Radiation Vasculopathy

Anticoagulation for Radiation-Induced Optic Neuropathy

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Keywords

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Abstract

Radiation-induced optic neuropathy (RION) is a severely disabling complication of radiotherapy, without any known effective treatment. Three patients, one female and two males, aged 60, 34, and 45 years, respectively, developed progressive deterioration in visual acuity over 1 month, 8 years, and 2 months, starting 3, 12, and 9 years after radiotherapy for nasopharyngeal carcinoma. They received 70.15, 60.89, and 56.11 Gy over a period of 6–7 weeks, with fractionated doses of 2, 1.79, and 1.81 Gy, respectively. Ophthalmological examination revealed a relative afferent pupillary defect in the latter 2 patients, best-corrected visual acuity was 6/12 or better in all. Visual field charting showed a superior altitudinal field defect in the first two, and generalised visual loss in the third patient in the symptomatic eyes. Anticoagulation with heparin bridging and oral warfarin with an INR target of 2.0–3.0 was commenced within 2 months of symptom onset. All showed improvement in visual fields within 2 weeks, and remained stable for at least 2 years while on warfarin. Our encouraging findings will need to be confirmed in a randomised controlled clinical trial.

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Introduction

Radiation-induced optic neuropathy (RION) is a well-known and devastating delayed complication of cranial radiotherapy [1]. It occurs among 10–100% of irradiated patients when doses of irradiation exceeding 60 Gy are used, and carries an extremely poor prognosis for visual recovery [2]. Treatments using steroids have yielded poor results [1–3]; hyperbaric oxygen and intravitreal bevacizumab may be temporarily helpful [4, 5]. Anticoagulation may be helpful in the management of cerebral radionecrosis, myelopathy, or plexopathy [6], but has not been efficacious for RION [2, 4, 7–11]. This may be due to therapy being started long after symptom onset [9] or the absence of bridging heparin that could have reduced the known prothrombotic state that occurs in the initial phase of oral warfarin use [10]. RION is a known complication of radiation therapy for nasopharyngeal carcinoma (NPC), a common cancer in East Asia for which radiation is the mainstay of therapy [1, 7, 11]. This is a report of anticoagulating 3 patients with RION from radiotherapy for NPC early after symptom onset with warfarin and bridging heparin.

Case Reports

Patient 1 was 60 years old when she was diagnosed with NPC. Her nasopharynx received 70.15 Gy of radiation in 35 daily fractions at 2 Gy per fraction over 7 weeks using 6 MV photons. Her left eye became progressively blind 2 years later. She was referred to the ophthalmologist when her right eye developed deterioration in vision over a 4-week period another year later. Ophthalmological examination revealed a relative afferent pupillary defect (RAPD), optic atrophy and a blind left eye; on the right side, the anterior segment, neuroretina were normal, without optic atrophy. Intraocular pressures were normal. Visual acuity in the right eye was 6/9 best corrected. Humphrey 24/2 static threshold perimetry showed a superior altitudinal field defect in the right eye (Fig. 1). Optic nerves magnetic resonance imaging (MRI) was normal. In-patient anticoagulation with heparin was immediately started, followed by warfarin. Improvement in her visual field defect occurred within 2 weeks, with significant recovery in the right superior temporal quadrant by 6 weeks. She was maintained on warfarin in the INR range of 2.0–3.0, with stabilisation of her visual field. She was taken off anticoagulation after a 2-year period, and remained stable for the following 2 years.

Patient 2 was 34 years old when he was diagnosed with NPC. His nasopharynx received 60.89 Gy of radiation in 34 daily fractions at 1.79 Gy per fraction over 7 weeks using a Cobalt teletherapy machine. He developed reduction in visual activity in the left eye 4 years later that remained static, and was referred to the ophthalmologist a further 8 years later when he developed further rapid deterioration in his vision in that eye. Ophthalmological examination was normal except for a left RAPD. Visual acuity in the left eye was 6/9 best corrected. Perimetry showed a superior altitudinal field defect in the left eye (Fig. 2). Optic nerves MRI was normal. In-patient anticoagulation with heparin was immediately started, followed by warfarin. His visual fields improved over the next few months. He was maintained on warfarin in the INR range of 2.0–3.0, with stabilisation of his visual field. He remains on warfarin. His visual fields have remained stable.

Patient 3 was 45 years old when he was diagnosed with NPC. His nasopharynx received 56.11 Gy of radiation in 31 daily fractions at 1.81 Gy per fraction over 6½ weeks using a Cobalt teletherapy machine. He was referred to the ophthalmologist 9 years later with a 2-month

history of progressive deterioration of his left eye vision. Ophthalmological examination was normal except for a left RAPD. Visual acuity in the left eye was 6/12 best corrected. Perimetry showed general visual loss in the left eye (Fig. 3). Contrast-enhanced optic nerves computed tomography (CT) was normal (MRI could not be performed as he had a metal implant in the right leg for a fracture). In-patient anticoagulation with heparin was immediately started, followed by warfarin. He felt subjectively better within a week. Perimetry subsequently revealed a residual superior altitudinal field defect. He was maintained on warfarin in the INR range of 2.0–3.0, with stabilisation of his visual field when he was last seen nearly 3 years after initiation of anticoagulation.

Discussion

Radiotherapy is the primary treatment modality for locally and regionally confined malignancies of the nasopharynx and paranasal sinuses, and may be an adjunctive treatment for intracranial tumours affecting the brain, base of skull, pituitary gland, or spinal cord [1]. Among the feared delayed complications of irradiation is RION, which is characterised by acute relentlessly progressive visual loss, visual field defects indicative of optic nerve or chiasmal dysfunction, absence of optic disc oedema, onset usually within a few years of irradiation, without neuroimaging or pathological evidence of tumour compression [1, 2].

The mechanism of radiation-induced damage is believed to be due to damage to the endothelium of feeding capillaries and arteries, including the vasa vasorum, leading to vascular occlusion, demyelination, free radical injury, direct damage to cellular DNA, and damage to the blood-brain barrier [1, 2, 12]. Histopathological findings include basal membrane detachment, cell pyknosis, loss of capillary segments, vessel wall thickening, endothelial proliferation, thrombosis, occlusion of the lumen, and occasional telangiectases. Structural effects include accelerated atherosclerosis, fibrosis, and thrombosis.

Heparin and warfarin achieve their anticoagulation effect inhibiting serum protein-mediated coagulation and secondarily reduce platelet aggregation and release [3, 6]. However, heparin also has other actions independent of its anticoagulant effect. It inactivates or prevents the release of many substances that mediate vascular injury, inflammation, permeability and oedema, such as histamine, serotonin, lysozymes, bradykinin and complement. It is able to affect cell processes such as phagocytosis, pinocytosis and chemotaxis. It inhibits arterial smooth muscle cell proliferation. It may be these effects that confer an additional positive influence on the deleterious effects of irradiation. Warfarin may too have some of these effects, but this is less well studied.

In our series, we anticoagulated 3 patients with RION with parenteral bridging heparin followed by warfarin. All had received conventional radiotherapy; none received chemotherapy, which is known to also increase the risk of RION [2]. All our patients responded favourably to anticoagulation. Maintenance of anticoagulation sustained the clinical benefit in our patients; discontinuation in one did not lead to worsening. This is unlike some authors who reported worsening of symptoms on discontinuation of anticoagulation that responded to re-initiation of anticoagulation [9].

All our patients improved soon after initiation of intravenous heparin, a finding also reported by others for radiation necrosis [13], where clinical improvement is seen within days. Studies of patients receiving only warfarin without heparin did not show this dramatic response, although a slow improvement did occur [14]. Also, studies reporting patients who

were already on therapeutic doses of warfarin for other indications who subsequently received irradiation showed that they were not protected against the occurrence of radiation-induced damage [15]; they were not given heparin during irradiation therapy or when complications occurred. We conclude that the positive response seen with heparin is due to actions in addition to its anticoagulant effect.

RION is potentially preventable. RION tends to develop when cumulative doses of radiation exceeding 50 Gy is used. Lower doses may thus reduce the risk of RION. Early detection by raising awareness among patients, family and clinicians and ophthalmic screening may be helpful so that treatment may be started as soon as possible [2].

This report describes a small number of patients with RION who were acutely anticoagulated and followed prospectively. Our results are supportive of earlier reports that suggest that anticoagulation with heparin and warfarin may benefit patients with delayed effects of irradiation. However, there are many unanswered questions. Is heparin really necessary? Will low molecular weight heparins be as effective or even better? What is the level of anticoagulation needed? How long should anticoagulation be continued for? Would the addition of antiplatelet agents enhance the effects of anticoagulants? Is there a role for the novel oral anticoagulants (NOACs)? Will the use of heparin just before or during irradiation reduce the frequency of RION? Randomised controlled trials are needed to answer these pressing questions.

Statement of Ethics

This research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The subjects have given their informed consent to publish their case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Narayanaswamy Venketasubramanian – neurologist, conceived the project, principal clinician who managed the patients, wrote the paper. Kong Yong Goh and Paul T Chew – ophthalmologists, managed the ocular aspects of the patients, interpreted the visual fields, reviewed the paper. NPC Study Group – provided data on the radiation doses administered to the patients.

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Fig. 1. Right eye perimetry of patient 1. **a** Pre-anticoagulation showing superior altitudinal field defect, and **b** 2 months post-anticoagulation showing improvement in the nasal quadrant.

Fig. 2. Left eye perimetry of patient 2. **a** Pre-anticoagulation showing superior altitudinal field defect, and **b** 2 months post-anticoagulation showing improvement in the temporal quadrant.

Fig. 3. Left eye perimetry of patient 3. **a** Pre-anticoagulation showing generalised visual loss, and **b** 4 months post-anticoagulation showing improvement in the inferior field and superior nasal quadrant.