

Case Report

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Intra-arterial chemotherapy for retinoblastoma: a case series report

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Abstract

Intra-arterial chemotherapy (IAC) has recently emerged as one of the most effective treatments for retinoblastoma. This treatment method reduces systemic toxicity by catheterising the ophthalmic artery with extreme precision. Although current data suggests success with the transradial route, it is traditionally performed through the transfemoral access, as is the case with most neurovascular procedures. We report the first case series in Ghana, as well as our technique, safety, and efficacy of transfemoral intra-arterial chemotherapy. We reviewed our database retrospectively and provided our technique and preliminary results from three consecutive individuals aged 2 to 16 years who underwent seven transfemoral IAC treatments. All of the IACs were completed successfully. Repeat IACs were performed on two patients, and a third session was performed on a third patient, all through the right femoral artery. There were no thromboembolic events or access site complications, such as hematoma. All patients were discharged home the same day of the procedure. In young patients with retinoblastoma, our case series confirms the safety and feasibility of transfemoral IAC. It will become the preferred sight-saving option when more experience is obtained, and the procedure becomes less expensive.

Keywords: Retinoblastoma, intra-arterial, chemotherapy, transfemoral, technique

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INTRODUCTION

Retinoblastoma (Rb) is the most prevalent intraocular cancer in children, with an incidence of 1 in 20,000 and accounting for about 3% of tumours in children under the age of 15. The annual global incidence is expected to be 8000 cases. The tumour usually develops before age five and affects the retina [1]. The prognosis for retinoblastoma patients is determined by their geographic location. The 5-year survival rate in industrialised countries such as the United States of America is approximately 90% [2]. Due to a variety of circumstances, such as advanced disease stage at presentation and a lack of treatment

alternatives, the survival rate in developing nations, including Ghana, is less than 50% [3]. Enucleation, external-beam radiation, systemic chemotherapy, thermotherapy, cryotherapy, and now intra-arterial chemotherapy are among the treatment options available (IAC). For both early and salvageable retinoblastoma, IAC has been the first treatment option. Yamane et al. [4] first introduced the procedure in 2004 by administering melphalan into the ipsilateral carotid artery of the affected eye. In 2008, Abramson et al. [5] significantly improved the procedure by super-selectively infusing the melphalan into the ophthalmic artery to reduce the systemic effect of the chemotherapeutic agent. Due to the high case fatality rate, more than 80% of advanced retinoblastoma (RE group D and E) are destined for enucleation in Ghana prior to IAC introduction. The treatment option is based on the tumour's

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extent at presentation, and it is based on the International Classification of Retinoblastoma or the Reese–Ellsworth classification.

Reese–Ellsworth classification was created in 1960 based on the clinical features at presentation, prognosis, ocular survival, and vision retention. Other features include clinical features upon presentation that correlated to a better or worse chance of ocular survival and vision on treatment with external-beam radiotherapy [6]. In 2006, Shield et al. created the International Classification of Retinoblastoma to produce a system that predicted ocular outcome and survival based on chemo-reduction [7]. In this report, we present three cases with a total of seven treatments in a resource-constrained country, as well as our technique, safety, and efficacy of transfemoral intra-arterial chemotherapy (IAC).

MATERIALS AND METHODS

At Euracare Ghana, we reviewed our prospectively maintained database of patients who received IAC for Rb via the transfemoral route between January and September 2021. A total of three patients were identified who received a total of seven IAC treatments in succession. The patients' ages ranged from 3 to 16 years old. Ethical clearance was obtained from the Cape Coast Teaching Hospital Ethical Review Committee. Before using their data for publication, all protected health information was redacted, and individual patient consents were obtained.

The intra-arterial chemotherapy was performed under general anaesthesia by the neuro-interventional team. The right femoral artery was accessed, and a 4-French arterial sheath (Terumo Corporation, Tokyo, Japan) was placed. A 4-French headway catheter (CathNet-Science, Paris, France) was then directed into the ipsilateral internal carotid artery of the targeted eye after heparinisation was given at a dose of 20-30 U/kg. Using hand injection, cerebral angiography was performed to identify the cerebral vessels and ophthalmic artery origin (Figure 1). Road mapping was performed (Figure 2), and a microcatheter (1.7-French

Headway microcatheter, Microvention, USA) and a 0.014-inch micro guidewire (Microvention, US) were directed to catheterise the origin/ostium of the ophthalmic artery. A repeat angiography was then performed to confirm the

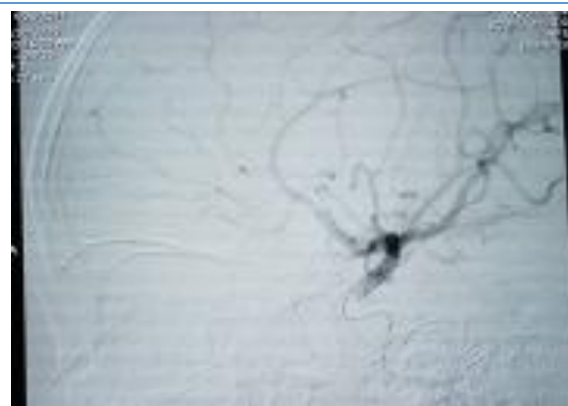


Figure. 2 – Road mapping the internal cerebral artery and its branches



Figure 3. Selective ophthalmic angiography

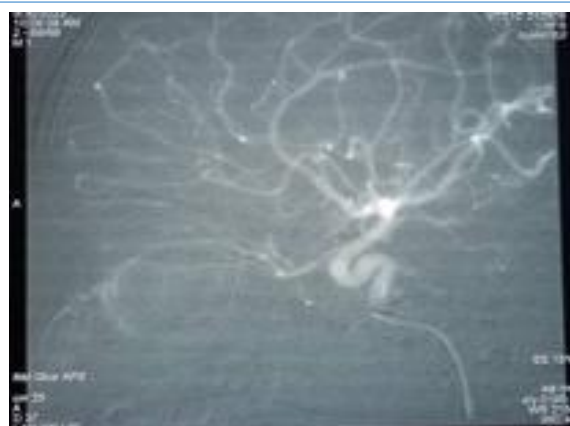


Figure 1. Cerebral angiography



Figure 4. Superselctive IAC Technique: Angiography during the infusion of the chemotherapy agent.

visualisation of the entire globe (Figure 3). The chemotherapeutic agent was infused directly into the ophthalmic artery for a period of 30 minutes (Figure 4). All ophthalmic artery cannulations were successful. There was no aberrant ophthalmic artery originating from the external carotid artery.

RESULTS

CASE 1 - A child, 1 year old, and female

At the age of 11 months, our first patient arrived in November 2019 with a history of a white spot in the right eye (RE) that had been detected since birth. Proptosis, redness, esodeviation, and leukocoria of the RE were evident. Multiple focal lesions were found in the left eye, leading to a diagnosis of bilateral retinoblastoma. A forced-choice preferential-looking test (Cardiff cards) was used to assess the visual acuity. She had six cycles of chemotherapy (Vincristine, Etoposide, and Cyclophosphamide), then RE enucleation with orbital implant, adjuvant treatment, and six additional cycles of chemotherapy. From April to June 2020, she had three 4-weekly cycles of IAC (Melphalan, Topotecan, and Cyclophosphamide) and four rounds of TPTT between July and August 2021. She is currently stable, and LE's tumours are regressing in type 1 and 4 patterns. The tumour was categorised as group B (cT1b, No, Mx) at her most recent appointment (August 2021), with a visual acuity of 6/9 (Cardiff).

CASE 2 - A child, 3 years, and female

Our second patient is a three-year-old female who was referred with a diagnosis of bilateral retinoblastoma after right enucleation and IV chemotherapy. She underwent two sessions of neoadjuvant systemic chemotherapy (Vincristine, Etoposide, and Carboplatin) before having her right eye enucleated four months later (17/07/2019). It was then followed by four more cycles of systemic

chemotherapy (Etoposide and Carboplatin) as well as a carboplatin course. Multiple tumour foci were found in the posterior region in March 2021, consistent with cT2bN0Mx (TMN classification) and Group D (IIRC) staging. She was found to have huge active tumours in the periphery, ranging in size from 6 to 8 DD, that were resistant to cryotherapy. She began IAC in March 2021 and completed two cycles. The first cycle began on March 31, and the second began on May 12, both of which were followed by cryotherapy a week later. The child was then discharged (on May 21) for follow-up. Her visual acuity was assessed using Matching tests such as the Kay pictures test.

CASE 3 - 2 weeks baby, and Male

In 2005, our third patient presented with right eye (RE) leukocoria, which had been noticed by his parents at the age of two weeks. He was diagnosed with bilateral retinoblastoma and underwent two cycles of chemotherapy (JOE protocol), then RE enucleation and orbital implant, followed by six cycles of adjuvant chemotherapy. Since this service was unavailable in Ghana at the time, he also received focal therapy for the left eye in South Africa. In May 2006, he was sent back to South Africa, where he received two more cycles of chemotherapy and whole-eye radiation via brachytherapy. He had chemotherapy and external beam radiation therapy (EBRT) for tumour recurrence in the gingival and palatal areas between May 2009 and June 2010. In June 2021, at the age of 16, he was diagnosed with recurrence. One of the tumours had a large volume of haemorrhage. All of the other tumours were quiescent. It was decided to administer IAC, which he has already received two cycles; the first cycle (cisplatin, melphalan, carboplatin) was received on July 1, and the second cycle (cisplatin, melphalan, carboplatin) was received on July 30, 21. He had two chemotherapy cycles since then (22/10/21 and 15/11/21). The Snellen chart was used to assess the vision.

Table 1. Summary of three cases who underwent Intra-arterial chemotherapy in limited-resource setting, Ghana

Case #	Age /sex	Affected eye	Presentation	IAC Examination	Findings	Management	outcome	complications
1	11mont hs/F	Bilateral	white spot, proptosis, redness, esodeviation and leukocoria	Melphalan, Topotecan and Cyclophosphamide	Multiple focal lesions, bilateral retinoblastoma	RE enucleation with orbital implant, and adjuvant chemotherapy	Discharged /stable	None
2	3years/ F	Bilateral	retinoblastoma , post Rt enucleation and IV chemotherapy	Melphalan, Topotecan and Cyclophosphamide	Multiple tumour foci	RE enucleation, cryotherapy	Discharged /stable	None
3	16years /M	Bilateral	Right eye (RE) leukocoria	Melphalan, Topotecan and Cyclophosphamide	Multiple tumour foci	RE enucleation, orbital implant chemotherapy, brachytherapy	Discharged /stable	None

DISCUSSION

Retinoblastoma (Rb) is a type of retinal tumour that affects children under the age of five [1,8]. Familial Rb can be unilateral or bilateral and has a genetic component, whereas sporadic Rb is generally unilateral and has no hereditary component. Several interventions have been employed in the hope of saving lives, preserving the eye, and preserving vision. External beam radiation, chemotherapy, and other targeted treatments have all been found to be effective, albeit with a risk of enucleation and other complications in comparison to the tumour's aggressiveness [9-11]. Intra-arterial chemotherapy is a challenging treatment that requires a high level of technical knowledge as well as a specialised centre. Consequently, several IAC efficacy and safety trials have been conducted in developed countries [1,5,8]. In developing countries, including Ghana, this is a new treatment for Rb. This paper presents our experience with three patients who received IAC treatment in a resource-constrained country, as well as our technique, safety, and practicality of IAC via the transfemoral route.

Since 2021, IAC has been used to treat intraocular retinoblastoma at our institution and has been shown to increase the likelihood of globe salvage as a secondary treatment (in eyes that have previously failed conventional treatments). The IAC procedure in all the cases was done in the second eye of the affected children who were previously diagnosed with bilateral retinoblastoma with one eye already enucleated. These second eyes all had residual vision, and the aim of the treatment was to preserve the second eyes and the residual vision with IAC alone or in combination with other focal treatments (where IAC was used to downstage the tumour). This objective had been achieved at the time of this case review, but the children continued to be closely followed up on for tumour recurrence and appropriate treatment intervention. Both super-selective and selective cannulation are available. The super-selective approach is preferred because it prevents the temporary closure of the internal carotid artery caused by a balloon catheter used in the selective IAC procedure. Data available shows that cannulation success rates have ranged from 79% to 100%, and a 100% success rate was achieved using a super-selective technique in this interventional case series [12,13].

Chemotherapy, enucleation with orbital implant, adjuvant chemotherapy, external beam radiation therapy (EBRT), and IAC were the interventions used in our cases. Following RE enucleation, all IACs were completed successfully. Repeat IACs were performed on two patients, and a third session was performed on a third patient, all through the right femoral artery. Although IAC has been demonstrated to be a safe treatment for intraocular retinoblastoma in multiple studies [12,14,15], this delicate technique is not without risks. Intra-arterial catheterisation, for example, might theoretically cause a stroke [16]. Despite this, no studies have found a link between IAC and stroke in retinoblastoma patients. No patient in our study

developed a stroke. Retinal precipitates have also been reported as complications. Wilson et al. [17] used a non-human primate model to postulate that retinal artery precipitates are the result of intricate interactions between various inflammatory mediators, leukostasis, and drug particles observed on electron microscopy. These pathways could also play a role in the development of Purtscher-like retinopathy [18] and retinal arteriole emboli [14], both of which have been hitherto documented. Furthermore, melphalan may have a limited life of stable concentration [19], contributing to drug particle aggregation. Even though melphalan was used in all seven cases of IAC, no retinal precipitates were identified.

Occlusive vasculopathy, such as vascular stenosis or total occlusion, may occur as a result of ischemia in the choroid and retina after IAC. Occlusive vasculopathy has been reported at rates of 0% to 38% in previous investigations [14,18]. Occlusive vasculopathy (ophthalmic artery occlusion) was not detected in any of our patients, which is consistent with existing literature [13,15]. It is uncertain if occlusive vasculopathy is caused by rheological changes caused by ophthalmic artery catheterisation or by medication toxicity to the choroidal vasculature and/or retinal pigment epithelium [14]. All patients were discharged home the same day of the procedure. Consistent with previous reports, our study found IAC to be a safe treatment for intraocular Rb. [20] In this study, IAC was used as a complementary treatment with others, such as chemotherapy, enucleation with an orbital implant, adjuvant chemotherapy, and external beam radiation therapy for patients with bilateral intraocular tumours. This confirms the assertion that IAC could be used as a main or supportive treatment for either unilateral or bilateral Rb and has a low risk of systemic side effects because it is delivered locally [11].

According to a systematic review by Yousef et al. [20], IAC is a promising new treatment that offers a high probability of surviving intraocular tumours, particularly in children. Eye salvage was achieved in 502 (66%) of all eyes across all studies. Eye salvage was 74 % for 124 first-line IAC eyes, 67 % for 172 second-line IAC eyes, and 61% for 461 unidentified eyes [20]. The effectiveness of IAC treatment was found to be influenced by Rb stage. Eye salvage rates of 86 % for 216 eyes with less advanced intraocular tumours and 57% for 456 eyes with more advanced intraocular tumours have been reported. Saiegh et al. [11] reported that IAC is a validated treatment approach for achieving tumour control, especially in individuals with advanced disease who would otherwise have to undergo enucleation. Similarly, an Indian study found that IAC treatment for globe eye salvage is safe and effective, although larger studies with longer follow-ups are needed to confirm these findings [10]. There is limited evidence on visual outcomes regarding the eye involved in IAC treatment. In a review, Yousef et al. [9] reported high chances of good visual acuity for most children who received IAC, while only a few may sustain severe visual

loss for eyes with foveolar involvement. Our patients reported good visual acuity on follow-up.

IAC offers numerous benefits. However, in many developing nations, a lack of resources, including budget constraints and a lack of specialised centres and technical expertise, does not promote IAC implementation. The current cost of IAC at Euracare Ghana is five thousand USD in addition to the cost of adjuvant chemotherapy, enucleation and radiation; patients pay out of pocket due to a lack of insurance coverage. Developing countries could adopt the current model in Thailand, whereby a special fund is set up and supported by donations from other foundations.

Conclusion

In young patients with retinoblastoma, our case series confirms the safety, feasibility and efficacy of transfemoral IAC. It will become the preferred sight-saving solution when more experience is obtained, and costs become less expensive.

DECLARATIONS

Ethical consideration

Informed consent was obtained from the participant's parents. The cases do not contain any information that could lead to the traceability of the patients. The study images were used with consent from Euracare.

Consent to publish

All authors agreed on the content of the final paper.

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None

Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

BDS, BBJ and DA conceived the topic, designed the protocol, and performed the procedures. BBJ drafted the manuscript. BDS, DA, VE, EKE and EJJ reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data

Data is available upon request to the corresponding author.

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