Pearls and pitfalls of intraarterial chemotherapy for retinoblastoma

A review

PASCAL JABBOUR, M.D.,1 NOHRA CHALOUHI, M.D.,1 STAVROPOULA TJOUKAKIS, M.D.,1 L. FERNANDO GONZALEZ, M.D.,1 AARON S. DUMONT, M.D.,1 ROHAN CHITALE, M.D.,1 ROBERT ROSENWASSER, M.D.,1 CARLOS G. BIANCOTTI, M.D.,2 AND CAROL SHIELDS, M.D.2

1Department of Neurosurgery, Thomas Jefferson University and Jefferson Hospital for Neuroscience; and 2Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Retinoblastoma is a deadly eye cancer in children, leading to death in 50%–70% of children in undeveloped nations who are diagnosed with it. This malignancy is the most common intraocular tumor in childhood worldwide. The good prognosis in developed nations is related to early detection and advanced treatments. With the advent of intraarterial chemotherapy, neurosurgeons have taken a central role in the treatment of this pediatric condition. Intraarterial chemotherapy is a novel treatment for retinoblastoma whereby chemotherapeutic agents are precisely delivered into the ophthalmic artery, minimizing systemic toxicity. This procedure has shown impressive results and has allowed a dramatic decrease in the rate of enucleation (eye removal) in advanced and refractory retinoblastoma. Recent reports have raised some concerns about the risk of ocular vasculopathy, radiation-related toxicity, and the potential for metastatic disease after intraarterial chemotherapy. In the authors’ experience of more than 3 years, tumor control is excellent with globe salvage at 67% and vascular events less than 5%, mostly related to improvement in technique. The role of this novel approach in the management of retinoblastoma has yet to be defined. As more centers are adopting the technique, the topic will decidedly become the focus of intensive future research. In this paper, the authors review and discuss current data regarding intraarterial chemotherapy for retinoblastoma.

(10.3171/2012.5.PEDS1227)

Key Words • intraarterial chemotherapy • melphalan hydrochloride • ophthalmic artery • retinoblastoma • oncology

Retinoblastoma is the most common primary intraocular malignancy in children, with a cumulative incidence of 53 per million for the first 14 years of life.22 Several advances in the detection and management of retinoblastoma have afforded a complete cure in many cases of this potentially fatal condition. Cure rates for patients harboring retinoblastoma are as high as 96% in the US,2 but the burden of the disease remains heavy in the developing world, especially in Asia and Africa, where mortality rates can reach 39% and 70%, respectively.22 Classic treatment options include enucleation (eye removal), external-beam radiotherapy, systemic chemotherapy, and focal therapies, such as cryotherapy, thermotherapy, laser photocoagulation, and plaque radiotherapy.11 For the last 2 decades, intravenous chemotherapy has been the mainstay of treatment for retinoblastomas.14,33,35,38 This route has provided improved control in retinoblastoma, with sparing of the eye and vision in some cases. In the last few years, chemotherapy by the intraarterial route, termed “intraarterial chemotherapy,” has garnered worldwide interest and has emerged as a promising treatment alternative for advanced and refractory retinoblastomas, in an attempt to avoid systemic complications. Impressive tumor response with a high rate of globe salvage has been reported with this technique.1,2,39 Today, IAC is steadily gaining popularity as a reliable treatment in the management of retinoblastoma. However, there remain concerns about issues related to chemotherapy and infusion techniques. Because neurosurgeons have become increasingly involved in the treatment of this condition in the pediatric population, we review and discuss current data regarding IAC for retinoblastoma.

Clinical Features and Classification

The most common presenting features of retinoblastoma are leukocoria (abnormal white reflection from
the retina of the eye) or strabismus. The typical ophthalmoscopic appearance of the tumor is a unifocal or multifocal whitish mass with feeding retinal artery and a draining vein. Approximately two-thirds of all retinoblastoma cases are unilateral, and one-third is bilateral. Patients with familial and bilateral retinoblastomas carry a heritable germline mutation (present in all cells of the body) and are at risk for second and third cancers. As such, up to 10% of these patients may develop neuroblastic intracranial malignancies, the most common of which is the usually fatal pineoblastoma (also known as “trilateral” retinoblastoma). On the other hand, unilateral sporadic retinoblastomas usually do not have a germline limitation and are therefore not heritable. Most cases of retinoblastoma are recognized by 3–5 years of age. Germline retinoblastoma usually presents between the ages of 3 and 18 months, whereas sporadic retinoblastoma presents between the ages of 18 and 24 months.

The most commonly used classification for retinoblastoma is the ICRB. This classification takes into account tumor size, tumor location and, most importantly, the extent of tumor seeding in the vitreous and subretinal space (Table 1). The ICRB reflects the natural history of retinoblastoma, with Group A referring to early disease and Group E to advanced disease, and assists in the prediction of globe salvage with chemotherapy. The tumor is confined to the retina in Groups A and B, spreads into the subretinal space and vitreous cavity in Groups C and D, and occupies more than 50% of the globe in Group E. The likelihood of salvaging the eye decreases from Group A to Group E. In a large study that included 249 eyes treated with systemic chemotherapy, Shields et al. demonstrated that the ICRB predicts treatment success rates. Treatment was found to be successful in 100% of Group A eyes, 93% of Group B eyes, 90% of Group C eyes, and only 48% of Group D eyes.

**The Rationale Behind IAC**

The importance of IAC stems primarily from the limitations of other treatment modalities. Focal therapies have little role in the treatment of advanced or extensive retinoblastomas and are typically reserved for smaller or less extensive disease. Enucleation is a straightforward and life-saving intervention in advanced retinoblastomas, but the procedure leads to permanent loss of vision, which may be especially problematic for patients harboring bilateral tumors. External-beam radiotherapy is considered a last-resort option because of its devastating local and systemic consequences, including cataract formation, ocular dryness, facial dysmorphism, and secondary cancers. Intravenous chemotherapy, using a combination of vincristine, etoposide, and carboplatin, can efficiently treat retinoblastoma and provide impressive long-term control. However, success rates with chemoreduction are typically lower for advanced retinoblastoma, especially those with vitreous seeds, which represents an important limitation for many children with tumors at advanced stages. As discussed above, Shields et al. reported that chemoreduction was successful in 100% of Group A eyes versus only 48% of Group D eyes. In addition, subretinal and vitreous seed recurrences were noted to be a major issue with chemotherapy.

Another pressing limitation of intravenous chemotherapy is the risk of serious systemic adverse events such as myelosuppression, ototoxicity, nephrotoxicity, gastrointestinal toxicity, failure to thrive, and secondary neoplasms, especially leukemias. Moreover, melphalan (1-phenylalanine mustard), the most effective chemotherapeutic agent against retinoblastoma, cannot be used systematically because of its high toxicity (myelosuppression) at therapeutic doses.

Intraarterial chemotherapy consists of delivering chemotherapy selectively into the ophthalmic artery, thereby minimizing systemic absorption and drug-related toxicity such as neutropenia, infection, need for transfusion, and secondary neoplasms. The reduced systemic toxicity decreases the need for hospitalization and allows for the use of highly effective drugs against retinoblastoma, namely melphalan as discussed above. Furthermore, because this drug is not used in protocols of intravenous chemotherapy, the risk of resistance to intraarterial melphalan in recurrent retinoblastomas is thought to be minimal. Another important advantage of this approach over systemic chemoreduction is the ability to administer significantly higher doses (10-fold) of chemotherapy directly to the tumor bed and seeds, which may increase the biological effect, enhance tumor control, and reduce the rate of recurrence. This presumed combination of efficacy, safety, precision, and novelty makes IAC such an appealing approach for dealing with retinoblastomas.

**The Technique**

Intraarterial chemotherapy for retinoblastoma was first described in 1954 by Reese and colleagues, who performed direct instillation of chemotherapy into the internal carotid artery on the side of the involved eye. Later in the 1990s, a group of Japanese investigators led by Mohri modified the technique by catheterizing the internal carotid artery from a femoral access point, occluding distal flow with balloon inflation, and delivering chemotherapy at the branch point of the ophthalmic artery.

---

**TABLE 1: The ICRB**

<table>
<thead>
<tr>
<th>Group</th>
<th>Defining Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>tumor &lt;3 mm in size</td>
</tr>
<tr>
<td>B</td>
<td>tumor &gt;3 mm in size or macular Rb location; juxtapapillary Rb location; clear subretinal fluid ≤3 mm from margin</td>
</tr>
<tr>
<td>C</td>
<td>tumor w/ focal seeding: subretinal seeds ≤3 mm from Rb; vitreous seeds ≤3 mm from Rb; subretinal &amp; vitreous seeds ≤3 mm from Rb</td>
</tr>
<tr>
<td>D</td>
<td>tumor w/ diffuse seeding: subretinal seeds &gt;3 mm from Rb; vitreous seeds &gt;3 mm from Rb; subretinal &amp; vitreous seeds &gt;3 mm from Rb</td>
</tr>
<tr>
<td>E</td>
<td>extensive tumor occupying &gt;50% globe or neovascular glaucoma; invasion of postlaminar optic nerve, choroid, sclera, orbit, anterior chamber; massive intraocular hemorrhage</td>
</tr>
</tbody>
</table>

* Rb = retinoblastoma.
Intraarterial chemotherapy

Abramson et al.\textsuperscript{1,3} described the selective cannulation of the proximal portion of the ophthalmic artery under fluoroscopic guidance for focal delivery of chemotherapy. We have used the latter technique for 3 years to treat patients with retinoblastoma at Thomas Jefferson University Hospital for Neuroscience in collaboration with the ocular oncology department at the Wills Eye Institute. Since then, we have accumulated tremendous experience and refinements in our techniques and protocols to address evolving challenges.

The procedure is performed under general anesthesia and continuous electrophysiological monitoring. All surfaces in the operating room are covered with plastic wrap, avoiding the use of cotton fiber material, including linen towels and patient’s draping material. After careful preparation of the puncture site in the groin, a 4-Fr pediatric arterial sheath is inserted into the femoral artery, and heparin is administered with a target activated clotting time between 200 and 300 seconds. Under fluoroscopic guidance, the ipsilateral internal carotid artery is catheterized with a 4-Fr catheter (1.3 mm diameter). Serial angiograms are performed to visualize the angio-anatomy and determine the best working angle. With the aid of a Synchro-10 microguidewire (Stryker), the ostium of the ophthalmic artery is selectively catheterized with a Prowler-10 microcatheter (Cordis Neurovascular), and a superselective injection is subsequently performed to confirm the position of the microcatheter and ascertain the lack of reflux into the internal carotid artery (Fig. 1). If the latter approach is unsuccessful, catheterization of the ophthalmic artery can alternatively be performed through the middle meningeal artery when a communicating branch between the 2 systems is well developed. Chemotherapeutic agents, diluted in 30 ml of saline, are then delivered in a pulsatile fashion over 30 minutes to ensure homogeneous drug delivery. The microcatheter is subsequently flushed with saline to avoid crystallization of the agent in the ophthalmic artery, and angiograms are obtained to rule out thromboembolic and hemorrhagic complications. After catheter withdrawal, sheath removal, and manual hemostatic compression, the child is closely observed and discharged the same day in the absence of complications. Oral aspirin (40 mg) is given for 2 weeks.

When all attempts to catheterize the ophthalmic artery have failed, we use the “Japanese technique” that involves rapid chemotherapy delivery through a catheter placed in the internal carotid artery at the takeoff of the ophthalmic artery with balloon occlusion of distal flow.\textsuperscript{47} Melphalan is the primary chemotherapeutic agent used in IAC given its efficacy and its short half-life (1.5 hours), making it an ideal candidate for local injection.\textsuperscript{15,33} This drug is usually used as a sole therapy, but topotecan can be added for advanced retinoblastoma with extensive vitreous seeds.\textsuperscript{15,24} The efficacy of carboplatin against retinoblastoma has been documented in systemic chemotherapy.\textsuperscript{12} However, this agent is rather avoided in IAC due its sclerosing effects on the ophthalmic vasculature\textsuperscript{33} and is reserved for bilateral tumors to reduce the cumulative dose of melphalan, or for cases in which treatment with melphalan plus topotecan was unsuccessful.\textsuperscript{15}

The Success of IAC

Our center and others have reported dramatic regression of advanced tumors in which other treatment modalities failed, along with impressive declines in the rate of enucleations using IAC for retinoblastoma (Fig. 2).\textsuperscript{3,15,29,33,39} In a large study on IAC treatment that included 259 catheterizations, Gobin et al.\textsuperscript{15} treated 95 eyes and reported 2-year ocular event-free survival rates of 81.7% for primary retinoblastomas and 58.4% for those that were initially treated with systemic chemotherapy or external-beam radiotherapy. Melphalan was the only drug used for most patients in their series, and the average number of procedures was 3.1 per eye. Enucleation was required in 19 cases (20%), all of which were advanced and extensive retinoblastomas. Significant neutropenia occurred in 11.4% of cases, but no patient required transfusion of any blood products.\textsuperscript{15} We have recently reported our 2-year experience with IAC in 17 patients with retinoblastoma;
of these patients, 13 were treated with primary and 4 were treated with secondary IAC (after failure of other methods). Complete tumor regression was noted in 88% of patients, all of whom remained recurrence free at follow-up. Eyes with subretinal and vitreous seeds showed complete response in 82% and 67% of cases, respectively. Globe salvage was achieved in 67% of children treated with primary IAC and 50% of those treated with secondary IAC. Transient cytopenia, not requiring transfusion, was seen in 6 patients. Peterson et al. treated 17 eyes with intraarterial melphalan; of these eyes, other treatment modalities had failed in 16. Moreover, these authors were able to avoid enucleation in 76% of patients. Systemic complications were limited to 11.5% of cases in their series. Interestingly, the authors concluded that they were able to dramatically reduce the rate of enucleation from 100% to 23.5% in this group of advanced and treatment-resistant retinoblastomas. The unique ability of IAC to cure tumors resistant to other treatment modalities underlines the superiority of this technique (Table 2). The fact that tumor regression is achieved using only 1 chemotherapeutic agent is another argument in favor of the unparalleled efficacy of this approach.

In a more recent report, we have demonstrated that only 1 or 2 cycles of IAC can be sufficient for Group C or D eyes with 100% tumor control. We caution, however, against the use of this “minimal exposure” protocol for Group E eyes or tumors with extensive seeding because of the metastatic potential and the high-risk features of such lesions.

The Japanese collaborators have extensively studied the cannulation technique. In a large study of 1452 procedures on 408 eyes, Suzuki et al. reported their 19-year experience with IAC for retinoblastoma using the Japanese technique. This technique involves catheterization into the internal carotid artery with balloon occlusion of distal flow without catheterization into the ophthalmic artery. The authors reported a technical success rate of 98.8% and an eye preservation rate of 100% in Group A, 88% in Group B, 65% in Group C, 45% in Group D, and 30% in Group E. The authors were also able to preserve a visual acuity of greater than 0.5 in 51% of all cases. No patient experienced severe systemic or cerebrovascular adverse events in their series. In a finding that seemed disparately striking at first glance, the same authors reported 12 secondary neoplasms with a cumulative incidence of 1.3% at 5 years, 4.8% at 10 years, and 5.8% at 15 years. However, all of these patients had received external-beam radiotherapy, and some were additionally treated with systemic chemotherapy. As such, in the small group of patients solely treated with IAC, no secondary neoplasms were noted. Thus, the findings of this study are clouded by the frequent use of other treatment methods and seem to reflect the safety and efficacy of a multimodality treatment for retinoblastoma rather than IAC alone.

Whether selective catheterization of the ophthalmic artery for drug delivery is beneficial compared with the Japanese technique is uncertain. One could argue that selective catheterization of the ophthalmic artery is technically difficult, could alter blood flow through the vessel, or could cause endothelial injury to the thin-walled artery. However, the microcatheter technique allows direct delivery of chemotherapy into the ophthalmic artery, which maximizes drug availability in the eye while systemic absorption is minimized. The rate of technical success with the microcatheter technique is nearly 100% in our hands and has been reported to be as high as 98.5% from other centers, underlining the feasibility of the technique in expert hands. In addition, the Japanese technique requires balloon occlusion of the internal carotid artery, which adds a layer of technical complexity to the procedure and could theoretically predispose the patient to thromboembolic and ischemic events.

Fig. 2. Images obtained in 5 cases showing response of a solid retinoblastoma before (A, C, E, G, and I) and after (B, D, F, H, and J) treatment with IAC.
Intraarterial chemotherapy

TABLE 2: Treatment success rates with primary systemic chemotherapy versus IAC for retinoblastoma

<table>
<thead>
<tr>
<th>ICRB Group</th>
<th>Treatment Success Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systemic Chemotherapy</td>
</tr>
<tr>
<td>A</td>
<td>100%</td>
</tr>
<tr>
<td>B</td>
<td>93%</td>
</tr>
<tr>
<td>C</td>
<td>90%</td>
</tr>
<tr>
<td>D</td>
<td>48%</td>
</tr>
<tr>
<td>E</td>
<td>45%</td>
</tr>
</tbody>
</table>

Regardless of technical nuances, IAC seems to provide impressive control of retinoblastoma. The technique has an established role as a salvage therapy when all other options have been exhausted and has been gaining ground as a primary treatment for advanced retinoblastoma as well.15,32

Limitations

Despite its proven efficacy, IAC has some limitations. As with chemoreduction, the success rate with IAC is lower for advanced tumors, namely those in Group E. We previously reported that globe salvage can be achieved in 100% of Group C and D eyes versus only 33% in Group E eyes.33 Seed recurrence can also be a problem, occurring in 9% of tumors with subretinal seeding and 11% of those with vitreous seeding.33 In their recent report, Eagle et al.13 found viable vitreous seeds on histopathology of enucleated eyes despite complete regression of the primary tumor after IAC. Vitreous seeds were also the most common indication for enucleation in their series. Nevertheless, the authors showed that when a complete tumor response was clinically evident, no signs of viable tumor was seen on histopathology, which proves that IAC can reliably eradicate retinoblastoma.13

Another limitation of IAC is the lack of control of potential metastatic disease because the systemic dose may be inadequate to eliminate extraocular tumor cells.41 Classically, eyes with advanced retinoblastoma have been treated with enucleation, and when high-risk features are detected on histopathology, adjuvant chemotherapy is administered to reduce the risk of metastasis.3 The inability to detect such features after IAC could, therefore, increase the risk of metastatic disease. In the report mentioned above, Eagle et al.13 studied 8 enucleated eyes after IAC and found optic nerve invasion in 3 eyes, laminar invasion in 1 eye, and choroidal invasion in 1 eye. Along similar lines, Vajzovic et al.45 examined 3 enucleated eyes and found high-risk features requiring chemotherapy in 2 eyes. In their series of 78 patients, Gobin et al.15 noted that 2 children developed metastatic disease after IAC and were subsequently treated with aggressive chemotherapy and radiotherapy. The risk of metastatic disease is therefore one of the most concerning issues with IAC. Likewise, in patients with germine mutations, IAC might not provide adequate protection against pineoblastoma and secondary tumors due to the low systemic absorption of chemotherapeutic agents. Finally, IAC requires dedicated centers with specialized expertise and sophisticated instrumentation, which limits its availability in continents such as Asia and Africa, where efficient treatment for advanced retinoblastoma is most needed.

Common systemic complications with IAC include neutropenia, bronchospasm, and iodine allergy. Neutropenia is typically mild and rarely requires an intervention according to published series.15,29,32 Bronchospasm is a potentially serious complication that occurs in 8.3% of procedures35 and can be reversed by discontinuation of the procedure and the administration of epinephrine. Iodine allergy is reported in approximately 7% of children and requires antiallergic premedication.35 Local complications at the femoral puncture site (hematoma, thrombembolism, and limb ischemia) are possible, especially given the need for repeated intervention. Thus far in our experience with more than 100 cannulations and in the published literature, only 1 groin hematoma29 and 1 transient femoral artery occlusion15 have been reported. Ischemic and hemorrhagic strokes are theoretically possible with IAC but have not been reported. There is only 1 report of a vascular spasm that occurred during cannulation of an anomalous internal carotid artery uneventfully.32

Common minor ocular adverse effects include eyelid edema, forehead erythema, thinning or loss of eyelashes, blepharoptosis, and transient ocular dysmotility.15,32 These side effects that occur in many cases can resolve spontaneously within a few months. More concerning is the risk of vasculopathy in the ophthalmic, retinal, and choroidal vessels. It was initially thought that such complications were rare, as Gobin et al.15 had only reported 4 cases of avascular retinopathy in their series of 78 patients. The authors might have overlooked ophthalmic vascular complications because they relied solely on clinical features to detect these abnormalities. Shields et al.35 have meticulously analyzed toxic vascular effects of IAC using fluorescein angiography to detect subclinical occluded vessels. They were able to detect 3 cases of retinal artery occlusion, 4 cases of ophthalmic artery stenosis, and 5 cases of later-onset chorioretinal atrophy in their series, many of which were not clinically visible. Using high-resolution fluorescein angiography in another report, the same group found that 46% of eyes had some degree of intraocular vascular alteration that was subclinical in most cases.8 They recommended using fluorescein angiography in all cases to detect vascular flow alterations after IAC. These seemingly common vasculopathies could be due to chemotherapy toxic effects on the endothelium, catheter-related insult to the vessel, chemotherapy precipitation, or foreign body embolization. Eagle et al.13 found histopathological evidence of ischemic retinal and choroidal atrophy in 5 of 8 enucleated eyes after local chemotherapy. In addition, they were able to identify a birefringent foreign material, composed of cellulose or fabric fibers, obstructing the vessel lumen in several cases. This was believed to be attributed to possible catheter-derived material, particulates of dust or cotton fibers, or even preoperative of chemotherapy during delivery.33 Delayed vitreous hemorrhage has also been reported with intraarterial melphalan injection, but this complication is rare.29 Because of the potential for sight-threatening complications,
Munier et al. have cautioned against the use of IAC for bilateral tumors, reserving the technique for advanced unilateral retinoblastomas.

Another concern with IAC is the cumulative toxic effect from repeated exposure to ionizing radiation, especially in children with germline mutation. Vijayakrishnan et al. found that radiation doses remained far below toxic levels for gonads, thyroid, and bone marrow but were possibly cataractogenic or even carcinogenic. The need to minimize radiation exposure in these children cannot be overstressed.

Conclusions

A number of studies have shown that IAC is a highly efficient treatment for advanced and refractory retinoblastoma. However, the procedure carries a risk of ocular and systemic complications that should be taken into account when discussing treatment indications. At present, the quantity and quality of evidence are preliminary. Hopefully, with experience, more data will become available, and the role of IAC will be better defined. Meanwhile, IAC should be used cautiously in selected cases.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Jabbour, Chalouhi, Shields. Acquisition of data: Jabbour, Chalouhi, Tjoumakaris, Shields. Analysis and interpretation of data: Jabbour, Chalouhi, Tjoumakaris, Gonzalez, Dumont. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Jabbour. Administrative/technical/material support: Jabbour, Chalouhi. Study supervision: Jabbour.

References

27. Munier FL, Beck-Popovic M, Balmer A, Gaillard MC, Bovey E, Binaghi S: Occurrence of sectoral choroidal occlusive vasculopathy and retinal arteriolar embolization after superselective...
Intraarterial chemotherapy

28.
29.
30.
31.
32.
33.
34.
35.
36.
37.
38.


Please include this information when citing this paper: published online July 13, 2012; DOI: 10.3171/2012.5.PEDS1277.

Address correspondence to: Pascal M. Jabbour, M.D., Department of Neurological Surgery, Division of Neurovascular Surgery and Endovascular Neurosurgery, Thomas Jefferson University Hospital, 909 Walnut Street, 2nd Floor, Philadelphia, Pennsylvania 19107. email: pascal.jabbour@jefferson.edu.