

# Retinoblastoma and its adverse events experienced

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## Abstract

*Background:* Retinoblastoma management has seen a paradigm shift with intra-arterial chemotherapy (IAC). Using IAC as primary management in this paediatric cancer is becoming more widespread in developing countries such as Malaysia. Considerable evidence shows that IAC has a more beneficial globe salvage rate than intravenous chemotherapy (IVC).

*Case presentation:* This case report describes a successful globe salvage in Group D retinoblastoma with primary IAC and the complications experienced with this mode of treatment, especially the vascular events seen which could possibly contribute to persistent poor vision despite a completely regressed tumour.

*Conclusion:* Despite the remarkable tumour regression and globe preservation, the patient's vision did not improve in the treated eye. We wish to explore the possibilities resulting in those complications and methods to reduce them in the future.

*Keywords:* globe salvage, primary intra-arterial chemotherapy, retinal ischaemia, retinoblastoma, vascular events

# Retinoblastoma dan kesan sampingan yang dialami

## Abstrak

*Latar belakang:* Rawatan retinoblastoma melihat anjakan paradigma dengan adanya kemoterapi intra-arteri (IAC). Menggunakan IAC sebagai rawatan dalam kanser pediatrik ini semakin meluas di negara membangun seperti Malaysia. Terdapat banyak kes yang membuktikan IAC berjaya menyelamatkan glob mata dibandingkan dengan kemoterapi intravena (IVC).

*Laporan kes:* Kes ini menunjukkan kejayaan dalam pemeliharaan glob mata retinoblastoma kumpulan D dengan menggunakan IAC sebagai rawatan utama. Namun demikian, kesan sampingan juga dialami dengan kaedah rawatan ini, terutamanya komplikasi vaskular yang mungkin pengurangan penglihatan walaupun glob mata dapat dikekalkan.

*Kesimpulan:* Walaupun glob mata terpelihara melalui rawatan IAC, tiada penambahbaikan penglihatan pesakit yang dilihat. Justeru, kami ingin mencari punca yang mengakibatkan komplikasi dan kaedah untuk mengurangkannya pada masa hadapan.

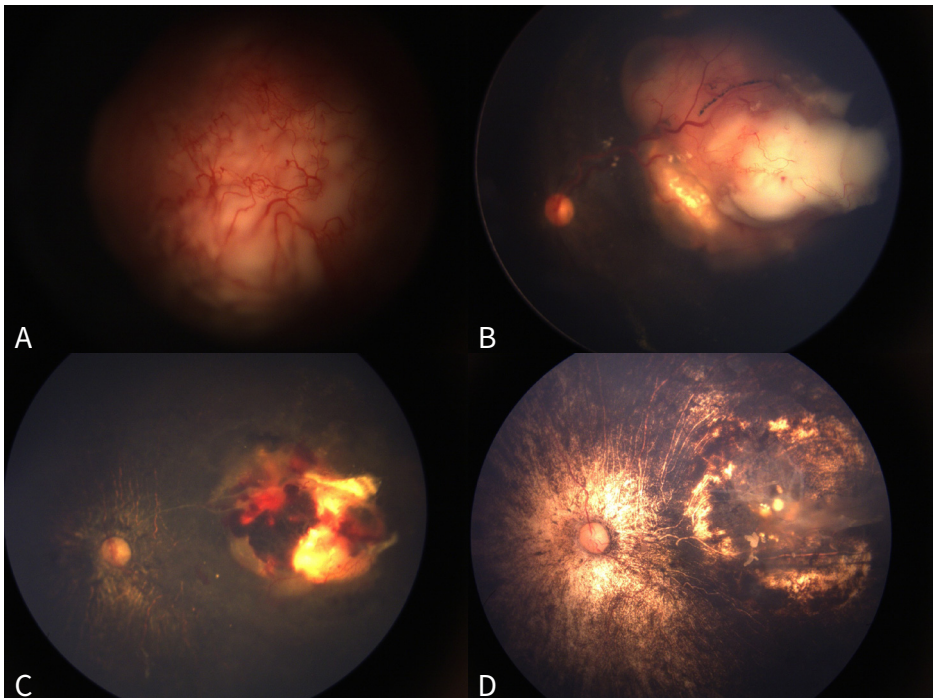
*Kata kunci:* iskemia retina, kemoterapi intra-arteri, komplikasi vaskular, pemeliharaan glob mata, retinoblastoma

## Introduction

The advent of intraarterial chemotherapy (IAC) is impactful, with a beneficial globe salvage rate of 100% in Group D retinoblastoma.<sup>1</sup> Response has been seen with a shorter duration of treatment,<sup>2</sup> avoiding the systemic risks of intravenous chemotherapy (IVC). We report a case of unilateral Group D retinoblastoma treated primarily with intra-arterial melphalan and topotecan, as well as the advantages and complications of this mode of treatment.

## Case presentation

A 3-year-old girl was referred to the paediatric ophthalmology team at Hospital Kuala Lumpur for unilateral retinoblastoma in the left eye (LE). Vision in the right eye (RE) was 6/7.5, while LE was light perception (LP). On examination under anaesthesia (EUA) of the LE, there was a large endophytic retinal mass with tortuous feeder vessels extending from the temporal half of the optic disc to the peripheral ends of the temporal arcade vessels, obscuring the macula (Fig. 1A). Diffuse, fine vitreous and subretinal seedings were visualised. The RE examination was normal. She was diagnosed with LE unilateral Group D retinoblastoma. The contrast-enhanced computed tomography scan confirmed the diagnosis. Bone marrow and lumbar puncture investigations did not show extraocular involvement.



*Fig. 1.* Fundus photo of the left eye. (A) Large endophytic retinal mass with multiple tortuous feeder vessels obscuring the optic disc and macula at the time of diagnosis. (B) After the first IAC, showing a markedly reduced tumour with fish flesh, revealing the optic disc. (C) Following the fourth IAC, regressing fish flesh with haemorrhage on the tumour, a pale disc with an ischaemic retina and sclerosed vessel. (D) Fundus photo of the left eye, seventeen months from diagnosis, after four cycles of IAC. Attenuated retinal and choroidal vessels with areas of choroidal ischaemia are seen surrounding the disc and macula.

She underwent a total of five attempts of IAC (of which only four were successful), supplemented with focal laser indirect ophthalmoscopy. During the first three successful rounds of IAC, melphalan 5 mg in 30 ml normal saline and topotecan 1 mg in 20 ml normal saline were given through the left ophthalmic artery by the interventional radiologist under general anaesthesia. The fourth IAC was unsuccessful and abandoned due to left ophthalmic artery spasm. On the last session of IAC, the chemotherapeutic agents were given through the middle meningeal artery in view of a failed prior attempt due to spasm of the left ophthalmic artery. Each IAC was given once a month, followed by an EUA two weeks post-IAC.

The tumour regressed significantly throughout the course of the treatment. On the first EUA post-IAC, the tumour shrank markedly in size and further regressed on subsequent EUA (Fig. 1B-C). At seventeen months from diagnosis, complete primary tumour regression was seen (Fig. 1D).



Fig. 2. Forehead erythema after the second IAC.

However, we experienced a few complications and difficulties with this case. On the fourth IAC attempt, the left ophthalmic artery could not be cannulated, and the procedure was abandoned. On the subsequent attempt, IAC was given via the middle meningeal artery. In addition, a transient hyperpigmented lesion was seen on the left forehead after the second IAC (Fig. 2). The child's retina was also ischaemic, which may account for the persistently poor LP vision despite a completely regressed tumour (Fig. 1D).

## Discussion

IAC has revolutionised paediatric cancer management, rendering excellent outcomes in globe salvage (90–100%) in retinoblastoma Groups A to E.<sup>3</sup> Primary IAC had a better eye salvage rate than secondary IAC (80.2% versus 58.4%).<sup>2</sup> As seen in our case, the treatment showed a complete response within seventeen months of treatment. However, vision remained as LP.

IAC has many advantages in comparison to IVC. Nevertheless, systemic side effects are inevitable with IAC. Neutropenia is seen, though its incidence is lower and less severe than its counterpart. They were reported to be 5.9% by Manjadavida *et al.*<sup>2</sup> and 11.4% by Gobin *et al.*<sup>4</sup> Our patient did not have neutropenia throughout the treatment.

The primary aim of retinoblastoma management is life salvage. Since IAC is a local therapy with no systemic chemoprotection, the concern of metastatic disease in advanced retinoblastoma persists. There have been few reported cases of metastasis following IAC worldwide.<sup>2,4,5</sup> Gobin *et al.* previously reported 2 of 78 patients who developed metastasis.<sup>4</sup> Metastatic deaths are rare with IAC (less than 3%) and they occur following refusal of enucleation and default.<sup>6</sup>

Being a neuroinvasive procedure, IAC poses the risk of neurological complications. A case of transient ischemic attack was reported by Ronjanaporn *et al.*,<sup>5</sup> while three cases of stroke have been reported thus far.<sup>7-9</sup> Muen *et al.* reported 40% cases of third cranial nerve palsy with ptosis and pupillary involvement following IAC.<sup>10</sup> Bronchospasm has been reported during 8% of procedures effectively treated by epinephrine bitartrate injection.<sup>4</sup> Fortunately, there was no reported death due to the procedure itself.<sup>2</sup>

Ocular side effects were observed with IAC, the most common being periocular oedema and hyperaemia (34%), ptosis (13.5%), and forehead erythema (3%). These complications were not permanent.<sup>2</sup> Transient forehead erythema was seen in our case, which was also reported by Gobin *et al.* in 14 out of 78 cases.<sup>4</sup> In addition, vasospasm of the ophthalmic artery is commonly encountered during IAC.<sup>2,4</sup> With improved techniques and expertise, ophthalmic artery spasm has been reduced from 27% to 0% currently.<sup>11</sup> Likewise, ophthalmic artery spasm occurred on the fourth IAC attempt in our patient.

Vision salvage is one of the major goals of IAC. Only a few studies have reported the final visual acuity post-IAC. The procedure carries the risk of permanent vision-threatening complications; however, the visual prognosis also depends largely on the pre-treatment status of the macula. If the macula has been affected at diagnosis with poor electroretinogram (ERG) pre-treatment, overall visual acuities are worse.<sup>12</sup> On the other hand, vision better than 6/12 was retained in 51% of cases sparing the foveola.<sup>13</sup> Associated ischaemic and occlusive chorioretinopathy remain major concerns. In spite of that, vascular events were reported in only 5% of all IAC treatments, and they were similar between primary and secondary IAC (18% versus 15%).<sup>14</sup>

Retinal ischaemia and choroidal vessel attenuation were seen in our case. The poor vision despite tumour regression could be attributed to either the retinal and choroidal ischaemia from IAC or the advanced disease affecting the macula. Our centre does not have ERG capability, and fundus fluorescein angiography was not conducted to prove their association. The fundus photo of this patient post-IAC showed severe choroidal atrophy, a possible reason for her poor vision (Fig. 1D). In line with this, subfoveal choroidal thickness was proven to be significantly reduced in treated eyes versus healthy control eyes.<sup>15</sup>

The exact reason for vascular events is not fully understood, whether related to cumulative drug toxicity, distribution, or delivery technique.<sup>2,11</sup> Steinle *et al.* reported a direct effect of melphalan on the vascular endothelium and monocytes,<sup>16</sup> while Francis *et al.* found that cumulative melphalan infusion was associated with modest ERG amplitude changes.<sup>17</sup> Laboratory and histopathologic studies have demonstrated ischemic retinal and choroidal atrophy after treatment with melphalan.<sup>11</sup>

Melphalan and topotecan were used in our case, as melphalan is the most potent agent for retinoblastoma, while topotecan is effective in advanced retinoblastoma with vitreous seedings.<sup>2</sup> The choice of these drug dosages was based on the patient's

age as an approximation of the eye size.<sup>2,4</sup> Reddy *et al.* concluded that visual complications might be minimised with age-adjusted melphalan dosages,<sup>18</sup> but Dalvin *et al.* could not prove such a hypothesis.<sup>11</sup> There is currently limited data on dosages adjusted to weight or body surface area, which may need to be considered. Weight, body surface area, and treatment response from earlier IAC could be a method to titrate the drug dosages to reduce ocular toxicity.

On the bright side, the main aim of globe salvaging was achieved, and systemic complications with IVC, such as febrile neutropenia or sepsis, were minimised. IAC suggests a promising role for globe salvaging in advanced retinoblastoma. Ocular vascular events may occur due to this treatment modality. However, the aim of globe preservation was achieved.

## Conclusion

This revolutionary treatment has shown its benefits in retinoblastoma, showing exceptional response in globe salvage, particularly in advanced retinoblastoma. Despite the remarkable tumour regression and globe preservation, the patient did not retain her vision in the treated eye. Chemotherapeutic agent dosage is now determined by the patient's age and disease severity. In the future, dosage adjustments in subsequent sessions may be considered in the event of vascular problems or ERG changes as a result of the therapy. Revision of the dosage of chemotherapeutic agents may be able to minimise treatment-associated complications. Weight or body surface area adjusted dosages could be explored in future studies.

## Declarations

### Informed consent for publication

Written informed consent was obtained from the patient's guardians for the publication of the clinical images and date contained in this case report.

### Competing interests

None to declare.

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