Radiotherapy for choroidal neovascularisation of age-related macular degeneration: a fresh perspective

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Degenerative macular disease with its accompanying choroidal neovascularisation (CNV) accounts for the majority of individuals registered as visually impaired in Western societies. To date no therapy has been shown to be uniformly effective in terms of improving or preventing visual loss and neither are there recognised treatment regimes for its prevention. Thus we continue to encounter patients whose CNV progresses inexorably to give rise to severe and irreversible central visual loss in the affected eye. A number of clinical studies are addressing a variety of new treatment modalities aimed at inducing the regression of new vessels within the CNV. Because of its unique and well-recognised physical properties, ionising radiation has been identified as a therapeutic agent which may beneficially influence the course of neovascularisation and scarring which are integral features of the macular disciform scar.¹ This perspective addresses fundamental issues such as the rationale for the use of radiotherapy, the selection of patients, the choice of radiation modality and dose and fractionation regime used in the various clinical studies to date.

Is there a clear rationale for the use of radiotherapy in the treatment of CNV of AMD within the context of phase 1 studies?

Experimental studies have shown that radiotherapy can effectively inhibit vascular endothelial cell proliferation *in vitro* and prevent angiogenesis *in vivo*.^{2,3} Experimental data exist to show that radiotherapy also reduces inflammation and scarring.^{4,5} Histopathological studies of human tissues show that angiogenesis, inflammation and scarring are the major components of CNV of age-related macular degeneration (AMD).⁶ An important and inevitable consequence of the scarring process associated with subretinal CNV is the distortion of retinal architecture, which is not only incompatible with normal

vision but all too frequently results in severe visual loss. Non-dividing cells are relatively radioresistant as damage is often expressed during mitosis.⁷ As retinal neurones and the retinal pigment epithelium are non-dividing cells they are likely to be radioresistant compared with the vasculature of the retina and choroid. Thus the radioresistance of the neural retina along with the ability of ionising radiation to minimise inflammation, involute preformed blood vessels and prevent scarring, were powerful reasons to consider its use in the treatment of CNV of AMD.

What evidence is there to suggest that visual outcome is influenced by radiotherapy in CNV of AMD?

Many of the published phase 1 studies propose a beneficial role for radiotherapy in terms of maintained visual function in patients with wet AMD.^{1,8–17} However, some have reported a lack of benefit and two studies have implied that treatment was associated with an adverse outcome.^{18–20} In one other study, which used a fractionation regime with fraction sizes significantly larger than those traditionally employed in radiotherapeutic practice, radiation-induced complications were noted.²¹ In this study by Mauget-Faysse *et al.*, 7.5% of treated eyes exposed to total doses between 16 Gy and 20 Gy given as four fractions developed optic neuropathy, retinopathy or choroidopathy as a result of radiotherapy.²¹ Although the authors suggest that an overall visual benefit was still evident despite the presence of complications at 2 years, it is recognised that optic nerve and retinal lesions induced by radiational insult can continue to manifest and increase and cause visual decline over time.

Two phase 3 trials also suggest a benefit. Bergink *et al.*²² showed that the risk of a 3 line visual loss was almost halved in treated patients with CNV at 12 months. A recent prospective randomised study by Char *et al.*²³ also suggests

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a treatment benefit, but the numbers included were small, follow-up short and the difference in outcome between treatment and control groups was marginal.

Were the treatment regimes selected in the phase 1 studies based on sound radiotherapeutic principles?

The effect of radiation exposure on cells and tissues is markedly affected by the total dose delivered and the fractionation schedule (i.e. whether given as a single exposure or as multiple exposures, with the time between each exposure also influencing the response of the tissue).^{7,24} Single doses in excess of 5 Gy and fractionated regimes exceeding 50 Gy usually result in tissue destruction and serious unwanted side effects in the eye.^{25,26} Smaller doses of radiation are reported to reduce inflammation and prevent scarring; therefore the early phase 1 studies which attempted to exploit the potential of radiotherapy in inducing regression of CNV used relatively low total doses (between 10 and 15 Gy) and fractionated delivery techniques.

Nonetheless, clinical trials on patients with cerebrovascular malformations have recently shown that regression of complex vascular structures is most efficiently achieved through the use of larger doses and fraction sizes than those used in standard fractionation regimes in traditional oncological practice.^{27,28} These findings suggest that radiotherapy at total doses of 18 Gy or less using fraction sizes of 2 Gy is likely to be less effective in the induction of vascular regression. However, increasing the fraction size increases the risk of optic nerve and retinal vascular damage and could lead to sight-threatening radiation retinopathy.^{25,26} Importantly, the cardiovascular status of AMD sufferers is already likely to be compromised due to age and the sharing of common risk factors,²⁹ and additional radiational insult is bound to jeopardise the retinal and choroidal circulation further, leading to a worse visual outcome. Thus any clinical trials employing non-standard fractionation regimes will have to consider the potential for the development of radiation retinopathy or optic neuropathy in later years.

External beam or brachytherapy?

A variety of methods have been used to deliver ionising rays to the macula of an affected eye. External beam sources and the appropriate radiotherapeutic expertise is generally readily available in most modern hospital facilities. However, an important disadvantage in the use of electron and photon beams is that the tissue surrounding the target is also exposed to gratuitous radiation. Theoretically the use of proton beams which are highly collimated with a defined Bragg peak should limit radiation exposure to the macular retina only. These advantages prompted Yonemoto and co-workers¹² to irradiate the maculae of patients with CNV with single doses of proton beams of 8 Gy or 14 Gy. Although regression of CNV was noted, a report from the same group in this issue of *Eye* confirms that a significant

number of patients developed radiation retinopathy.³⁰ Several investigators have used brachytherapy sources such as palladium and strontium plaques in the treatment of CNV.^{31,32} Striking involutional changes occur in the CNV of brachytherapised eyes; however, a marked visual benefit has not been demonstrable. Possible reasons for this include pre-existing photoreceptor and retinal pigment epithelium loss due to AMD itself or radiation-induced atrophy of the choriocapillaris with subsequent retinal pigment epithelium and photoreceptor loss.

Patient selection

The natural history of the neovascular process is one of progressive visual loss which is accompanied by expansion of the CNV in some directions and involution of pre-existing channels in other regions. In addition there is exudation, atrophy and patchy fibrosis. On angiographic evaluation, the main morphological feature of a CNV is one of fluorescein leakage, which may be classified as classic (when the leaking vessels are clearly delineated and seen early in the angiographic sequence) or occult (when the leakage is indistinct and occurs late in the angiographic sequence).³³ Visual change is more predictable in eyes with classic CNV in that visual loss is often rapid and extensive. In occult CNV the clinical course is more variable, with some eyes retaining good acuity for prolonged periods of time.^{34,35} Clinical studies have demonstrated that a significant proportion of eyes with occult CNV will develop a classic component with time, thus suggesting that the latter is a manifestation of a more advanced angiogenic process.^{34,35} As the available radiobiological evidence suggests that rapidly dividing cells are more sensitive to the effects of ionising radiation, it would be logical to assume that occult CNV, which is likely to reflect an earlier stage of the angiogenic process and therefore to contain more mitotically active endothelial cells, would be more amenable to treatment with radiotherapy.

Most of the phase 1 studies and all phase 3 trials currently in progress have used selection criteria to maximise inclusion of patients with classic CNV, as the natural history of visual loss is more predictable and a treatment effect is therefore more likely to be detected in this group. The large phase 3 trials are yet to report, and the data from the available phase 1 studies and small phase 3 trials have proven difficult to interpret with respect to identifying a better outcome group based on the morphology of the CNV.

Is there sufficient evidence to adopt radiotherapy as a treatment for CNV of AMD?

There is no sound evidence that treatment with radiotherapy preserves vision and prevents further visual loss in patients with CNV of AMD. The anecdotal evidence of phase 1 trials does, however, provide the justification for randomised controlled clinical trials of radiotherapy in selected groups of patients with CNV.

Since the smaller phase 3 trials that have reported have shown only a marginal benefit, the results of the larger multicentre, randomised controlled clinical trials of external beam radiotherapy for CNV of AMD should be awaited. Until these large-scale trials report, the proliferation of small uncontrolled studies and the ad-hoc treatment by radiotherapy of patients with CNV should be actively discouraged.

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