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 systemic 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 3-year overall survival rate of children with RB is 87% to 99% in developed countries.[3] 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.[3] 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 anesthesia.
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 (ev3Neurovascular, 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 chemotherapy 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. 3 patients have retina hemorrhage after IAC. It resolved completely in subsequent examinations, 2 cases have choroid atrophy and 1 case has ptithesis bulb. There are no patients had ophthalmic artery spasm or other serious complications.

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

| Table 1 | Characteristics of the 61 patients of unilateral advanced intraocular retinoblastoma. |
|---------|---------------------------------------------------------------|
| Parameters | Distribution |
| Sex | Male 32 (62.5%) 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%) |
| Group D | 48 (78.7%) |
| Group D | 32 (84.2%) |
| Globe salvage | 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%) |
| ptithesis bulb | 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.
patients end-tidal CO2 suddenly decreased and airway resistance respond well to intravenous epinephrine bitartrate infusion. The our patients, 7 cases have bradycardia and hypotension which similar to the rates in previous reports.[12] The total globe salvage in our study, the technical success rate of IAC is 100% (189/189), is 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 hypertensive. With the rapid growth of annotated data and the increasing computational power, deep learning allows for a subtle tumor recurrence of RB.[25] OCT is a useful 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 allows 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 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

Conceptualization: Junyang Zhao. Data curation: Zhongqi Wang. Formal analysis: Changhua Wu. Methodology: Jing Li. Project administration: Dan Song. Supervision: Changfeng Wang. Validation: Yang Yang. Visualization: Minglei Han, Lei Guo. Writing – original draft: Liang Wang.

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