

Intra-arterial chemotherapy for unilateral advanced intraocular retinoblastoma

Results and short-term complications

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Abstract

Intra-arterial chemotherapy (IAC) has become an essential technique for the management of advanced intraocular retinoblastoma (RB). In this study, the aim of this article is to describe the clinical results and the short-term complications of IAC performed in our hospital.

We retrospectively analyzed patients with newly diagnosed unilateral advanced intraocular (group D or E) RB undergoing IAC from October 2016 to December 2017 in our hospital. We recorded the data including age, gender, cycles of IAC, pathway of arteries approached (ophthalmic artery or middle meningeal artery), ocular and systematic complications, globe salvage.

Sixty-one patients underwent IAC performing 189 procedures with a median of 3.1 sessions per eye (range, 1–5 sessions). The overall globe salvage rate is 78.7% (Group D (84.2%), and Group E (69.6%) and followed-up. Short-term ocular complications include eyelid edema (15 cases), ptosis (5 cases), forehead congestion (3 cases), retina hemorrhage (5 cases), choroid atrophy (2 cases), phthisis bulbi (1 case), bradycardia and hypotension during the procedure (7 cases), myelosuppressions (6 cases), and nausea and vomiting (5 cases).

IAC is safe and effective for the treatment of unilateral advanced intraocular RB with a very low complication rate.

Abbreviations: FMA = femoral artery, IAC = intra-arterial chemotherapy, OCT = optical coherence tomography, RB = retinoblastoma.

Keywords: advanced, intra-arterial chemotherapy, retinoblastoma, therapy

1. Introduction

Retinoblastoma (RB) is malignant tumor of the retina in infancy and childhood, which is diagnosed in 1 of 18,000/20,000.^[1] Approximately 1100 to 1500 new Chinese cases of RB are diagnosed every year.^[2] With many therapeutic modalities have been developed, including external beam radiation, focal therapies (laser photocoagulation therapy, thermotherapy, and cryotherapy), enucleation, systemic chemotherapy and intra-arterial chemotherapy (IAC), the 5-year overall survival rate of children with RB is 87% to 99% in developed countries.^[2] With this treatment approach, ocular salvage was favorable in eyes with less advanced tumors (Groups A–C), while enucleation is still unavoidable and is the preferred treatment in eyes with

advanced tumors in most countries worldwide (Groups D–E).^[3,4] IAC allows reaching a high concentration of the chemotherapeutic drug in the eye with minimum systemic toxicity.^[5] It is effective for advanced intraocular RB, allowing improved globe salvage and reducing systemic chemotherapy toxicities.^[6] In China, most patients with RB are always at a relative advanced stage without timely diagnosis and appropriate treatment. In this study, we retrospectively reviewed the outcome of IAC for unilateral advanced intraocular RB and summarized its short-term complications, meanwhile we share our experience how to treat and prevent the short-term complications of IAC.

2. Patients and methods

We retrospectively analyzed patients with newly diagnosed unilateral advanced intraocular (group D or E) RB undergoing IAC from October 2016 to December 2017 at our hospital. All patients were classified by the International Classification of RB. They had received no prior treatment to the eye before IAC. It would be excluded if they had received the others treatments or had extraocular invasion, documented metastatic disease or structural brain abnormalities. This retrospective study was approved by the ethics committee of Qilu Children's Hospital of Shandong University. The parents had been informed the procedure, the complication, expected outcomes and the associated risks of the IAC. And part of patients performed focal therapies (laser therapy or cryotherapy) or intravitreal melphalan in conjunction with or after completion of IAC.

The indication of IAC is given after the examination of patients having RB performed. The chemotherapeutic agents used in the protocol included melphalan and topotecan. It had been performed by the interventional radiologists under general

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anaesthesia of all the IAC. The femoral artery (FMA) is punctured by Seldinger technique, and 75 IU/kg of heparin is administered to avoid thrombosis. The ipsilateral internal carotid artery is catheterized with a 4-F Cobra guide catheter (Terumo, Tokyo, Japan) under X-ray guidance. We obtain the road mapping of the ophthalmic artery from the internal carotid artery by serial arteriograms. A 1.7-F microcatheter (ev3 Neurovascular, Inc., Irvine, CA) was selectively catheterized at the ostium of the ophthalmic artery under fluoroscopy and an angiogram of the ophthalmic artery was taken. Then we infused the chemotherapeutic drugs which had been filtered directly through the microcatheter. Whenever the ophthalmic artery was not appropriate for selective catheterization, the middle meningeal artery technique was used as an alternative.^[4] At the conclusion of the infusion, the microcatheter was withdrawn and the sheath was removed. Haemostasis of the FMA was then achieved by manual compression for 10 to 15 minutes.

We recorded the data including age, gender, cycles of IAC, pathway of arteries approached (ophthalmic artery or middle meningeal artery), ocular and systematic complications, globe salvage.

3. Results

This study retrospectively reviewed 61 patients of unilateral advanced intraocular RB (29 patients (47.5%) were female and 32 (52.5%) were male), performing 189 procedures with a median of 3.1 sessions per eye (range, 1–5 sessions). The median age of patients at first IAC was 16 months (range, 2–69 months) and the average weight of patients was 12.35 kg (range, 4.5–25.0 kg). According to IIRC, 61 eyes were classified as Group E (n = 23, 37.7%), Group D (n = 38, 62.3%). Characteristics of patients and eyes are shown in Table 1.

Treatment features are shown in Table 2. A total of 189 arteries were cannulated (184 ophthalmic arteries and 5 middle meningeal arteries) with a technical success rate of 100%. Other treatments included laser therapy, cryotherapy and intravitreal melphalan performed in conjunction with or after completion of IAC. There are 74 procedures (39.2%) were infused with single-agent melphalan, 97 procedures (51.3%) infused with melphalan plus topotecan, 7 (3.7%) procedures infused with melphalan plus carboplatin and 11 (5.8%) procedures infused with melphalan, topotecan, and carboplatin.

Of the 61 eyes, 2 cases received enucleation after the first IAC because their parents gave up globe salvage. 11 patients had to be enucleated for tumor recurrence (3 eyes), serious vitreous opacities (1 case) or deposit (2 cases), unable to identify whether the optic nerve invaded (3 cases) or failed responding to IAC (2 eyes). The overall globe salvage rate was 78.7% (48/61) during follow-up according to calcification or inactivation of tumors. Globe salvage was achieved in Group D (n = 32/38, 84.2%) and Group E (n = 16/23, 69.6%).

The treatment complications are listed in Table 3. Cardio respiratory events during the navigation of the micro catheter through the cavernous ICA are present in 7 procedures. They respond very well to intravenous epinephrine bitartrate infusion. No patients suffer an anaphylactic shock to the drugs.

Ocular complications include eyelid edema (24.6%, 15/61), ptosis (8.2%, 5/61), and forehead congestion (4.9%, 3/61), which can relieve itself after the end of the treatment. 5 patients have retina hemorrhage after IAC, It resolved completely in subsequent examinations. 2 cases have choroida atrophy and 1 case has phthisis bulbi. There are no patients had ophthalmic artery spasm or other serious complications.

Table 1

Characteristics of the 61 patients of unilateral advanced intraocular retinoblastoma.

| Parameters | Distribution |
|--------------------------|------------------|
| Sex | |
| Male | 32 (52.5%) |
| Female | 29 (47.5%) |
| Age at IAC (months) | 16 (2–69) |
| Weight at first IAC (kg) | 12.35 (4.5–25.0) |
| IIR Classification | |
| Group D | 38 (62.3%) |
| Group E | 23 (37.7%) |
| Globe salvage | 48 (78.7%) |
| Group D | 32 (84.2%) |
| Group E | 16 (69.6%) |

IAC=intra-arterial chemotherapy.

Table 2

Treatment features of intra-arterial chemotherapy in 189 procedures for the 61 patients of unilateral advanced intraocular retinoblastoma.

| Parameters | Distribution |
|-------------------------------------|--------------|
| Number of IAC cycles (sessions) | 3.1 (1–5) |
| Catheterization technique | |
| Ophthalmic artery | 184 |
| Middle meningeal artery | 5 |
| IAC medications | |
| Melphalan | 74 (39.2%) |
| Melphalan + topotecan | 97 (51.3%) |
| melphalan + carboplatin | 7 (3.7%) |
| Melphalan + topotecan + carboplatin | 11 (5.8%) |

IAC=intra-arterial chemotherapy.

Table 3

Complications of intra-arterial chemotherapy for the 61 patients of unilateral advanced intraocular retinoblastoma.

| Complications | No. of eyes or patients (%) |
|--------------------------|-----------------------------|
| eyelid edema | 15 (24.6%) |
| ptosis | 5 (8.2%) |
| forehead congestion | 3 (4.9%) |
| retina hemorrhage | 5 (8.2%) |
| choroid atrophy | 2 (3.3%) |
| phthisis bulbi | 1 (1.6%) |
| cardiorespiratory events | 7 (11.5%) |
| myelosuppression | 6 (9.8%) |
| nausea and vomiting | 5 (8.2%) |

*Some patients had more than 1 complication.

Within 1 week after surgery, there are 6 cases with different degrees of myelosuppression, only 2 cases have serious myelosuppression, which mainly shows a significant decline in neutrophils, and it is normal after subcutaneous injections of granulocyte-stimulating factor. And 5 patients have mild nausea and vomiting (2–4 times). There are no secondary neoplasms and no damage to liver or renal function because of IAC.

4. Discussion

Advanced RB is primary malignant tumor of the retina with poor prognosis. Enucleation, which has been replaced by intravenous

chemotherapy as first-line treatment for RB since 1990s, is still used as second-line treatment after the failure of intravenous chemotherapy^[7] and first-line therapy of the advanced RB in order to get a good prognosis in history. But the aim of the management of RB is not only to save lives but also to save eyes even preserve vision which is a therapeutic challenge with a variety of treatments, including systemic chemotherapy, subconjunctival injection of carboplatin, intravitreal injection of melphalan and IAC.^[8] It is noteworthy that IAC has become an essential technique in the treatment of advanced intra-ocular RB with favourable outcomes and fewer adverse effects.^[2] The first report of IAC for the treatment of RB began in 1958 using triethylene melamine by Reese.^[9] After decades of development, the technology is better. In 2006, Gobin and his colleagues modified the technique which selective catheterization of the ophthalmic artery and injection of chemotherapy, usually melphalan with or without topotecan through the micro catheter.^[7] It can reach a high concentration of the chemotherapeutic drug in the eye with minimum systemic toxicity^[5] and it is safe and effective in the treatment of advanced intraocular RB.^[7] In addition, it can be useful for eyes that fail standard treatments or for some eyes as a primary treatment.^[10] IAC was initially developed as primary therapy for the treatment of patients with unilateral advanced RB because of its well globe salvages.^[11] In our study, the technical success rate of IAC is 100% (189/189), is similar to the rates in previous reports.^[12] The total globe salvage of unilateral advanced RB is 78.7% (48/61) when IAC is used as primary therapy. It is consistent with previous reports.^[13] According to article of Shields,^[14] the patients who had no prior treatment to the eye before IAC have higher rate of globe salvage (72%), comparing to those patients who received IAC as second-line therapy (62%), and part of patients have been performed focal therapies (laser therapy or cryotherapy) or intravitreal melphalan in conjunction with or after IAC. All patients in our reports are unilateral advanced RB (Groups D - E), so the prognosis is poorer than less advanced tumours and there are 2 cases received enucleation after the first IAC because their parents gave up globe salvage.

Serious adverse cardiorespiratory events including systemic hypotension, bradycardia, and/or respiratory compliance decrease, similar to that observed in acute bronchospasm, is the serious complications during IAC, and its mechanism remains unclear but has been attributed to autonomic reflexes.^[15-17] In our patients, 7 cases have bradycardia and hypotension which respond well to intravenous epinephrine bitartrate infusion. The symptom is similar to Klumpp's previous report:^[18] at first, the patients end-tidal CO₂ suddenly decreased and airway resistance increased, followed by a subsequent deterioration in the oxygen saturation. The O₂ saturation and the End-tidal CO₂ became normal after intravenous epinephrine bitartrate infusion, while the patients had hypotensive. With the rapid growth of annotated data and the increasing computational power, deep learning methods have been widely exploited,^[19] there have no predictive factors were identified,^[20] and we found that the effect of IAC was not affected by those factors, and there were no subsequent complications. So far, there are no ophthalmic artery spasms or other serious complications.

IAC has been widely applied to the treatment of advanced intra-ocular RB, while there are no unified standard regimens of chemotherapy drugs for RB. Melphalan, not being used for systemic chemotherapy because of its high toxicity, was the most common chemotherapy drug used for IAC of RB. The dose of melphalan depends on the age of patients and it has been well

tolerated when given intra-arterially at doses of less than 0.5 mg/kg.^[7] When the clinical response is not good enough with melphalan alone or as a rescue therapy in eyes that recurred, 2 or 3 drugs were used which was based on our clinical judgment of the ocular status:^[21] melphalan, topotecan, and/or carboplatin. In our study, we gave melphalan in all procedures (n=189), ranging in dosage from 3mg to 7.5mg, in the process of IAC including 74 procedures were infused with single-agent melphalan because we pay attention to reduce the chemotherapy toxicity. However, melphalan plus topotecan or carboplatin were used in which the clinical response is not good enough with melphalan alone or the patients of RB with vitreous seeds or subretinal seeds, even procedures infused with melphalan, topotecan and carboplatin. Besides limited samples, sometimes we choose the different chemotherapy regimens in the same patient in different cycles of IAC according to condition of eyes, so we cannot compare the difference of the outcome with different treatment regimen: melphalan plus topotecan, melphalan plus carboplatin or with melphalan, topotecan, and carboplatin. Certainly, how to choose the best regimens is our new protocol in the future clinical work. Although IAC can infuse higher concentrations of drugs directly to the tumor, this route of administration is not devoid of local toxicity. The most common complications are eyelid edema.^[22] The complications occurred in our cases include eyelid edema (24.6%, 15/61), ptosis (8.2%, 5/61) and forehead congestion (4.9%, 3/61), which can relieve itself after the end of the treatment. It may be local reactions related to the drug perfusion to the ophthalmic artery terminal branch except the central retinal artery, and most of the complications could recover itself. Meanwhile, we found that use of contraction vascular drugs on the forehead or eyelid could effectively reduce the incidence of these complications before IAC. In addition, 5 cases have vitreous hemorrhage which resolved completely. It may be related to the concentration of the chemotherapeutic drugs or infusion pressure, and it may also be contributed for drastic calcifications of tumor pulls lots of nourish blood vessels in tumor. Two cases have choroidal atrophy which occurred respectively following the third and the fourth sessions of IAC. Tuncer S proposed that the incidence of choroidal atrophy may be related to the preparation of the chemotherapeutic drugs in a non-filtered fashion to remove particulates,^[21] we also filter the chemotherapeutic drugs before being infused to ophthalmic artery. In addition, we think that it may also be attributed to the cycles of IAC, the dose of chemotherapeutic drugs and the different sensitivity for the drugs in children. Optical coherence tomography (OCT), has a higher resolution than ultrasound^[23] which is a relatively radiation free and noninvasive imaging modality,^[24] is an important tool for in vivo evaluation of the microstructure of the retina and choroid in RB management and allow for a subtle tumor recurrence of RB.^[25] OCT is a useful and well-tolerated diagnostic modality for RB. Recently, we have already started to record the retina changes after IAC on OCT. Unfortunately, we don't have enough data of OCT in this research. This is the deficiency of this study and it will be included in our next research. In addition, we found that 1 case has phthisis bulbi because of the vascular toxicities of chemotherapy drugs, so we adjust the dosage of drugs to reduce the side effects.

As a new local chemotherapy instead of systemic chemotherapy, arterial infusion can minimize the adverse toxicities associated with systemic chemotherapy^[26] while providing higher concentrations of chemotherapeutic agents directly to the tumor,^[22] but it still has the possibility of myelosuppression. In our study, there are 6 cases with myelosuppression more or

less, but only 2 cases had serious myelosuppression, which mainly manifested as a significant decline in neutrophils, and it returned to be normal after subcutaneous injection of granulocyte-stimulating factor. 5 patients have mild nausea and vomiting (2–4 times), it also is associated with the toxicity of chemotherapy drugs. There are no secondary neoplasms and no damage to liver or renal function because of IAC.

Our retrospective analysis of 61 eyes with RB shows that there are no severe complications, although some patients have minor side effects. And overall ocular preservation rate is 87% in unilateral advanced RB when IAC is used as primary therapy. Now IAC is an established technology in the armamentarium of RB therapy.^[13,27,28] The technique has multiple advantages, most notably sparing the globe and achieving excellent control of retinal tumors.^[29]

5. Conclusions

Through the retrospective study which patients with newly diagnosed unilateral advanced intraocular RB undergoing IAC at our hospital in China, we describe a minimally invasive procedure with promising short-term results for the treatment of RB with a very low complication rate. But there are no unified standard regimens of chemotherapy medicines for RB, and the data on longer follow-up is needed to evaluate our results more accurately.

Author contributions

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