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Current Management of Uveal Melanoma

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Introduction

Ocular melanoma originates from the pigment-producing melanocytes within the eye. The word uvea means grape-like in Greek, and so this descriptive word has been assigned to the pigmented tract within the eye which includes the choroid, ciliary body, and iris (uveal tract). Uveal tumours are located either in the iris (4%), ciliary body (6%), or choroid (90%) [1]. Conjunctival melanomas are rare and can arise in any part of the conjunctiva [1]. Until more recently, the rarity of conjunctival melanoma has impeded progress in the management of these patients.

Uveal melanoma is not the same as cutaneous melanoma, it has distinct characteristics and requires a specialised approach. On the other hand, conjunctival melanomas share common genetic mutations with cutaneous melanoma (BRAF), and the mechanism of metastasis is also via the lymphatics, making the monitoring and treatment of this disease similar to cutaneous melanoma but very different to uveal melanoma.

In this article, I will be focusing the discussion on uveal tract melanomas and how best we can approach these lesions when encountering them in our clinics.

Although uveal melanoma is relatively rare, it is the most common primary intra-ocular malignant tumour in adults [2]. The incidence of uveal melanoma is 5 to 7 new cases per million people per year in Western countries [1,2]. The incidence of this disease can vary by geographical location, but in general, uveal melanoma is more commonly diagnosed in Caucasian populations and less frequent in those of African or Asian descent [2]. The fair skin individual with lightly coloured eyes and frequent sun exposure have a higher prevalence of uveal melanoma [3]. Other host susceptibility factors for uveal melanoma include inability to tan, ocular or oculodermal melanocytosis, cutaneous or iris or choroidal naevus, and germline BRCA1- associated protein 1 mutation [3].

Role of Biopsy

Diagnosis of uveal melanoma relies on a comprehensive ophthalmic examination, including a dilated fundus examination, optical coherence tomography (OCT), ultrasound imaging and infrequently fluorescein angiography. 25G/27G transretinal choroidal biopsy has become an integral part of the management of these patients. A tumour biopsy may fall into the category of a diagnostic biopsy or prognostic biopsy but is invasive and requires a dedicated team, from the surgeon to the histopathologist, in order to yield positive cytogenetic results. Cytogenetic studies have highlighted the importance of identifying chromosomal aberrations and genetic mutations to assist in predicting patient survival. Monosomy 3 is an independent risk factor for metastasis and has been widely reported on for more than two decades [4]. Monosomy 3 is associated with higher incidence of clinical and histopathologic risk factors including larger tumour diameter, ciliary body tumour location, extraocular extension, epithelioid cell type, high mitotic rate, and increased vascular loops [5]. The 3-year mortality rate in patients with tumours with monosomy 3 is 50%, and for those with no monosomy 3 is 0% [4]. Recently the advancements in molecular genetic testing have highlighted BAP1 loss (BRCA1 associated protein, located on chromosome 3) which strictly correlates with metastasis development and poor prognosis [5,6]. BAP1 loss is associated with monosomy 3.

Genetic analysis is strongly encouraged to assist with survival modelling. The graphical abstract below is a good summary highlighting cytogenetic prognostic markers and biochemical pathways correlated to uveal melanoma metastases [7].

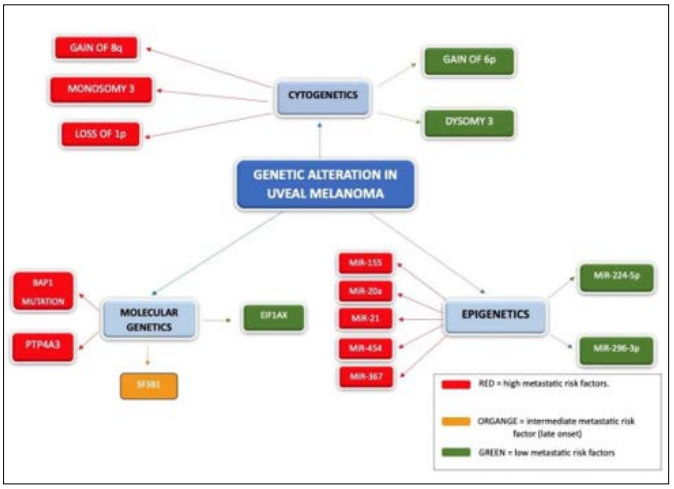

Figure 1: Graphical Abstract of Genetic Alterations in Uveal Melanom

Recently the term liquid biopsy has been discussed in academic papers. This refers to a minimally invasive technique that involves the analysis of Circulating Melanoma Cells (CMC), cell-free DNA (cfDNA) or exosomes in the blood stream or other bodily fluids. Liquid biopsy holds promise as a less invasive method to detect

and analyse genetic mutations or chromosomal abnormalities associated with the disease, but while liquid biopsy shows potential, it is not yet widely used in routine clinical practice for uveal melanoma.

Management

While local tumour control is outstanding, almost 50% of patients develop metastases within 10 years of diagnosis [2,8]. Uveal melanoma has the potential to spread to other parts of the body, particularly the liver (89%), lung (29%) and in a small percentage of patients, bone (17%) [2]. Diligent surveillance and monitoring of patients at baseline and after treatment for the rest of the patient's life are crucial to detect any potential metastases early on and to initiate appropriate interventions. Unless the melanoma involves the optic nerve and is spreading in a retrograde manner, MRI brain is not indicated. Baseline blood tests including LFT combined with liver ultrasound and CXR are more than adequate. Serum biomarkers used in cutaneous melanoma (S-100) may play a small role in uveal melanoma when monitoring for recurrence of treated metastatic liver disease. Try exercise caution and avoid ordering unnecessary expensive investigations.

Ocular treatment options for uveal melanoma depend on various factors, including the tumour thickness, location and the patient's overall health. Iris melanomas are low risk tumours with only a small percentage metastasizing to the liver (4%) [9]. Small iris melanomas (<3 mm basal diameter) in an asymptomatic patient can be monitored for growth and if there is change, treatment includes partial iridectomy, iridotrabeculectomy or iridocyclectomy (removal of a portion of the iris and ciliary body indicated in tumours with ciliary body extension) [10,11]. Plaque radiotherapy is beneficial for tumours with extensive tumour seeding and large tumours, while enucleation is indicated for eyes with diffuse iris melanomas, and those with recurrent tumours [2].

Currently, the most widely used first-line treatment options for choroidal and ciliary body melanomas are radiation therapy, resection (endorescetion or local resection) and enucleation.

Lasers

Transpupillary Thermal Therapy (TTT) has traditionally been used in treating small melanomas less than 4mm. A large study showed a direct correlation between higher rates of local tumour recurrence and high-risk tumour features (at diagnosis) when treating primary small choroidal melanomas [12]. I prefer using TTT as an adjunctive treatment for large tumours following radiation therapy.

Photodynamic Therapy (PDT) has been used in the treatment of small choroidal melanomas, however local control is not comparable to other modalities. In a study carried out by Moorfields Eye Hospital, small melanomas treated with PDT were followed up for 5 years showing only a 38.4% success rate in local tumour control [13]. PDT is not a feasible option.

Radiotherapy

There are two main types of radiation therapy when addressing ciliary body and choroidal melanoma: plaque brachytherapy (Iodine-125, Ruthenium-106, Palladium-103, or Cobalt-60) and teletherapy (proton beam, or stereotactic radiosurgery using gamma knife / cyber knife).

In South Africa, Ruthenium-106 and Iodine-125 plaques are available. Tumours up to 16mm in basal diameter and 12mm in thickness can be treated by this modality [2]. Larger than that or juxtapapillary tumours and tumours located in the posterior pole are better treated with teletherapy (gamma knife is extensively used in Johannesburg) [14-17].

Endoresection and Local Resection

Peripheral large choroidal melanomas with a narrow base that may be ineffectively treated with brachytherapy alone due to their thickness, are good candidates for a surgical endoresection and consolidative brachytherapy to the base of the tumour. Previously it was thought that this may increase the risk of metastases to the liver as choroidal blood is contaminated with tumour cells during the surgery. This has been disproved by Damato et al 18. Local resection (exoresection) is reserved for small ciliary body tumours that extend less than 3 clock hours of the ciliary body and have no extrascleral extension.

Hypotensive general anaesthesia is required in these cases due to the high risk of intraoperative subretinal haemorrhage and major intraoperative bleeding. This type of anaesthesia is risky in patients with comorbidities.

The alternative to radiation or combined endoresection and radiation is enucleation, which is reserved for large tumours with a poor visual prognosis.

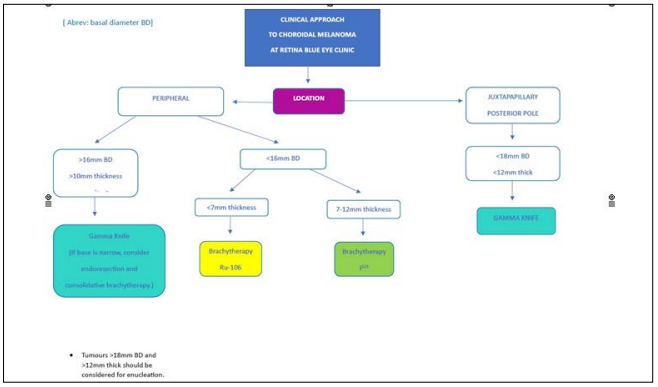

Figure 2: A Basic Approach to Managing Choroidal Melanomas in Clinical Practice

Newer Methods on the Horizon

There are currently no approved targeted therapies for the treatment of early-stage ocular melanoma. One treatment currently in preclinical development is light-activated AU-011, a novel virus-like particle targeted therapy for the treatment of primary uveal melanoma. The drug is administered through intravitreal injections and activated by laser to produce targeted, rapid, tumour necrosis while sparing healthy ocular tissue [19].

Side Effects of Radiotherapy

Both Brachytherapy and Gamma Knife Radiotherapy will result in some shape or form of radiation retinopathy, optic neuropathy or maculopathy. The average time to onset is six months to three years [20]. The risk is higher when treating younger patients, diabetics, patients with large tumours and tumours close to the nerve or posterior pole [20,21]. Treatment of this condition includes intravitreal injections with Anti-VEGF agents, triamcinolone, dexamethasone implant and periocular steroid preparations [22]. More recently, the use of prophylactic intravitreal anti-VEGF agents injected four monthly seems to delay the onset of this disease [21].

Surveillance and Treating Metastatic Disease

After treatment, regular follow-up visits are crucial to monitor

the patient's ocular health and detect any potential recurrence or metastatic spread of the tumour. Current treatment options for metastatic disease which are available here in South Africa include systemic immunotherapy (Tebentafusp, a molecular targeted therapy which recently has shown much promise when compared to chemotherapy) and liver-directed therapies, such as resection, radioembolization, chemoembolization, immunoembolization, isolated and percutaneous liver perfusion (DELCATH) and thermal ablation [20-22].

Supportive Care

Managing uveal melanoma also involves providing supportive care to address the physical, emotional, and psychological needs of patients. Support groups, counselling services, caring practitioners and their support staff can help patients cope with the challenges associated with the diagnosis, prognosis and treatment of uveal melanoma.

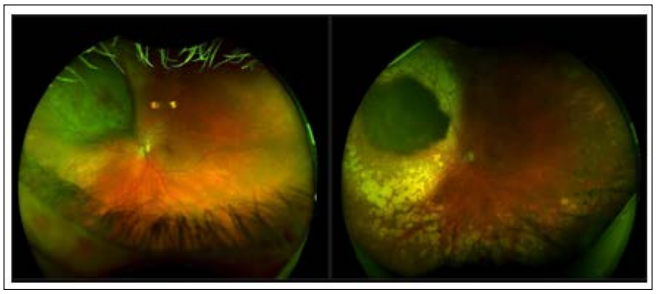

Figure 3: STAGE 4 (T2a; N0, M1) Tumour Treated with a Ruthenium-106 Plaque. Developed Metastases Three Years Following Treatment

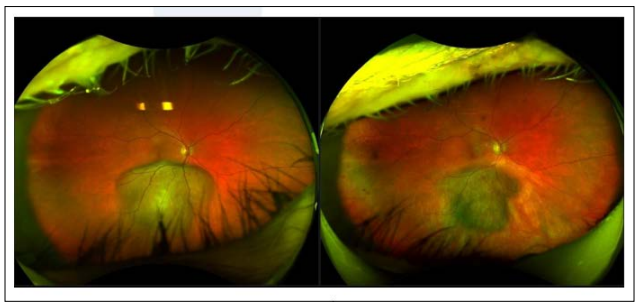

Figure 4: STAGE 2A (T2a; N0, M0) Tumour Extending into the Macula Treated with Gamma Knife Radiotherapy. Vision Improved from 0.6 to 1.0 following Treatment

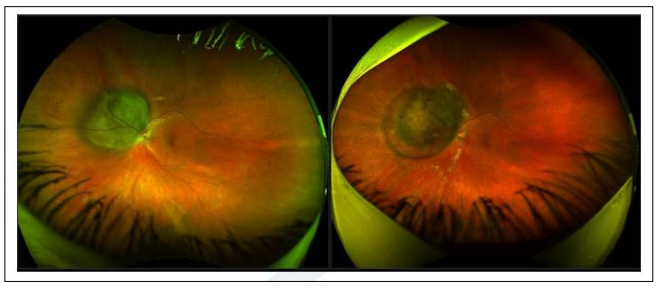

Figure 5: STAGE 2A (T2a; N0, M0) Juxtapapillary Tumour Treated with Gamma Knife Radiotherapy. Developed Radiation Retinopathy at Nine Months following Treatment but Vision Remains 1.0

Conclusion

Ocular melanoma is a complex condition that requires a comprehensive and individualised management approach. Advances in diagnostic techniques, treatment modalities, and supportive care have improved the prognosis for patients with ocular melanoma.

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