Update on Intraocular Oncology

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Introduction
Ocular oncology has been evolving with new imaging techniques and treatment modalities. Imaging techniques have revolutionized the understanding of the basic concepts of the tumor pathology and have provided insights into the development of newer modalities of treatment. In the practice of Oncology, the primary focus has always been to save the life of the individual suffering from any carcinoma and this was also true for intraocular tumors with practicing ophthalmologist needing to perform enucleation for most of the intraocular tumors like the retinoblastoma in the children and choroidal melanoma in adults. With developments in ophthalmology and with changing trends in diagnostic and management modalities, the attention has shifted from purely saving the lives to improving the quality of life. The quest to improve the quality of life in cancer survivors has led to the discovery of new techniques that can salvage the eye and the vision while simultaneously destroying the cancer tissue. In the most common pediatric cancer, the retinoblastoma, the survival rates are nearly 100%. The success rates as per the International Classification of Retinoblastoma with standard intravenous chemotherapy and radiation therapy are: group A (100%), B (93%), C (90%), D (48%), and E (25%).

Intraocular tumors treated by brachytherapy with recommended doses
- Choroidal melanoma: 85 Gy
- Retinoblastoma: 40 Gy
- Vasoproliferative tumors: 40 Gy
- Choroidal hemangioma: 40 Gy

Brachytherapy team
- Plaque surgeon
- Radiation oncologist
- Medical physicist

Commonly used isotopes in brachytherapy
- Ruthenium (Ru)-106
- Palladium (Pd)-103
- Iodine (I)-125
- Strontium-90 (90Sr)

Dose calculation is done using the plaque simulator software version (Bebig GmbH, Berlin, Germany). The longitudinal, circumferential and apical diameters of the tumor are important parameters to be measured using ultrasonography.

Structure of Indian plaque
Indian plaque is manufactured by Bhabha Atomic Research Center called ‘BARC I-125 Ocu-Prosta seeds’. Radioiodine (125I) adsorbed on palladium-coated silver rod encapsulated by titanium capsule. Slotted, unslotted, rimmed, unrimmed gold plaques are available. COMS plaques are circular rimmed plaques.
Technique
Placement of plaque
It is performed under peribulbar or retrobulbar anesthesia for adult patients and under general anesthesia for children. After cleaning, prepping and draping of the involved eye, localized peritomy is made in the involved quadrant. Tagging of the rectus muscle is done. Localization of the tumor is done with transillumination or scleral depression. Plaque containing the seeds is anchored to sclera. Conjunctiva is closed with sutures. Eye should be covered with lead shield and patient to be kept in isolation for a period of 4–5 days depending on the dosimetry.

Removal of plaque
It is also performed under aseptic precautions as described above. Localized peritomy is made in the involved quadrant. Anchoring sutures are cut. Plaque is removed with seeds in to. Seeds have to be counted and checked. Conjunctiva is closed with sutures. The radioactive seeds are returned back to Bhabha Atomic Research Center.

Limitations in choroidal melanoma
- Tumor more than 12 mm in apical height or 20 mm in basal diameter.
- Gross extraocular extension.
- Painful blind eyes.
- Eyes with no perception of light.

Complications of brachytherapy
- Radiation cataract.
- Radiation retinopathy.
- Radiation optic neuropathy.

Intra-arterial chemotherapy (IAC)

Definition
Intra-arterial chemotherapy is a targeted therapy against retinoblastoma that involves the delivery of potent chemotherapy directly into the ophthalmic artery.

Evolution
The first initiative was made in 1954 by Reese et al.6 In 1966, Kiribuchi shared his success story with injection of 5-fluorouracil into the frontal or supraorbital artery of children with retinoblastoma.7 The technique of IAC has evolved over the past 15 years with Japanese investigators showing success with delivery of melphalan into the ophthalmic artery by occluding distal flow in the internal carotid artery using catheterization and...
balloon occlusion.\textsuperscript{8,9} Gobin and Abramson of the USA refined further by cannulating the proximal ophthalmic artery precisely under fluoroscopic guidance for chemotherapy to perfuse the eye selectively without perfusing the brain.\textsuperscript{10}

**Team**

Ocular oncologist, endovascular neurosurgeon, pediatric oncologist

**Japanese technique**

The Japanese technique was called selective ophthalmic arterial infusion (SOAI) therapy. The SOAI system consists of a micro-balloon, guiding catheter and a flushing hub. After selective catheterization to the cervical segment of the internal carotid artery by the guiding catheter, the micro-balloon was propelled to the portion just distal to the orifice of the ophthalmic artery. During temporary occlusion of the internal carotid artery, melphalan was infused from the introduced catheter tip.\textsuperscript{11}

**American technique**

Performed under general anesthesia with anticoagulation [intravenous heparin (75 IU/kg)] in the operation theatre. Femoral region is cleaned, draped and 4-French arterial sheath is placed. The catheter is guided into the ipsilateral internal carotid artery using fluoroscopic guidance. Serial arteriogram is done for deciding the best approach. Ipsilateral proximal portion of the ophthalmic artery is catheterized with a microcatheter and a confirmatory angiogram is then performed. Chemotherapy is diluted in 30 ml of saline is delivered using a pulsatile, non-laminated technique manually over 30 min. Once the infusion is completed, a post-infusion arteriogram is done. The catheters are withdrawn and the femoral sheath is removed. By manual compression the hemostasis of the femoral artery is achieved. Child is kept on oral aspirin (40 mg) for 2 weeks.\textsuperscript{12}

**Dosage**

- Melphalan: starting at 2.5 mg for 3 months to 5.0 mg for a 3 years
- Topotecan: starting at 0.3 mg for 3 months to 0.4 mg for a 3 years
- Carboplatin: 30 mg for 6 months to 3 years

**Eyes that would benefit from IAC**

- Primary IAC: International Classification of Retinoblastoma (group C, group D and group E)
- Secondary IAC: other modalities have failed

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**Fig. 4.** The pre- and post-brachytherapy of a medium sized choroidal melanoma with features of radiation retinopathy at 2 years.
Eyes that should not be considered for IAC

- Possibility of tumor regression with focal therapy (laser/trans pupillary thermotherapy/cryotherapy)
- Possibility of tumor regression with brachytherapy
- Possibility of tumor regression with intravenous chemotherapy
- Neovascular glaucoma
- Presence of invasion into the optic nerve
- Presence of invasion into the choroid
- Presence of extrascleral extension
- Anaphylactic reaction with previous IAC
- Poor visualization of the tumor
- Persistent retinal detachment

Complications from IAC

- Ophthalmic artery stenosis
- Occlusion of central retinal artery/branch retinal artery occlusion/ciliary arteries
- Orbital vascular occlusion
- Eyelid edema
- Blepharoptosis
- Cilia loss
- Orbital congestion
- Temporary extraocular dysmotility
- Retinal pigment epithelial mottling
- Radiation-related toxic effects

Concern

- Anomalous origin of the ophthalmic artery
- Blood dyscrasia

Intravitreal injections in intraocular oncology

Definition

Intravitreal chemotherapy is a targeted therapy against retinoblastoma seeds in the vitreous that involves the delivery of potent chemotherapy directly into the vitreous.

Evolution

Ericson et al. were the first to initiate the intravitreal chemotherapy for retinoblastoma in the year 1960. The superior efficacy of melphalan was established by Inomata and Kaneko. Later, Kaneko presented his unpublished data on achieving eye salvage rate of 51% by treating 41 eyes with intravitreal injection of 8–30 μg melphalan and ocular hyperthermia for vitreous seeds. Since then melphalan hydrochloride, topotecan hydrochloride and methotrexate have been in use.

Team

Ocular oncologist, anesthetist and pediatric oncologist.

Dosage

- 20–40 μg of melphalan hydrochloride
- 8–20 μg of topotecan hydrochloride

Technique

It is performed under general anesthesia after cleaning and draping of the involved eye using a sterile technique. Melphalan is available as a freeze-dried powder is prepared using the provided sterile diluent with concentration of 20 μg/0.1 ml. The half-life is ~90 min. Injected through the pars plana (3 mm from limbus, beveled approach) with a 30 G needle 1–2 clock hours away from the vitreous seed cryotherapy is applied to the injection site to include the needle in the ice ball withdrawing the needle through the ice ball during the first freeze. Triple freeze thaw cryotherapy is then completed. The eyeball should be moved with forceps vigorously to cause drug dispersion throughout the vitreous cavity and preferably to the site of vitreous seeds.

Eyes that would benefit

Persistent/recurrent/viable vitreous retinoblastoma seeds with good regression of the solid tumor.

Eyes that should not be considered for intravitreal chemotherapy

- Presence of viable solid intraretinal retinoblastoma
- Presence of viable subretinal seeds
- Presence of uveal or optic nerve invasion
- Risk for metastatic disease

Complications

- Focal retinal pigment epithelial mottling
- Risk for extraocular subconjunctival extension
- Vitreous hemorrhage
- Retinal detachment
- Intraocular infection

Conclusion

Developments in intraocular oncology have been overwhelming in the past three decades with excellent responses to conservative treatment in both retinoblastoma and choroidal melanoma.
Solid tumors in retinoblastoma have shown good regression patterns with chemotherapy/focal thermal laser/localized brachytherapy. Subretinal tumor seeds show partial or complete response to therapy. Vitreous seeds are the least responsive and remain a major challenge. Management of small choroidal melanoma by observation or plaque radiotherapy remains controversial. Medium choroidal melanoma is better managed by brachytherapy as brachytherapy yields equivalent overall and melanoma metastasis-specific survival rates to enucleation for medium-sized melanomas. Large choroidal melanoma management still remains a challenge in terms of eye sparing techniques.

References

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