The use of hypochlorous acid in an irradiation ulcer of the lower eyelid – a case study

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Radiation therapy represents an important cornerstone in the treatment of numerous cancers, as evidenced by the fact that approximately 50% of patients with cancer will receive this form of treatment. In 95% of these individuals, radiation therapy causes some form of skin injury as high doses of radiation causes significant harm to healthy tissue and skin. Management of injuries due to ionising radiation is challenging, with injuries ranging from acute redness to full ulceration of the skin. This can cause considerable anxiety and discomfort to patients. This case study explores the use of hypochlorous acid (HOCl) in the treatment of acute radiation injury of the lower eyelid skin.

Keywords: radiation skin injury, radiation wound, radiation dermatitis, treatment of radiation dermatitis, hypochlorous acid, inflammation after radiation, reduction in scarring, scarring treatment, ectropion

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Introduction

During treatment of cancers, radiation treatment (RTx) can injure any healthy tissue, as in this case, the lower eyelid. Here, the skin has rapid cell turnover and therefore is sensitive to the effects of radiation.[1] Damage to the skin from radiation is usually referred to as radiation dermatitis, or radiation injury.[2] The degree of injury depends mainly on the radiation intensity and the patient's tissue sensitivity to the radiation.[1] Acute radiation injury to the skin, which generally occurs during the first four weeks, may include erythema, pigmentation changes, dry desquamation and wet desquamation. During the acute period, full-thickness damage may occur, resulting in tissue necrosis and ulcers.[3] Ionising radiation creates free radicals and reactive oxygen intermediates that lead to DNA and protein damage, as well as damage to cellular membranes of rapidly proliferating tissue.[4,5] Following radiation, there is a raised level of pro-inflammatory cytokines, with inflammation of the treated area one of the most notable features.[1] In such cases, the use of a topical anti-inflammatory may alleviate discomfort and accelerate healing.[6]

Study case presentation

Patient history

A 75-year-old female presented with an ulcer on the right lower eyelid after RTx for incomplete excision of squamous cell carcinoma (SCC). 60 Gray in 30 fractions commenced one month after surgery at a frequency of 5 per week. After 15 fractions, the skin of the lower eyelid was inflamed and by the 28th treatment, the lower eyelid had become ulcerated and RTx was paused for a week to allow for healing. Trifectiv® Plus hypochlorous acid 0.038% treatments were commenced and a week later the last two RTx were completed.

Wound dressings

Day 0 – The patient presented with an ulcerating lesion measuring 35 x 20 mm, 39 days after radiation had commenced. The wound extended to the right lower tarsal edge and had a bloody exudate, with severe inflammation. Hypochlorous acid (HOCl) 0.038% was sprayed onto the wound and was covered with a gauze dressing saturated with the HOCl. The wet gauze dressing was applied onto a single layer of non-medicated paraffin gauze and fixed with adhesive tape.

Day 1 – The HOCl/paraffin gauze was repeated.

Day 2 – 21 HOCl was introduced as the primary wound cleanser and spray, 3 x per day. The wound was kept open.

Day 13 to 21 – Resolution of inflammation, moderate ectropion of the lower eyelid. The ectropion was largely resolved by day 21 and by day 30, no ectropion was present. Maintenance spraying of HOCl (1–2 x per day) was encouraged to further assist in the prevention of scarring.[7]

Wound progress

Wound healing was rapid during the first 16 days, even whilst the patient received a further two radiation treatments. During this time, the wound inflammation dissipated, the serous exudate stopped by day 3 and an eschar had formed by day 16 with very little residual inflammation, even in the surrounding tissues. After another five days of HOCl application, re-epithelisation of the eyelid was complete with no signs of inflammation (see Figure 1). Within four weeks after starting HOCl treatment, the wound appeared healed with full restoration of lower eyelid function. These events, with pictures of the wound healing process, are depicted in Figure 1.

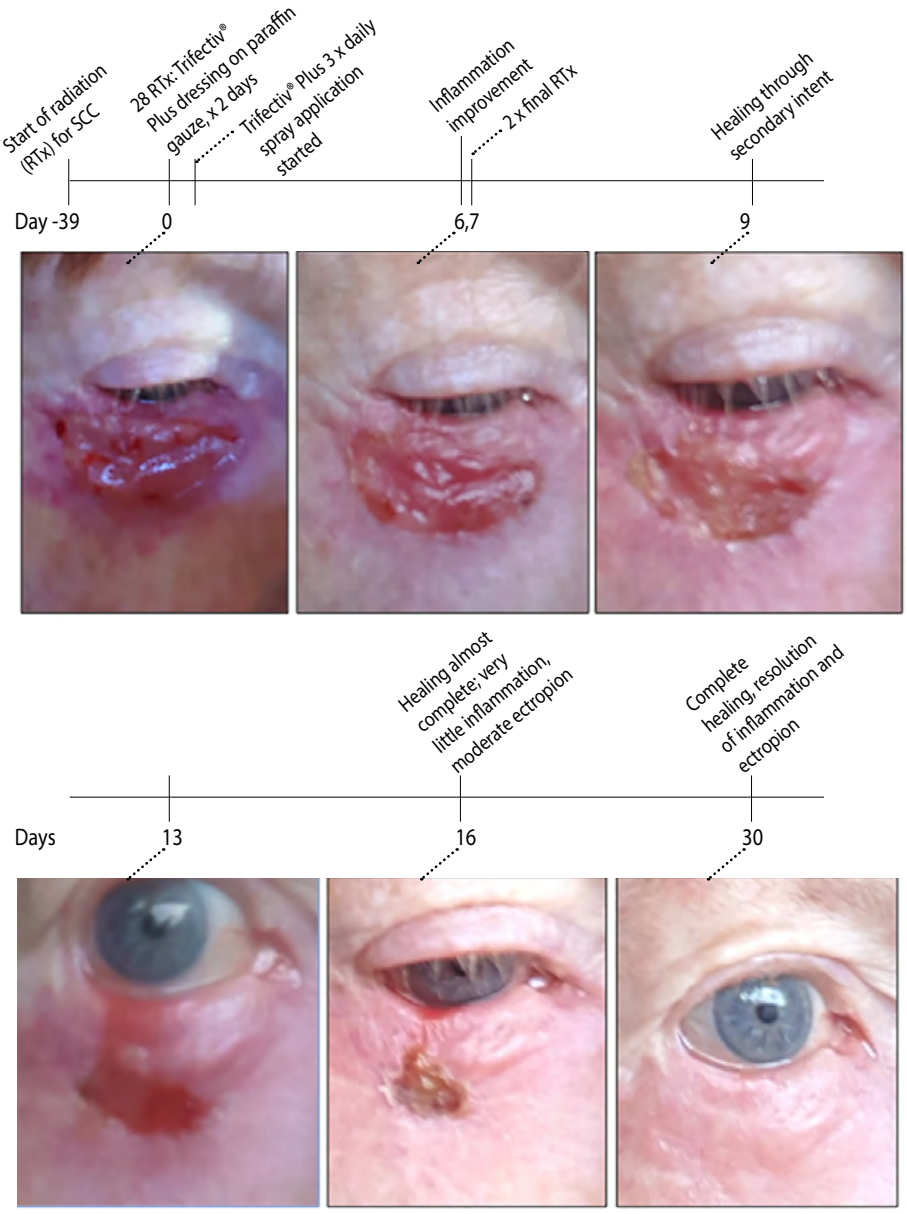

Figure 1

Discussion

SCC is the second most common eyelid malignancy after basal cell carcinoma (BCC), occurring in the lower lid approximately 60% of the time.[8] The presentation is often a painless nodular lesion with irregular rolled edges, pearly borders, telangiectasia and central ulceration, similar to BCC.[9] SCC invades along the trigeminal, oculomotor and facial nerves and can present as asymptomatic perineural invasion detected on histologic examination or symptomatic perineural invasion. SCC with perineural invasion has a recurrence rate of up to 50%, and post-operative or stand-alone radiotherapy for all SCC's with perineural invasion or incomplete excision has been suggested.[10]

High levels of proinflammatory cytokines are released with irradiation of tissue, leading to inflammation as well as tissue damage. Injury and death of endothelial cells lead to microvascular damage and tissue hypoxia. Basal keratinocytes, which are essential to wound repair and re-epithelialisation, are injured or killed. Over the course of radiation therapy, efforts of surviving basal keratinocytes to heal the skin are repeatedly undermined as, with each treatment, the damage is exacerbated. Injury and death of stem and progenitor cells result in the impairment of their ability to replace various functional cells.[2]

Scarring of the lower eyelid and ectropion may develop after the treatment of eyelid carcinomas (particularly ones involving the lower eyelid). The incidence of soft tissue necrosis is typically less than 3%.[11] The management of radiation injury to the skin, especially grade 4 in which there are skin necrosis and full-thickness wounds, is complex[5] with no accepted standards regarding specific modalities that are based upon irrefutable conclusions from randomised clinical trials.[4] A variety of different skin care products, as well as corticosteroid cream have been proposed for erythema and dry desquamation. If an infection is present, topical antibiotic ointment such as Neosporin or silver sulfadiazine 1% have been suggested.[4] Pentoxifylline, a methylxanthine derivative, and alpha-tocopherol (vitamin E) could be beneficial to combat fibrosis.[6] Hyperbaric oxygen therapy may reverse radiation injury. Investigations are now being pursued based upon evidence that hyperbaric oxygen treatment increases the number of stem cells at the radiation injury site, which could assist in improving micro-vasculature.[4]

Ionising radiation initiates cellular responses driven by activation of nuclear factor kappa B proteins (NF kB) and can induce radiation dermatitis, a common adverse side effect in patients undergoing radiation therapy.[12] Therefore, direct inhibitors of the NF kB pathway should be useful in clinical medicine. HOCl functions in vivo to attenuate the NF kB driven disease process of acute radiation dermatitis. Leung et al. in their in vivo mouse models inferred that HOCl is predominantly inhibiting NF kB signaling in keratinocytes.[12]

HOCl may help treat chronic non-healing wounds, including sacral decubitus pressure and diabetic foot ulcers.[13] In order to provide a wound with the best environment in which to heal, it is important to eradicate infection and to control inflammation.[14-16] Trifectiv® Plus

has proven efficacy against a large number of pathogenic organisms including methicillin-resistant *Staphylococcus aureus* (MRSA) and its anti-inflammatory effect has been described in a case of burn injury.[17]

The primary pathophysiology of the radiation injury is hypoxia due to the progressive obliteration of the microvasculature and fibrosis that follows radiation.[4] Oxygen plays a critical role in the growth of new capillaries, and the control of infection. Perfusion and delivery of O_2 to tissue are closely related.[13]

A study investigated effects of topical HOCl in the treatment of patients with venous leg ulcers, including time to wound healing. By assessing micro-circulatory integrity (oxygenation), it was demonstrated that most patients had elevated transcutaneous oxygen pressure levels in peri-wound tissues 15–30 seconds after exposure to HOCl and continued to have elevated oxygen pressure levels some 72 hours after exposure.[7,18] HOCl could therefore have a potential beneficial effect of raising oxygen levels in irradiated tissues, thereby counteracting hypoxia. This will have to be verified with transcutaneous oximetry.

In this case study, the patient presented with a radiation-induced ulcer of the right lower eyelid. Even though two further radiation treatments were planned, she needed to stop treatment to allow for healing in the wound. After the start of treatment with HOCl, the anti-inflammatory effect of the HOCl reduced her inflammation in the wound, allowing healing to progress.

HOCl also induces the production of cellular growth factors. The complete absence of a cytotoxic effect of HOCl on human cells form an important component in its ability to promote healing in wounds.[19]

Conclusion

Care of patients with radiation dermatitis, including ulceration of the skin may be possible using HOCl. This complication can be anticipated and may be treated with the use of HOCl, which has been proven in vivo to counter the NF kB pathway responsible for the various degrees of inflammation associated with radiation. Its effect on the modulation of inflammation and infection, which has a high risk of being present in open wounds, ultimately yields improved outcomes. The patient in this case study, despite the development of a skin ulcer, responded well to the local application of HOCl, first with dressings and then by spray application. The results suggest that treatment of radiation wounds with HOCl should be investigated where the wounds are not following the normal wound-healing trajectory according to the wound healing phases.

Conflict of interest

H Roos: Co-founder of Trifectiv (Pty) Ltd

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