Neuroimaging

Verification of supraselective drug delivery for retinoblastoma using intra-arterial gadolinium

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Summary

We present a description of retinoblastoma treated with supraselective intra-arterial chemotherapy, demonstrating selective delivery of the infused chemotherapeutic agent into the tumor bed by MRI. A 7-month-old presented with group E (international classification) unilateral retinoblastoma. We treated the patient with several rounds of intra-ophthalmic artery melphalan. Gadolinium was infused along with melphalan to visualize the distribution of this chemotherapeutic drug. Intraoperative MRI was obtained within 15 min after treatment and showed increased enhancement of the tumor and subretinal space. We demonstrate here that supraselective administration of chemotherapy into the ophthalmic artery appears to result in drug delivery to the tumor and subretinal space.

BACKGROUND

Selective intra-arterial chemotherapy is a new strategy for treating retinoblastoma. It is believed to result in an increased concentration of drug to the tumor, thus reducing systemic side effects. In 2004, Yamane *et al* reported the selective infusion of a chemotherapeutic agent into the ophthalmic artery by temporarily occluding the internal carotid artery with a balloon just distal to the ophthalmic artery origin.¹ There was a 98% technical success rate without any major complications. With improved endovascular techniques, catheterization of the ophthalmic artery itself, allowing direct drug infusion, has become possible in pediatric patients.² Gobin *et al* recently published a 4 year experience of intra-arterial chemotherapy via selective ophthalmic catheterisation.³ At the 2 year follow-up, 81.7% of 43 eyes treated primarily by intra-arterial chemotherapy did not require subsequent radiotherapy or enucleation. Neutropenia (absolute neutrophil count <1000/mm³) was observed following 29 (11.4%) of 255 treatment sessions; none required transfusion. No patients had permanent extraocular complications.

While selective infusion of chemotherapeutic agents into the ophthalmic artery likely results in a high local concentration of drug to the affected eye, confirmation of the distribution of the chemotherapy to the tumor with the supraselective ophthalmic artery approach has not been established. Here we show the localization of the infused chemotherapeutic agent utilizing a novel operating suite that has biplane angiography, 3 T intraoperative MRI, and microsurgical operating capabilities.

CASE PRESENTATION

A 7-month-old patient presented following a 2 month history of leukocoria in the right eye. The patient's

medical history was significant for being an identical twin, and there was no family history of eye diseases, including retinoblastoma.

INVESTIGATIONS

The ophthalmic evaluation showed that visual acuity was negative for fix and follow of the right eye. The left eye demonstrated central, steady, and maintained normal fixation. Intraocular pressures were 20 mm Hg in the right eye and 11 mm Hg in the left eye. Examination of the fundi demonstrated group E (international classification) advanced retinoblastoma of the right eye with total retinal detachment but no evidence of neovascularization of the iris (figure 1A, C). The left eye was normal. Following discussion of the therapeutic options, intra-arterial chemotherapy was chosen for the treatment plan with the patient's family's informed consent.

TREATMENT

The right femoral artery was accessed percutaneously, and a 4 French sheath was placed. A 4 French Berenstein catheter was utilized to select the right common carotid artery. The ophthalmic artery was selected with a 1.5 French Marathon microcatheter (EV3, Plymouth, Minnesota, USA). Melphalan (5 mg diluted in 30 ml of normal saline) was infused over 30 min. At the time of the second and third doses of intra-arterial chemotherapy (administered at 6 weeks and 12 weeks after the initial treatment, respectively), 0.2 ml of gadolinium was also mixed into the chemotherapy in order to visualize the localization of the infused agent. Institutional review board waiver was obtained for this off-label use of gadolinium.

Within 15 min following each treatment, an intraoperative MRI was obtained (figure 2). For the first treatment,

Figure 1 Retinal detachment improved with chemotherapy. (A) Retinal photograph of the right eye before intra-arterial chemotherapy, showing a large retinoblastoma and retinal detachment. (B) Retinal photograph of the right eye 3 weeks after the second treatment of intra-arterial melphalan, showing decreased size of the retinoblastoma and decreased retinal detachment. The optic disc is now visible. (C) Axial T2 weighted MRI taken at the onset of treatment showing retinal detachment with a large subretinal fluid collection (arrow indicates retina). (D) Axial T2 weighted MRI following the second treatment showing markedly decreased tumor size and retinal detachment.

no intra-arterial gadolinium was infused and the MRI with intravenous gadolinium demonstrated no enhancement of the subretinal fluid (figure 2A). MRI images obtained following the subsequent treatments in which gadolinium was mixed with the chemotherapy demonstrated enhancement (and therefore chemotherapeutic agent localization) within the tumor and subretinal fluid (figure 2B, C). Although gadolinium contrast remains predominantly extracellular, it provides a good indicator of the intracellular sites of action of the melphalan. Increasing enhancement of the tumor was observed with successive treatments, suggesting improved chemotherapeutic penetration as the tumor regressed. Notably, no enhancement was observed within the retro-orbital space,

vitreal humor, or surrounding structures supplied by adjacent branches of the internal carotid artery. This provided confirmation of selective catheterization and injection of the ophthalmic artery and, to our knowledge, provides the first imaging localization of the delivered chemotherapy.

OUTCOME AND FOLLOW-UP

By the time of the third treatment, the tumor had shrunk from 14.5×12 mm to 9×7 mm, with decreased retinal detachment (figure 1B, D). Additional treatments are planned using the same protocol to achieve complete tumor control. No major systemic side effects have been observed. Perioperative complications have been limited to

Figure 2 Intraoperative axial T1 weighted MRI images. (A) Immediately after the first treatment of intra-arterial chemotherapy with intravenous gadolinium. The mass measures 14.5×12 mm. Note there is no enhancement of the subretinal fluid in the absence of intra-arterial gadolinium. (B) Immediately after the second treatment using intra-arterial gadolinium. Note the enhancement of the subretinal space in the right eye due to the intra-arterial gadolinium, indicating the location of the infused chemotherapeutic agent. (C) Immediately after the third treatment using intra-arterial gadolinium showing maximal 9×7 mm dimensions of the residual tumor. Note the increased contrast enhancement of tumor, which suggests increased tumor penetration.

two instances of bronchospasm that resolved with intravenous epinephrine.

DISCUSSION

Supraselective intra-arterial delivery of chemotherapy for retinoblastoma is being increasingly utilised.^{3–5} In this report, we provide the first imaging evidence of chemotherapeutic agent localization into the subretinal space and the tumor using gadolinium as a marker. This finding provides strong evidence that chemotherapy administered in this way reaches the subretinal space and would therefore have a therapeutic effect on subretinal tumor seeds. In contrast, the chemotherapy showed no evidence of vitreous penetration as expected; therefore, vitreous tumor seeding would not be expected to respond to this technique. While it is difficult to conclusively prove the precise co-localization of gadolinium and melphalan *in vivo*, for practical reasons gadolinium might be the best surrogate marker for targeted chemotherapy delivery. These preliminary findings of this technique will nonetheless require confirmation with additional cases. Intra-arterial injection of gadolinium contrast remains an off-label use but it is thought to be an acceptable risk for this select patient population.⁶

Learning points

- ▶ Intra-arterial gadolinium acts as a surrogate marker for localization of intra-arterial chemotherapy delivery.
- ▶ Intra-arterial melphalan localizes into the subretinal space and the tumor but not into the vitreous space.
- ▶ Further investigation of this technique with additional cases will be required to confirm these preliminary findings.

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Competing interests None.

Patient consent Obtained.

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