Topical fluorouracil after surgery for ocular surface squamous neoplasia in Kenya: a randomised, double-blind, placebo-controlled trial

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Summary

Background **Ocular surface squamous neoplasia (OSSN) is an aggressive eye tumour particularly affecting people with HIV in Africa. Primary treatment is surgical excision; however, tumour recurrence is common. We assessed the effect of fluorouracil 1% eye drops after surgery on recurrence.**

Methods **We did this multicentre, randomised, placebo-controlled trial in four centres in Kenya. We enrolled patients with histologically proven OSSN aged at least 18 years. After standard surgical excision, participants were randomly allocated to receive either topical fluorouracil 1% or placebo four times a day for 4 weeks. Randomisation was stratified by surgeon, and participants and trial personnel were masked to assignment. Patients were followed up at 1 month, 3 months, 6 months, and 12 months. The primary outcome was clinical recurrence (supported by histological assessment where available) by 1 year, and analysed by intention to treat. The sample size was recalculated because events were more common than anticipated, and trial enrolment was stopped early. The trial was registered with Pan-African Clinical Trials Registry (PACTR201207000396219).**

Findings **Between August, 2012, and July, 2014, we assigned 49 participants to fluorouracil and 49 to placebo. Four participants were lost to follow-up. Recurrences occurred in five (11%) of 47 patients in the fluorouracil group and 17 (36%) of 47 in the placebo group (odds ratio 0·21, 95% CI 0·07–0·63; p=0·01). Adjusting for passive smoking and antiretroviral therapy had little effect (odds ratio 0·23; 95% CI 0·07–0·75; p=0·02). Adverse effects occurred more commonly in the fluorouracil group, although they were transient and mild. Ocular discomfort occurred in 43 of 49 patients in the fluorouracil group versus 36 of 49 in the placebo group, epiphora occurred in 24 versus five, and eyelid skin inflammation occurred in seven versus none.**

Interpretation **Topical fluorouracil after surgery substantially reduced recurrence of OSSN, was well-tolerated, and its use recommended.**

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See **Online** for appendix

Introduction

Ocular surface squamous neoplasia (OSSN) covers a range of conjunctival and corneal diseases, from intra-epithelial dysplasia to invasive squamous cell carcinoma.[1] Risk factors for OSSN include ultraviolet radiation, HIV infection, and human papillomavirus infection.[2] In temperate regions, OSSN is uncommon, usually growing slowly, and most often affects elderly men. By contrast, in sub-Saharan Africa, OSSN is more common and aggressive.[3] It affects younger adults, predominately women (around two-thirds of cases), and is strongly associated with HIV infection (in about 70% of cases). OSSN has a wide range of clinical phenotypes and late presentation with invasive orbital disease is not uncommon (figure 1). Surgical excision is the mainstay of treatment, although primary chemotherapy has also been used (appendix). OSSN often recurs after surgery. The highest recorded recurrence is 67%.[4] Recurrence is a particular problem in sub-Saharan Africa, where it typically occurs in 30–40% of patients.[4–7] In temperate climates, recurrence typically occurs in 5–25% of patients (appendix). Surgical outcomes seem to be affected by delays in diagnosis, tumour size, histological grade, ocular location, scleral invasion, excision margin involvement, prior excision, and coexisting xeroderma pigmentosum.[5,8,9] Several adjunctive treatment regimens are used during or after surgery to reduce recurrence: cryotherapy, topical chemotherapy (mitomycin and fluorouracil), interferon alfa-2b, retinoic acid, and radiotherapy (appendix p 1, 3, 7, 11, 13, 14). Most data on adjuvant treatment are case series. There is one previous randomised trial, from Australia, which assessed the effectiveness of topical mitomycin and there are no trial data on interventions for people with HIV.[10,11] Radical surgery (enucleation or exenteration) is usually needed for advanced disease.[12]

The antimetabolite fluorouracil is often used in ophthalmology, particularly for its anti-scarring properties during surgical procedures (trabeculectomy, pterygium

Research in context

Evidence before this study

Ocular surface squamous neoplasia (OSSN) is an eye cancer, common in people with HIV. A Cochrane systematic review from 2013 showed no evidence from trials for the effectiveness of interventions used in this population. We searched electronic databases (PubMed, Embase, The Cochrane Library), clinical trial registries (WHO International Clinical Trials Registry Platform and the US National Institutes of Health ClinicalTrials.gov), and international conference proceedings of HIV/AIDS and AIDS-related cancers from the AIDS Education Global Education System for studies published up to Aug 31, 2015, irrespective of language or publication status. We used the terms "randomized controlled trial", "controlled clinical trial", "randomized", "placebo", "drug therapy", "randomly", "trial", "conjunctiva*", "ocular surface", "carcinoma", "cancer", "neoplasia", "neoplasm", "neoplastic", "dysplasia", "dysplastic", "squamous", and "squamous cell". We found only one trial, on topical mitomycin in a non-HIV-infected population in Australia. We identified some case series and case reports (appendix). Only series that reported recurrence as an outcome were included.

Added value of this study

Our study provides the first evidence from a trial of the effectiveness of fluorouracil as adjunctive treatment for OSSN. Our results show that the simple and relatively inexpensive use of 4 weeks of fluorouracil 1% eye drops after surgical excision substantially reduced the relative risk of recurrence compared with placebo and was safe. There were transient side-effects, such as watery eye, discomfort when taking the drops, and eyelid skin inflammation but these were mostly mild and resolved in a few weeks after completion of 4 week treatment.

Implications of all the available evidence

Recurrence is a huge issue in the management of this common and aggressive eye disease. Fluorouracil does not need stringent storage conditions and cytotoxics have a low risk of contamination. It is on the WHO Essential Medicines List, and is a widely available and low-cost option, particularly in sub-Saharan Africa, which has the highest incidence of OSSN in the world. Translation of these trial results into clinical practice is therefore feasible.

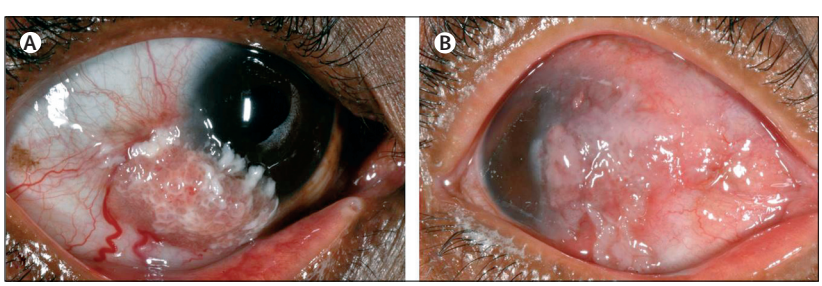

Figure 1: **Ocular surface squamous neoplasia**
Moderately differentiated conjunctival squamous cell carcinoma, (A) moderate size, (B) large lesion involving the cornea, limbus, and extending to the fornix. Fornix involvement is often associated with orbital spread.

excision, and lacrimal surgery).[13] Eye drops containing 1% fluorouracil have also been used for several years to treat patients with OSSN after tumour excision (appendix p 11), on the basis of case series, which suggest that fluorouracil reduces tumour recurrence and is safe.[14–20] However, there are no data from trials. Fluorouracil is widely available and relatively cheap in sub-Saharan Africa, therefore, if shown to be an effective adjuvant, it would be a deliverable intervention.

We assessed whether use of fluorouracil 1% eye drops could reduce recurrence of OSSN following surgical excision in Kenya.

Methods

Study design and participants

We did a double-blind, parallel-group, randomised, placebo-controlled trial at four centres in Kenya: Kenyatta National Hospital Eye Clinic in Nairobi, PCEA Kikuyu Eye Unit in central Kenya, Sabatia Eye Hospital in western Kenya, and Kitale District Hospital in the north Rift Valley.

We enrolled consecutive patients presenting with suspicious conjunctival lesions. Entry criteria were: histologically proven OSSN involving two or fewer quadrants; attendance for follow-up within the first 2 months after excision; healing of the excision site; and age at least 18 years. Exclusion criteria were: previous treatment with topical antimetabolite drugs such as fluorouracil or mitomycin to the same eye or systemic cytotoxic drugs; extensive disease requiring more radical surgery than a simple excision; and pregnant or breastfeeding mothers. Patients were not enrolled if they did not think that they could return for follow-up.

All participants gave written informed consent before enrolment. Ethics approval was granted by the Kenyatta National Hospital/University of Nairobi ethics and research committee and the London School of Hygiene & Tropical Medicine ethics committee. Approval was also obtained from the Kenya Pharmacy and Poisons Board to produce and use the active intervention drops because they are not commercially available.

An independent data and safety monitoring board oversaw the study, confirmed data integrity, and approved the results and report for release. Trial personnel received good clinical practice training and certification. This study adhered to the tenets of the Declaration of Helsinki.

Randomisation and masking

Participants were randomly assigned (1:1) to either fluorouracil 1% or placebo eye drops. The fluorouracil eye drops were prepared by dilution of fluorouracil