of advanced intraocular retinoblastoma.

Materials and methods

Materials

120 children (160 eyes) who were admitted to our hospital and diagnosed with advanced intraocular retinoblastoma were selected as objects of study for a retrospective analysis and divided into two groups according to the treatment methods. In the control group, there were 60 children (80 eyes) treated with conventional therapy, including 34 boys and 26 girls, ranging in age between 6 months and 5 years. In the observation group, there were 60 children (80 eyes) treated with intra-arterial chemotherapy, including 32 boys and 28 girls, ranging in age between 5 months and 6 years. (1) Inclusion criteria: the informed consent was obtained. The imaging materials, clinical histories, and the follow-up data were complete. The patients were not allergic to lipiodolography. The patients were diagnosed with retinoblastoma in Phase D or Phase E through MRI, CT, ocular ultrasound examination and a fundus examination before treatment. Their disease conforms to the diagnostic criteria of retinoblastoma in the *Guidelines for the Diagnosis and Treatment of Retinoblastoma* [11]. The patients suffered from this disease in a single eye or both eyes. (2) Exclusion criteria: this study excluded patients who were not willing to participate in the study, those quitting midway, and those with a dysfunction of the vital organs.

Methods

The children in the observation group were treated with intra-arterial chemotherapy. They received an MRI, a CT, an ocular ultrasound examination, fundus photography, and other examinations before their operations. The children were kept in a supine position during treatment. After achieving the ideal effect of the intravenous anesthesia, the infiltration anesthesia was performed around the femoral artery sheath subcutaneously. The Seldinger technique was used to puncture the right femoral artery, after which the 4F femoral artery sheath was implanted to perform the systemic heparinization. A 4F elbowed catheter was placed in a C2 vertebral level position of the internal carotid artery on the side of the affected eye to observe the opening of the ophthalmic artery carefully. A microcatheter was used for guidance to find for the opening of ophthalmic artery. After the microcatheter was implanted in the opening of the ophthalmic artery, radiography was performed to carefully observe the development of the central retinal artery and understand the specific staining situation of the blood capillaries and choroid membranes. If some contrast media flowed into the carotid artery, the micro catheter would have to be adjusted repeatedly to repeat the radiography so that the contrast media got into the ophthalmic artery completely and the choroid membranes were clearly stained. This indicated that the microcatheter was put in the right place successfully. The chemotherapeutics were pumped along the microcatheter, i.e. 7.5 mg melphalan (approval number: SFDA approval number H20020002; manufacturer: Qilu Pharmaceutical Co., Ltd.; specification: 2 mg) combined with 30 mg carboplatin (approval number: SFDA approval number H10920028; manufacturer: Qilu Pharmaceutical Co., Ltd.; specification: 0.1 g). The time was controlled at 30 min or more. After pumping, a trace amount of the contrast media were injected manually at a slow speed to ensure the ideal position of the microcatheter, the good development of the central retinal artery, and the successful injection of all the chemotherapeutics into the ophthalmic artery. If the contrast media overflowed and could not be regulated effectively, the middle meningeal artery-ophthalmic artery pathway was adopted with no need for radiography of the external carotid artery. Under the guidance of a path graph, a micro catheter was

placed in the orbital position of the middle meningeal artery. If the imaging results showed that the contrast media got into the ophthalmic artery successfully and the choroid membranes were clearly stained, the chemotherapeutics could be injected into this position. Upon the completion of the chemotherapy, the angiographic catheter and artery sheath were removed. After achieving the ideal effect of the hemostasis by compression, the compression bandaging was performed. The right hip joint was immobilized for 6 h after the operation. It was necessary to carefully observe the arteriopalmus of the right dorsum pedis, the vital signs, and the consciousness of children.

The children in the control group were treated with conventional therapy. If the diameter was small, the children were treated with cryotherapy. If the diameter was large, the children were treated with intraocular radionuclide applicator therapy.

Observation targets

The evaluation standards on the curative effect [12, 13]: according to *Response Evaluation Criteria in Solid Tumors* issued by WHO, the clinical effects include four standards, i.e. complete remission, partial remission, control, and progression, and the complete remission rate + the partial remission rate = the total effective rate of treatment.

Tumor thickness and maximum tumor diameter: the tumor thickness and maximum tumor diameter were measured using an ultrasound examination before the treatment and at 4 weeks, 8 weeks, and 12 weeks after the treatment in the two groups.

Serological indicators: 4.0 ml morning fasting venous blood was collected from the two groups respectively before the treatment and at 4 weeks, 8 weeks, and 12 weeks after the treatment. An ELISA kit was used for the quantitative determination of the levels of survivin, livin, neuron-specific enolase (NSE), and the other serological indicators. The kit was provided by Hebei Changtian Pharmaceutical Co., Ltd.

Statistical methods

SPSS 22.0 was used for the statistical analysis. The measurement data were represented as the means ± standard deviations. An independent-samples *t* test was used for the data in conformity with a normal distribution and a Mann-Whitney U test was used for the data not in conformity with a normal distribution. A paired-samples *t* test was used for the comparisons before and after the treatment in the groups. The enumeration data were represented by [n (%)]. An X^2 test was used for the comparisons of the enumeration data between the groups. $P<0.05$ meant that the comparison was statistically significant.

Results

Comparison of the general data between the observation and control groups

In the observation group, there were 32 male children, accounting for 53.33%, and 28 female children, accounting for 46.67%. In the control group, there were 34 male children, accounting for 56.67%, and 26 female children, accounting for 43.33%. The children were 5 months-6 years old in the observation group, with an average age of (3.18±0.19), and the children were 6 months-5 years old in the control group, with an average age of (3.15±0.16). In the observation group, there were 28 children in Phase D, accounting for 46.67%, and 32 children in Phase E, accounting for 53.33%, according to the II RC staging. In the control group, there were 26 children in Phase D, accounting for 43.33%, and 34 children in Phase E, accounting for 56.67%, according to the II RC staging. In the observation group, 40 children had the disease in a single eye, accounting for 66.67%, and 20 children had the disease in both eyes, accounting for 33.33%. In the control group, 40 children had the disease in a single eye, accounting for 66.67%, and 20 children had the disease in both eyes, accounting for 33.33%. There were no significant statistical differences in the general data of the two groups, including gender, average age, II RC staging and having the disease in a single eye or both eyes ($P>0.05$) (**Table 1**).

Comparison of the clinical effects between the observation group and the control group

In the observation group, there were 22 children in complete remission, accounting for 36.67%, 23 children in partial remission, acc-

Table 1. Comparison of the general data between the observation and control groups [n (%)]/($\bar{x} \pm s$)

Data		Observation group (n=60)	Control group (n=60)	t/X^2	*P*
Gender (cases)	Male	32 (53.33)	34 (56.67)	0.135	0.714
	Female	28 (46.67)	26 (43.33)		
Age (years old)		3.18±0.19	3.15±0.16	0.936	0.351
II RC staging					
Phase D		28 (46.67)	26 (43.33)	0.135	0.714
Phase E		32 (53.33)	34 (56.67)		
Disease situation: single eye or both eyes					
Single eye		40 (66.67)	40 (66.67)	-	-
Both eyes		20 (33.33)	20 (33.33)		

Note: - refers to none.

Table 2. Comparison of the clinical effects in the two groups [n (%)]

Group	Number of cases	Complete remission	Partial remission	Control	Progression	Total effective rate
Control group	60	8 (13.33)	20 (33.33)	18 (30.00)	14 (23.33)	28 (46.67)
Observation group	60	22 (36.67)	23 (38.33)	13 (21.67)	2 (3.33)	45 (75.00)
X^2						10.108
P						0.001

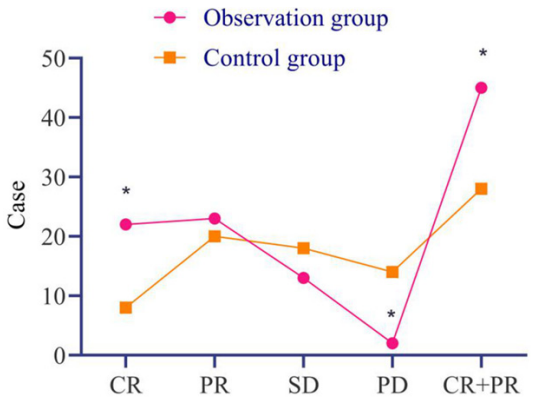

Figure 1. Analysis of the clinical effects in the observation and control groups. The children in complete remission accounted for 36.67% in the observation group, which was higher than the 13.33% in the control group ($P<0.05$); those in partial remission accounted for 38.33% in the observation group and 33.33% in the control group ($P>0.05$); those in control accounted for 21.67% in the observation group and 23.33% in the control group ($P>0.05$); and those in progression accounted for 3.33% in the observation group, which was lower than the 23.33% in the control group ($P<0.05$). The total effective rate was 75.00% in the observation group, which was higher than the 46.67% in the control group ($P<0.05$). *indicates compared with the control group, $P<0.05$.

ounting for 38.33%, 13 children in control, accounting for 21.67%, and 2 children in progression, accounting for 3.33%, with a total effective rate of 75.00%; and in the control group, there were 8 children in complete remission, accounting for 13.33%, 20 children in partial remission, accounting for 33.33%, 18 children in control, accounting for 30.00%, and 14 children in progression, accounting for 23.33%, with a total effective rate of 46.67% ($X^2=10.108$, $P<0.05$) (**Table 2** and **Figure 1**).

Comparison of the tumor thickness and the maximum tumor diameter between the observation group and the control group

There was no statistical difference in tumor thickness or maximum tumor diameter before treatment in the two groups ($P>0.05$). The tumor thickness and the maximum tumor diameter were all significantly reduced at 4 weeks, 8 weeks, and 12 weeks after the treatment in the two groups compared with before the treatment, which indicated a decreasing trend ($P<0.05$). The tumor thickness and maximum tumor diameter in the observation group were smaller at 4 weeks, 8 weeks, and 12 weeks after the treatment than in the control group, which indicated that the difference had a statistical significance ($P<0.05$) (**Table 3**; **Figures 2** and **3**).

Table 3. Comparison of the tumor thickness and the maximum tumor diameter between the observation and control groups ($\bar{x} \pm s$, mm)

Time	Tumor thickness	Maximum diameter of tumor
Before treatment		
Control group (n=60)	6.39±0.65	11.05±1.05
Observation group (n=60)	6.42±0.62	11.09±1.02
t	0.259	0.212
P	0.796	0.833
4 weeks after treatment		
Control group (n=60)	5.99±0.56	9.99±1.02
Observation group (n=60)	4.02±0.25	7.11±0.18
t	24.882	21.538
P	0.000	0.000
8 weeks after treatment		
Control group (n=60)	5.48±0.42	7.68±0.92
Observation group (n=60)	3.22±0.32	4.52±0.38
t	33.154	24.591
P	0.000	0.000
12 weeks after treatment		
Control group (n=60)	3.69±0.31	5.29±0.42
Observation group (n=60)	2.12±0.15	3.05±0.18
t	35.313	37.972
P	0.000	0.000

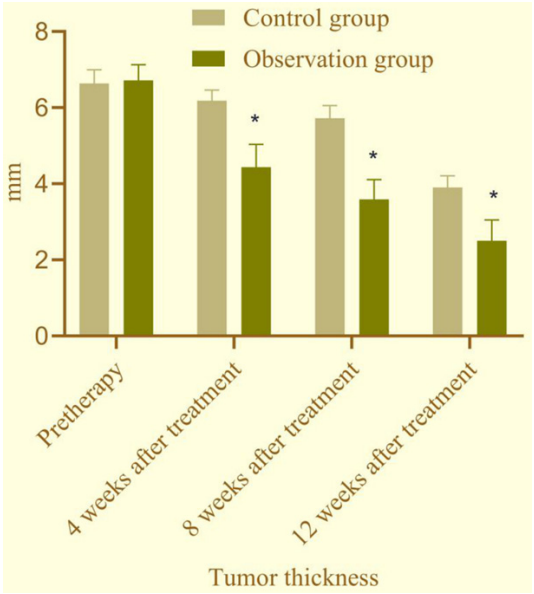

Figure 2. Analysis of the tumor thickness in the observation and control groups. The tumor thickness in observation group was lower than it was in the control group at 4 weeks, 8 weeks, and 12 weeks after the treatment ($P<0.05$). *indicates compared with the control group, $P<0.05$.

Comparison of survivin, livin and NSE between the observation and control groups

There was no statistical difference in the levels of survivin, livin or NSE before the treatment in the two groups ($P>0.05$). The survivin, livin and NSE levels of the two groups at 4 weeks, 8 weeks, and 12 weeks after the treatment were significantly reduced compared with those before treatment, which indicated that the difference had a statistical significance ($P<0.05$). The survivin, livin and NSE levels in the observation group were lower than in the control group at 4 weeks, 8 weeks, and 12 weeks after the treatment, which indicated that the difference had a statistical significance ($P<0.05$) (**Table 4**).

Discussion

Retinoblastoma is a malignant ocular tumor that is very common among children. Advanced intraocular retinoblastoma is very likely to undergo extraocular transfer, leading to the death of the children. In order to save the children's lives, the eyeball should be enucleated in general [14, 15]. So it is very necessary to make a definite diagnosis as soon as possible and actively take the corresponding therapeutic measures to enhance the survival rate of children with retinoblastoma [16].

The pathogenesis of retinoblastoma is concealed, and the children cannot clearly describe the problems of abnormal eyesight, so the disease has generally developed into the advanced stages by the time they see a doctor [17, 18]. Also, most indicators have high expressions in blood of children with retinoblastoma. NSE, one of the indicators with a higher sensitivity, is closely correlated with the severity of the disease [19]. Furthermore, survivin and livin are also effective indicators used to monitor the retinoblastoma in clinical practice. Survivin is an inhibitor of the apoptosis proteins with the lowest relative molecular weight in the whole family and can inhibit cell apoptosis. Meanwhile, it can regulate mitosis effectively and play a vital role in the regulation of cellular stress reactions, thus inhibiting cell apoptosis [20, 21]. Livin is also an inhibitor of apoptosis proteins and can inhibit cell apoptosis effectively

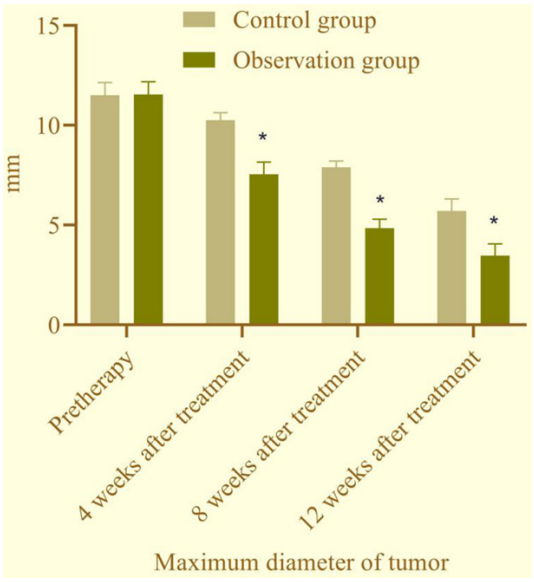

Figure 3. Analysis of the maximum tumor diameter in the observation and control groups. The maximum tumor diameter in the observation group was lower than it was in the control group at 4 weeks, 8 weeks, and 12 weeks after treatment ($P<0.05$). *indicates compared with the control group, $P<0.05$.

[22]. These two are indirect inhibitors of apoptosis, mainly playing an important role through the Caspase signaling pathway [23, 24]. This study showed that the survivin, livin and NSE levels in the observation group were lower than the levels in the control group at 4 weeks, 8 weeks, and 12 weeks after the treatment ($P<0.05$). This implies that intra-arterial chemotherapy, compared with conventional therapy, could achieve better effects in the treatment of advanced intraocular retinoblastoma and thus inhibit the migration and invasion of malignant tumors effectively.

What's more, it was found in this study that the total effective rate was 75.00% in the observation group, which was higher than the 46.67% in control group, and the tumor thickness and maximum diameter of the tumors in the observation group were lower than those in the control group at 4 weeks, 8 weeks, and 12 weeks after treatment ($P<0.05$). This implies that intra-arterial chemotherapy, in comparison with conventional therapy, had a higher total effective rate in the treatment of advanced intraocular retinoblastoma and could reduce the tumor thickness and maximum tumor diameter. Therefore, the intra-arterial chemotherapy could get into the ophthalmic artery through the superselection of the microcatheter. Then, the position of the microcatheter head was determined after the radiography to determine whether the contrast media overflowed. Eventually, the chemotherapeutics were pumped for treatment after a good staining of the choroid membranes [25, 26]. With respect to this treatment method, the chemotherapeutics were injected through the ophthalmic artery, which could obviously enhance the concentration of local chemotherapeutics and reduce the incidence of myelosuppression. Moreover, when the chemotherapeutics were injected through the ophthalmic artery, the drugs could get into the systemic circulation and then flow into the tumor lesion along the systemic circulation and finally have a secondary chemotherapy role [27]. Abramson and other scholars [28] reported on children treated with the superselective chemotherapy of the ophthalmic artery for the first time. According to the results, 9 children were treated with intra-arterial chemotherapy 27 times, including 7 children whose eyeballs were not enucleated, which achieved a partial recovery of eyesight. The total effective rate was 77.8%, which fully proved the efficacy of intra-arterial chemotherapy. Venturi and other scholars [29] researched 38 children (41 eyes) who were treated with intra-arterial chemotherapy within 3 years. The results showed that the eyeball retention rate was as high as 85.4%, which also proved the efficacy of intra-arterial chemotherapy.

In conclusion, the total effective rate of intra-arterial chemotherapy is clear in the treatment of advanced intraocular retinoblastoma. This intra-arterial chemotherapy could effectively improve the level of the serological indicators and reduce the tumor thickness and maximum tumor diameter. But at the same time, the results were not comprehensive enough due to the small sample size and short research period. So, in-depth research should be further conducted in the future.

Disclosure of conflict of interest

None.

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Table 4. Comparison of the serological indicators between the observation and control groups ($\bar{x} \pm s$)

Time	Survivin ($ng.L^{-1}$)	Livin ($ng.L^{-1}$)	NSE ($\mu.gL^{-1}$)
Before treatment			
Control group (n=60)	26.28±2.52	399.86±26.52	26.39±3.18
Observation group (n=60)	26.32±2.48	399.92±26.35	26.42±3.15
t	0.088	0.012	0.052
P	0.930	0.990	0.959
4 weeks after treatment			
Control group (n=60)	22.53±2.41	345.26±12.25	22.15±2.58
Observation group (n=60)	17.52±1.05	288.02±10.15	15.12±2.25
t	14.762	27.870	15.907
P	0.000	0.000	0.000
8 weeks after treatment			
Control group (n=60)	20.06±2.35	301.15±8.52	16.35±2.52
Observation group (n=60)	15.02±1.03	240.02±7.15	10.25±1.28
t	15.215	42.572	16.717
P	0.000	0.000	0.000
12 weeks after treatment			
Control group (n=60)	17.38±1.25	252.36±7.06	11.89±2.06
Observation group (n=60)	13.05±1.03	180.02±6.18	5.12±0.28
t	20.708	59.721	25.224
P	0.000	0.000	0.000

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