Editorial

Updates in the Management of Retinoblastoma

Retinoblastoma is the commonest childhood intra-ocular malignant tumour, with an approximate incidence of 1 in 15,000–20,000 live births worldwide. Advances in treatment over the last quarter century have led to a survival rate that is over 90% in developed countries[1]. While paradigm shifts have occurred in conservative treatment, enucleation (removal of the eye) remains the mainstay for treatment for advanced disease. With improved survival rates, there has been an impetus to treat retinoblastoma without removal of the eye and to preserve vision.

Previously external beam radiotherapy (EBR) was extensively used to avoid enucleation. However well recognised side effects such as second cancers in the field of radiation, particularly if given in the first year of life, have limited its use to salvage treatment in order to avoid enucleation.[2]

Recently there is a trend away from enucleation and external beam radiotherapy towards focal conservative treatments. This is reflected in the Reese-Ellsworth classification, which predicted chance of eye salvage by EBR, being replaced by the International Intraocular Retinoblastoma classification (IIRC).[3]

Such conservative treatments include primary intravenous chemotherapy followed by tumour consolidation with focal measures such as thermotherapy, cryotherapy, and plaque radiotherapy.[4] The most commonly used chemotherapy drugs include carboplatin, etoposide, and vincristine (CEV) given every 3 weeks through central venous access line. This regimen has become the standard primary treatment for IIRC Groups B, C, and D, though variations in protocols exist amongst specialist centres.[3,5]

Concerns about the side-effects of multidrug systemic chemotherapeutic agents including bone marrow suppression, hearing loss and acute myeloid leukaemia stimulated the development of novel approaches for selectively delivering chemotherapy to the globe to avoid the potential complications of systemic drugs. Intra-ophthalmic artery chemotherapy (intra-arterial chemotherapy/ ophthalmic artery chemosurgery; OAC) has received much recent attention. It was first performed in 1954 by Reese in New York, USA followed by the Japanese group led by Kaneko in 1993, who delivered the chemotherapy drug, melphalan, into the internal carotid artery using a balloon to prevent spread into the brain.

In 2006, Abramson and colleagues modified the technique and introduced direct intra-ophthalmic artery catheterisation to treat patients with retinoblastoma, using a microcatheter placed at the ostium of the ophthalmic artery rather than directly into the ophthalmic artery to get a higher concentration of the chemotherapeutic agent into the ophthalmic artery.[6] This technique showed promise in curing eyes with large retinal tumours. The treatment can be given as a primary treatment or as salvage treatment to prevent enucleation or external beam therapy. The IIRC group E (most advanced) eyes are a clinical spectrum, and although group E eyes have been treated with this modality as a primary treatment, these were not buphthalmic nor did they have high intraocular pressures. Eyes with such advanced features should still be treated by enucleation. Tumours that seed into the vitreous cavity or subretinal space are still difficult to control. Ocular salvage at four years follow-up was achieved in 58% of eyes that had previous treatment failure with intravenous chemotherapy and/or EBR.[6]

The greatest concern about using this method for advanced retinoblastoma (Group D or E eyes) is that it does not prevent potential metastatic disease and it has its own complications. In a report of 78 patients undergoing OAC, there were 2 that developed metastases requiring aggressive systemic chemotherapy.[6] In addition, radiation is used to visualise the position of the catheter and provide an angiogram of the ophthalmic artery in this technique. Although this is a low dose, it is essential to minimise radiation for patients with genetic retinoblastoma. Systemic complications e.g. severe vasovagal response from catheterisation and local effects such as choroidal ischaemia have been reported.[7]

The position of the catheter, the dose of melphalan and previous radiation (either brachytherapy or EBR)

can limit vision in patients with previously healthy foveolas.[8] Most reports have used melphalan as a chemotherapeutic agent but topotecan has also been recently used as an adjunct drug.[6]

Vitreous seeds are the most difficult tumour feature to control and various strategies have been employed from radiotherapy, second line chemo-therapy to enucleation. Intravitreal chemotherapy melphalan via specific safety-enhancing injection techniques (intravitreal melphalan injection, 20-30 µg, by transconjunctival pars plana route with concomitant triple-freeze cryotherapy at the injection site during needle withdrawal for prevention of extraocular seeding in a hypotensive eye) has also been tried with good outcomes for persistent vitreous seeds.[9]

Intra-ophthalmic artery chemotherapy and intravitreal chemotherapy offer weapons in the arsenal of therapies that might save the eye in patients with retinoblastoma. However, there are still potential complications to consider, and, consequently, these procedures should be performed at institutions with expertise in the care of patients with retinoblastoma. Multicentre prospective studies with large numbers are essential in order to predict which patients will benefit long term from attempts at eye salvage.

REFERENCES

1. **MacCarthy A, Birch JM, Draper GJ, Hungerford JL, Kingston JE, Kroll ME, Stiller CA, Vincent TJ, Murphy MF.** Retinoblastoma: treatment and survival in Great Britain 1963 to 2002. Br J Ophthalmol. 2009; 93: 38–9.
2. **Chan MP, Hungerford JL, Kingston JE, Plowman PN.** Salvage external beam radiotherapy after failed primary chemotherapy for bilateral retinoblastoma: rate of eye and vision preservation. Br J Ophthalmol. 2009;93: 891-4.
3. **Linn Murphree.** A Intraocular retinoblastoma: the case for a new group classification. Ophthalmol Clin North Am, 2005; 18: 41-53.
4. **Shields CL, De Potter P, Shields JA.** Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthalmol. 1996; 114: 1330–8.
5. **Chan HS, DeBoer G, Thiessen JJ, Budning A, Kingston JE, O'Brien JM, et al.** Combining cyclosporin with chemotherapy controls intraocular retinoblastoma without requiring radiation. Clin Cancer Res. 1996; 2: 1499-508.
6. **Gobin YP, Dunkel IJ, Marr BP, Brodie SE, Abramson DH.** Intra-arterial chemotherapy for the management of retinoblastoma: four-year experience. Arch Ophthalmol. 2011; 129: 732-7.
7. **Muen WJ, Kingston JE, Robertson F, Brew S, Sagoo MS, Reddy MA.** Efficacy and complications of super-selective intra-ophthalmic artery melphalan for the treatment of refractory retinoblastoma. Ophthalmology. 2012:119: 611-6.
8. **Tsimpida M, Thompson DA, Liasis A, Smith V, Kingston JE, Sagoo MS, Reddy MA.** Visual outcomes following intraophthalmic artery melphalan for patients with refractory retinoblastoma and age appropriate vision. Br J Ophthalmol. 2013; 97: 1464-70.
9. **Munier FL, Gaillard MC, Balmer A, Soliman S, Podilsky G, Moulin AP, Beck-Popovic M.** Intravitreal chemotherapy for vitreous disease in retinoblastoma revisited: from prohibition to conditional indications. Br J Ophthalmol. 2012; 96: 1078-83.

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