Intra-arterial chemotherapy for retinoblastoma: the beginning of a long journey

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ABSTRACT

Conservative management of retinoblastoma has evolved from external beam radiotherapy to systemic chemotherapy by intravenous route and now to localized chemotherapy by intra-arterial route in some cases. With 16-year experience, systemic chemotherapy has been found effective for minimal to moderately advanced retinoblastoma with tumour control of 90% or better, few side effects and even hope for return of some vision. Localized intra-arterial chemotherapy with delivery under fluoroscopy and catheterization of the ophthalmic artery is now undergoing evaluation and appears to provide striking control for retinoblastoma, particularly recurrent tumour seeds following other therapies. The limitations and complications of this approach have yet to be defined. Toxicity of the chemotherapy to the delicate retinal vessels is unknown. Despite its allure, intra-arterial chemotherapy should be used with caution, as in other fields of paediatric oncology it has been found to provide no advantage over intravenous chemotherapy. Time will tell.

Key words: cancer, chemotherapy, eye, intra-arterial chemotherapy, retina, retinoblastoma.

Imagine it is 1979 and you are referred to an ocular oncologist because your 2-year-old daughter has been diagnosed with intermediate stage (Group C) unilateral retinoblastoma. You are told that enucleation could save her life with a 1-h surgical procedure and she would most likely live a healthy long life wearing an ocular prosthesis with little anticipated systemic complications. Sounds like a favourable compromise, trading an eye for life and no systemic complications.

Imagine it is 1989 in the same scenario and you are told that external beam radiotherapy would be the treatment of choice, but she might not have much vision. She could need multiple doctor visits for cataract surgery and glasses as a youngster, followed by chronic dry eye requiring lifelong eye lubrication, corneal vascularization with foggy vision, orbitofacial dysmorphism with an asymmetric face and a risk for life-threatening second cancers. Like a run-on sentence, the risks go on and on. And we did not realize many of these risks until decades after this therapy was used.

Imagine it is 1999 and you are encouraged to consider the new therapy of systemic chemoreduction on a monthly basis for 6 months. You are told that this method could save the eye and might even allow for some visual recovery. Fortunately, the previous risks of dry eye, cataract and facial dysmorphism are gone. But there are new concerns about transient pancytopenia, permanent auditory and renal toxicity, and potential risks for second cancers, especially leukaemia. The visual outcome is improved, but trade-offs are intimidating.

Now it is 2009 and your doctor instructs you that the most advanced method is intra-arterial chemotherapy whereby a neuro-interventional radiologist or neurosurgeon will thread a catheter into your child’s leg, through the abdomen and thorax, into the vital internal carotid artery and make a difficult, tight semi-u-turn into the ophthalmic artery to pulse chemotherapy into the eye. You are told of the risks of
stroke, haemorrhage, loss of limb or eye and possible immediate loss of life. Stop. Hold on. Does salvage of the eye merit this gamble?

We have trudged a long journey in retinoblastoma management over the past decades. As a group, we have achieved several profound accomplishments such as improved life prognosis, predictable improvement in visual acuity, reduction in the need for enucleation and external beam radiotherapy and its consequences, and reduction in cosmetic deformity. This journey has been slow and tedious, but for reasonable goals. We are now cautiously facing a change.

We are awakening to the foggy sunrise of a change in therapy for this highly malignant cancer. Mind you, this cancer has been successfully controlled with current methods of chemoreduction. However, we are confronted with a new dilemma, namely intra-arterial chemotherapy. Why the change? Were our old methods incompetent or too toxic? Not really, as excellent control of Groups A, B and C retinoblastoma were achieved with less than 10% failure. As anticipated, more advanced retinoblastoma (Group D) showed less control (48%) but with the addition of subconjunctival carboplatin, control has improved. With regard to toxicities, in our experience, they were mostly transitory with anticipated drop in blood counts that recovered typically without the need for blood transfusion. Was chemoreduction too expensive? Not in our hands. By strictly monitored protocol, all children received six cycles of chemotherapy and were monitored appropriately. Most children did not require vascular access ports and few needed hospitalization for treatment-related fever. Considering the value of lifelong vision, chemoreduction was (and still is) a bargain. So is there really a need to reassess our attack on retinoblastoma with risky and expensive neuroinvasive tactics using toxic and potentially-carcinogenic weapons? Well, the irresistible attractiveness of this new route is the touted focal delivery with hopefully less systemic side effects and toxicity. Sounds reasonable. Let’s explore the facts.

In the late 1980s, Inomata and Kaneko found that the long-used, potent chemotherapy drug, melphalan, was the most effective agent against retinoblastoma compared with 11 other anti-cancer drugs by in vitro colony assay on double agar layers. Kaneko et al. treated six patients with retinoblastoma that was recurrent following radiotherapy using 40 mg of intracarotid artery melphalan plus hyperthermia and cured two patients of the malignancy. However, severe bone marrow toxicity and hair loss were complications. They then attempted to minimize systemic toxicity with a more focal delivery system of balloon occlusion of the distal internal carotid artery with delivery of a lower melphalan dose of 5–10 mg/m². Between 1989 and 1999, they commented in a review article that they had carried out catheterization of the internal carotid artery with distal balloon occlusion for delivery of chemotherapy in 176 patients (551 catheterizations) with excellent technical success but there were no data provided on tumour control or specific treatment complications. They noted side effects of vomiting and commented on the lack of long-term tumour control and treatment complications was not published. In 2008, Abramson et al. used a similar but slightly more direct technique to cannulate specifically into the ophthalmic artery for chemotherapy infusion without the need for distal balloon occlusion of the internal carotid artery. They reported on 10 children with advanced retinoblastoma who were treated with one to several sessions of intra-arterial (ophthalmic artery) chemotherapy using one or a combination of melphalan, carboplatin or topotecan. Seven eyes were successfully saved. Two eyes came to enucleation for persistent retinal detachment and there was no residual viable tumour on histopathology. One eye failed ophthalmic artery cannulation. No patients developed severe systemic side effects. They commented that ‘the treatment response was dramatic; the senior author has never observed such an impressive response of vitreous seeding from any other single treatment modality for retinoblastoma’. The locally administered chemotherapy was about one-tenth the usual systemic dose. In that report, the authors admitted that ‘some of these cases . . . (required) supplementary thermotherapy, brachtherapy, and external beam irradiation’. Based on preliminary data, they concluded that this new approach could provide retinoblastoma control with minimal side effects.

The aforementioned pioneering studies sparked excitement for this new therapy with courageous investigation into an innovative way to control
retinoblastoma. However, both experiences\textsuperscript{11–14} suffered from lack of clean data and organized protocols as there were different chemotherapy agents, different doses and numerous additional therapies with relatively short-term follow up. To quote Lin and O’Brien, the Japanese studies were ‘difficult to determine how effective the intra-arterial injections would be if used alone’ and the Abramson study was ‘difficult to determine whether this method [intra-arterial chemotherapy] is effective in increasing globe salvage rates on its own’.\textsuperscript{15} So the true value of intra-arterial chemotherapy for retinoblastoma has not yet been shown.

The advantage of intra-arterial chemotherapy is the focal delivery of chemotherapy with presumed minimal systemic side effects. In a pilot study from Wills Eye Institute in collaboration with Jefferson Hospital for Neurosurgery, we have used intra-arterial chemotherapy over the past 18 months for selected children with retinoblastoma who failed systemic chemoreduction or those with unilateral disease in which avoidance of systemic therapy and enucleation was preferred with family consent. By protocol, mid-dose melphalan (5 mg) for three sessions was used to evaluate the benefit of this single agent therapy. Thermotherapy, plaque radiotherapy, external beam radiotherapy, sub-Tenon’s chemotherapy and other therapies were withheld to avoid confounding the data. Of our first 11 cases with follow up, the main side effects were transient ipsilateral eyelid oedema, mild ptosis and transient systemic cytopenia, none requiring transfusion. Tumour control with complete regression of retinoblastoma, resolution of retinal detachment, and resolution of vitreous and subretinal seeds was observed initially in all cases (Figs 1,2). However, recurrence of

\begin{figure}[h]
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\includegraphics[width=\textwidth]{image1}
\caption{Intra-arterial (ophthalmic artery) melphalan for retinoblastoma that has failed previous treatment. Macular retinoblastoma after standard six cycles of chemoreduction with recurrent fleshy subretinal tumour seed (arrow) atop the calcified regressed mass (a) showed complete regression (arrow) after two cycles of intra-arterial chemotherapy (b).}
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\begin{figure}[h]
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\includegraphics[width=\textwidth]{image2}
\caption{Intra-arterial (ophthalmic artery) melphalan for retinoblastoma as a primary treatment. Macular retinoblastoma (International Classification of Retinoblastoma Group C) (a) treated with two cycles of intra-arterial melphalan showed complete regression (b). Extensive retinoblastoma (International Classification of Retinoblastoma Group E) (c) treated with four cycles of intra-arterial melphalan showed complete regression (d). However, long-term follow up is necessary.}
\end{figure}
vitreous seeds (one case), chronic vitreous haemorrhage (one case) and incomplete vitreous seed regression (two cases) requiring additional therapy was noted. In all 11 cases, the intraretinal retinoblastoma showed complete regression for the short follow up, but vitreous seeds posed the main problem for recurrence, similar to standard chemotherapy. Another concern was the problem of embolic events to the globe, ranging from transient ischemia to complete ophthalmic artery obstruction (Fig. 3). Further detailed analysis of our results using single agent intra-arterial melphalan is pending and will be published. Thus the preliminary results might appear favourable, but long-term control and complications justifiably need to be scrutinized and are forthcoming.

The enthusiasm for intra-arterial chemotherapy for retinoblastoma varies among the ophthalmic community. The risks for cerebral haemorrhage, thrombosis, embolism and infection, and arterial endothelial toxicity, stenosis, and occlusion, with risk for limb loss and globe loss are grim hazards to assume. The curiosity for this technique was evident at the biennial International Society of Ocular Oncology meeting in Cambridge, England in September 2009. There were 11 presentations from the USA, Asia and Europe on intra-arterial chemotherapy for retinoblastoma with short-term results and complications. Most illustrated favourable preliminary results with dramatic tumour regression, but no clear data on long-term control. Dunkel et al. found systemic non-ocular toxicity of grade 3 or 4 neutropenia in 26% of 38 patients, but no patient required transfusion and there were no patients with clinically detectable stroke. Mahajan et al. explored radiation toxicity from fluoroscopy during this procedure and found the cumulative radiation doses from three cycles of intra-arterial chemotherapy to the skin, bone, brain, eye, lens and thyroid were 150 mGy, 120 mGy, 75 mGy, 150 mGy, 150 mGy and 5 mGy, respectively. Depending on the technique, they commented that doses could be fivefold if the technique of digital subtraction angiography was used. They warned that ‘doses in this range may increase the absolute risk of a fatal cancer by up to 1% and probably higher in retinoblastoma patients’ and advised that ‘cerebral angiography should be monitored carefully and a concerted effort should be made to use optimal techniques which minimize radiation dose to these children’.

We have explored radiation exposure in our series at Wills Eye Institute/Jefferson Hospital for Neurosurgery and found that the fluoroscopic radiation dose to the gonads, abdomen, thorax and brain were well within safe limits, using an experienced team in paediatric brain catheterization and minimal exposure technique at our institution. The estimated dose to the lens with three catheterizations could be cataractogenic. It should be recognized that radiation exposure, even from computed tomographic scans, should be minimized in children as they are at a relatively greater risk for developing radiation-related cancers than adults. This is due to the more rapidly dividing cells in children and the longer life expectancy. The effects of even low-dose radiation in retinoblastoma children with germline mutation could be more serious.

Intra-arterial chemotherapy is not new. It has been studied extensively for specific cancers of the brain, bone, liver and other organs. Enthusiasm has varied for this technique as a single modality or in combination with systemic chemotherapy, radiotherapy, or pre- or post- infusion surgical excision. In 2000, Madajewicz et al. found that intra-arterial chemotherapy for patients with glioblastoma multiforme of the brain provided longer survival if delivered before rather than concomitant with radiotherapy. However, Shapiro et al. carried out a large randomized comparison of intra-arterial versus intravenous carmustine in 315 patients with malignant glioma, with or without additional intravenous 5-fluorouracil and found reduced survival for the intra-arterial group (P = 0.03) plus related toxicities of encephalopathy (9.5%) and ipsilateral visual loss (15.5%). Similar lack of benefit was observed in 2000 by Kochi et al. using intra-arterial versus intravenous nimustine for...
glioblastoma. In 2006, Imbesi et al., in a randomized phase III comparison study, found no better tumour control and no fewer systemic side effects with intra-arterial versus intravenous nimustine for newly diagnosed glioblastoma. For paediatric malignancies, this novel intra-arterial approach can be used with improved outcomes for high-risk sarcomas, particularly osteosarcoma with methods of chemotherapy combined with liposomes, embolization before surgery, radiosensitization and anti-vascular endothelial growth factor. When used as a monotherapy, intra-arterial infusion of cisplatin, a particularly active drug against osteosarcoma, initially appeared more efficacious than intravenous infusion. However, the literature showed that the intra-arterial superiority was diminished when cisplatin was combined with other drugs. Trials investigating the role of intra-arterial cisplatin in addition to systemic chemotherapy for osteosarcoma (study COSS-86) showed no benefit of this strategy over intravenous cisplatin. Bacci et al. found that the benefit of neoadjuvant intra-arterial over intravenous cisplatinum was not evident when this drug was used in combination with aggressive multiagent preoperative four drug systemic chemotherapy for non-metastatic osteosarcoma of the limb. So the debate continues over role of intra-arterial versus intravenous approach for some systemic malignancies. These ‘lack of benefit’ reports do not mean that we should abandon this technology for the eye, but it does offer a sobering warning that we should investigate this technique with scientific caution.

One last comment with hindsight from observations at the International Society of Ocular Oncology meeting in Cambridge. Following the stunning presentations on intra-arterial chemotherapy for retinoblastoma, comments from some experienced retinoblastoma specialists in the audience offered prudent perspectives. Brenda Gallie, MD pleaded that an organized collaborative prospective effort at a few experienced centres be organized to properly evaluate the risks and benefits of this new technique before it becomes mainstream. Her opinion was commended. And another voice spoke from the audience making a plea to not abandon the life-saving technique of enucleation for advanced retinoblastoma as it avoids the unknown local and systemic toxicities of this therapy in an eye with established blindness. Said a different way, an eye with extensive retinoblastoma and blindness should be an indication for enucleation. Jerry Shields, MD was applauded for that statement.

So imagine next week you are faced with the tugging decision for management of your child with unilateral retinoblastoma. Are you willing to assume the risks of intra-arterial chemotherapy or should you consider more standard methods of chemoreduction, plaque radiotherapy or enucleation? Is the anticipated globe salvage with hopeful electroretinogram detection of some visual potential in your preverbal child worth the risk? Before we enter this new era, let’s slowly and meticulously evaluate its potential, limitations, and local and systemic toxicities in a comprehensive organized fashion. It might be a long journey over many years before the true promise and complications of this technique are realized.

References

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