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Verteporfin and other cytotoxics for the eye

What are cytotoxics? (Background)

Cytotoxic drugs have a role in ophthalmology units in the treatment of a few conditions, examples of which are outlined below. As with other conditions requiring these drugs, therapy is initiated and monitored by specialists.

Ocular disease (non-oncological)

Age-related macular degeneration: verteporfin (Visudyne®)

- **Action** - this is a light-activated compound which selectively exerts its cytotoxic effects on the subretinal neovascular membrane found in wet age-related macular degeneration. It is preferentially taken up by rapidly dividing endothelial cells of the developing vessels; laser light is then applied. Its energy is taken up by the photosensitive verteporfin causing damage to the vascular endothelial cells and thrombotic occlusion of the blood vessels with the neovascular membrane.
- **Administration** - photodynamic therapy (PDT) is offered to those patients with a visual acuity of 6/60 or above. It is carried out in an outpatient setting: verteporfin is infused intravenously over 10 minutes and then 5 minutes later, a laser diode is applied to the target area on the retina. The treatment can be repeated at 3-monthly intervals.
- **Ocular side-effects** - transient visual disturbances occur in up to 38% of patients, but resolve spontaneously with time in the vast majority of people.[1]

- **Systemic side-effects** - photosensitivity: patients are advised to avoid bright light during treatment and for 48 hours thereafter. Hypersensitivity reactions, nausea, pruritus, fever, back pain, hypercholesterolaemia and reactions at the site of injection.

- Note that verteporfin photodynamic therapy has largely been replaced as a first-line therapy for late AMD, in favour of anti-vascular endothelial growth factor drugs. The National Institute for Health and Care Excellence (NICE) recommends that it is only used as an adjunct to these drugs as a second-line treatment in a randomised controlled trial.[2]

- The Royal College of Ophthalmologists recommend photodynamic therapy as an option for patients with polypoidal choroidal vasculopathy who are not responding to anti-VEGF.[3]

- A global shortage of verteporfin occurred in 2021, with ongoing shortages occurring in the years following.[4]

Age-related macular degeneration: anti-vascular endothelial growth factor treatment

- **Action** - these are agents that interfere with angiogenesis by binding to vascular endothelial growth factors (VEGFs) to prevent endothelial cell proliferation. Ranibizumab (Lucentis®), aflibercept (Eylea®), and brolucizumab (Beovu®) are all licensed for the treatment of AMD in the UK.[2] [5] Bevacizumab (Avastin®) is not licensed for AMD, but is considered to be of equivalent effectiveness and safety to ranibizumab and aflibercept,[2] and is considerably cheaper than those drugs. [6] Pegaptanib (Macugen®) is also licensed for AMD, but NICE deemed it to be less effective than ranibizumab, and not cost-effective to use.[7]

- **Administration** - NICE guidelines give a list of criteria for the use of anti-VEGF agents in wet AMD.[2] Anti-VEGF agents are administered directly into the vitreous of the eye under sterile conditions. Three doses are given at four-weekly intervals in the first instance and the patient's response is monitored according to strict protocols before further treatment is given; many units found the bi-monthly follow-up required for aflibercept easier to meet than the monthly follow-up required with ranibizumab.[3]

- **Ocular side-effects** - these may be related to the procedure, which is invasive, or to the drug itself. Complications are uncommon but may include endophthalmitis, traumatic lens injury, retinal detachment, uveitis and periocular infections.[8]
- **Systemic side-effects** - hypersensitivity reaction, thrombo-embolic phenomena.[8]

Glaucoma: 5-fluorouracil, mitomycin C[9]

- **Action** - 5-fluorouracil prevents normal cellular division by irreversible combination with cellular enzymes. Mitomycin C's alkylating properties inhibit DNA replication.
- **Administration** - subconjunctival injection during or soon after a trabeculectomy procedure to suppress episcleral fibrosis of the drainage bleb.
- **Ocular side-effects** - there may be local irritation and failure of action. Mitomycin C may increase the risk of cataract formation in the long-term.[10]
- **Systemic side-effects** - not seen with topical injection but, should the drug inadvertently enter the circulation, they include: oral mucositis, hyperuricaemia, nausea and vomiting, bone marrow suppression, alopecia and disruption of reproductive function. The very small quantities used are unlikely to cause these effects.

Other conditions

- PDT is also sometimes used, off-label, to treat chronic central serous retinopathy,[11] , ocular haemangiomas, choroidal melanomas, and retinal angiomatous proliferations.[4]
- PDT has been used in the treatment of choroidal neovascularisation associated with high myopia, although, again, anti-VEGF treatments have largely taken over.[4]
- Certain patients with severe or chronic uveitis associated with non-infectious, multi-system disease such as Behçet's disease and Vogt-Koyanagi-Harada syndrome show poor response to conventional steroids and eventually necessitate ciclosporin, azathioprine or chlorambucil. [12] [13]

Cytotoxic drugs in ophthalmic oncology

- Tumours can arise within the globe (retina, choroids, iris), the optic nerve and the surrounding tissues (eyelid, conjunctiva, orbit) but can also be exogenous (metastatic deposits from primary carcinomas elsewhere).[14]

- Treatment of these lesions tends to revolve around radiotherapy, thermotherapy and surgery but chemotherapy finds a place in the treatment of metastatic disease, particularly in debulking large tumours, such as in the case of retinoblastoma.[15] Intravitreal chemotherapy has been successfully used to avoid enucleation in some cases.[16]

- Topically applied chemotherapy has been used in more superficial lesions such as conjunctival melanomas and squamous cell carcinomas,[17] [18] especially where there is poor definition of lesion margins. Otherwise, surgical excision is the mainstay of therapy.

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