Current management of uveal melanoma

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Epidemiology

Uveal melanoma has an incidence of 6 per million per year in Caucasians, presenting in adulthood at a mean age of 60 years [1]. About 90% of uveal melanomas involve the choroid, the remainder arising in ciliary body and iris. The main predisposing factors, apart from fair skin and number of cutanous naevi, are intraocular melanocytoma and ocular melanocytosis [2].

Presentation

Choroidal melanomas present with blurred vision, visual field loss and flashing lights, usually as a result of macular involvement by the tumour or exudative retinal detachment. Ciliary body melanomas tend to cause cataract and other lens abnormalities. Iris melanomas are noticed either because of ocular hypertension or a cosmetic defect. Untreated, uveal melanomas cause secondary glaucoma, uveitis, and phthisis, also growing extraocularly into the orbit.

In the UK, about 40% of patients are asymptomatic, their tumour being detected on routine examination by an optometrist or ophthalmologist, either as part of a bi-annual check or as a result of screening for diabetic retinopathy [3]. Conversely, about 20% of patients with ocular symptoms report that their tumour was not detected when they first presented [3]. Experience in other countries is similar [4,5].

Diagnosis

Uveal melanomas can usually be diagnosed by slit-lamp examination or ophthalmoscopy on the basis of size, colour and secondary effects on adjacent tissues. Ultrasonography is useful for measuring tumour dimensions and assessing areas not visible on clinical examination, for example, in the presence of cataract. Angiography, CT and MRI are rarely helpful, so if the diagnosis is uncertain after clinical examination then biopsy is performed, using either a 25G needle or vitrector. Sequential examination has long been considered acceptable as a means of distinguishing large naevi from small melanomas; however, with mounting evidence that uveal melanomas metastasise early there is growing controversy about delaying treatment in patients whose tumour may be life-threatening.

Ocular treatment

The main objective of treatment is generally considered to be the prevention of metastatic spread, but it is increasingly apparent that systemic micrometastases are already present by the time the patient first becomes aware of the primary ocular tumour [6].

For many years, the standard form of treatment was removal of the eye (i.e. enucleation). This mutilating treatment has been superseded by methods aimed at conserving the eye when ever possible, preferably preserving useful vision. So-called ' conservative' therapies include: (a) ruthenium or iodine brachytherapy, proton beam radiotherapy or stereotactic radiotherapy; (b) transpupillary thermotherapy delivered with a diode laser; and (c) local resection, with the tumour removed either intact, through the sclera, or after fragmentation with a vitrector, through a hole in the retina. In most patients, it is possible to conserve the eye with useful vision, usually using a multimodality form of treatment, for example, combining local resection or laser treatment with adjunctive brachytherapy [7].

In the US, the Collaborative Ocular Melanoma Study (COMS) has shown that the chances of survival after conservative treatment are not statistically different from ocular removal [8].

Metastatic disease

Metastatic spread develops haematogenously and usually involves the liver. Various prognostic classifications have been proposed [9]. Factors associated with an increased mortality include: (a) large tumour

diameter; (b) ciliary body involvement; (c) extraocular spread; (d) epithelioid cell type; (e) closed laminin loops; and (f) cytogenetic abnormalities such as loss of chromosome 3 and gains in chromosome 8. The presence of abnormalities in both chromosome 3 and 8 reduces the five-year survival probability from 90% to only 40% [10, 11]. This finding makes it possible to target screening and any adjuvant therapy at high-risk patients.

There is no consensus about the ideal protocol for screening for metastatic disease. Some rely on biochemical liver function tests, others prefer liver imaging, and many do not screen at all [12, 13]. The median survival after detection of metastatic disease is about eight months [14]. Treatment is generally disappointing, although some long-term survivals occur [15].

It is generally agreed that there is an urgent need for some form of systemic treatment for sub-clinical micrometastases, but randomised, prospective studies have been hampered by the rarity of uveal melanomas and the lack of effective therapy. The improved prognostication provided by cytogenetic studies should facilitate the evaluation of any promising therapeutic agents that become available, because fewer patients would be required for the study to have sufficient statistical power.

Psychological care

Many patients with uveal melanoma suffer psychological morbidity because they are threatened with early death, visual handicap and facial mutilation. More ocular oncology centres are therefore involving psychologists in the multidisciplinary team, so that the patients' well being can be restored. Various disease-specific questionnaires have been developed to measure patient-centred outcomes [16,17].

Collaborative research

Various organisations have been established to develop mulitcentre collaboration and these include the European Ophthalmic Oncology Research Group, the Ocular Oncology Research Society, and the International Society of Ocular Oncology. An internet environment called geoconda.com has also been developed to facilitate multicentre collaboration.

Conclusions

Advances in the treatment of uveal melanomas have improved conservation of the eye and vision but have had no apparent impact on survival. Recent cytogenetic studies indicate that there are two different types of uveal melanoma: (a) low-grade, ' good' , melanomas, which even without treatment are entirely non-lethal, causing only ocular disease; and (b) high-grade, ' bad' tumours, which almost always metastasise and which do so at an early stage, before diagnosis and treatment.

It is quite possible that treatment will soon be based on molecular cytogenetic studies: patients with a good melanoma will be treated only to preserve vision whereas those with a bad melanoma will also receive systemic adjuvant therapy, the ocular treatment being regarded only as palliative, except in patients with a very small tumour in whom there might be some hope of preventing metastasis.

It is anticipated that the management of patients with uveal melanoma will change profoundly in the next few years, relying more on systemic adjuvant therapy based on molecular tumour classification.

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