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Novel and topical: immune-response modifier for skin cancer

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The drug imiquimod, a novel immune-response modifier used to treat genital warts, is showing promise as a topical treatment for superficial basal-cell carcinoma (sBCC). In a recently reported Phase II dose-ranging trial, the cancer was cleared in almost 90% of patients given a once-daily application of imiquimod 5% cream[1].

BCC is the most common type of skin cancer, and its incidence is increasing; in Australia it affects ~788 in 100,000 people. It is usually a result of DNA damage from overexposure to the sun, and occurs mainly in fair-skinned populations. It is not life-threatening and rarely metastasizes, but if left untreated it can invade deep into the tissue and cause significant local destruction, nerve damage and disfigurement.

Approximately 15% of BCCs are classed as superficial (sBCC), and these lesions occur principally on the trunk of the body and often exceed 1 cm in diameter. They appear as a shiny pink or red-brown patch, and are not usually invasive.

The standard treatments are surgical excision, curettage (scraping away the top layer of skin), electrodesiccation or cryosurgery, for which cure rates are between 80 and 99% (Ref. 2). However, these methods are painful and can leave unsightly scarring or pigmentation changes. They are also resource-intensive, because they have to be administered by medical personnel in a clinic.

BCCs are capable of spontaneous regression, which is thought to be a result of an immune response mediated by activated $CD4^+$ T cells. These infiltrate the tumour and can trigger regression by releasing cytokines: Wong and colleagues found that interferon (IFN)-γ was significantly elevated in actively regressing BCCs compared with non-regressing tumours[3]. IFN-α injected into the lesion has also been used successfully to treat BCC (Ref. 2).

Immune-response modifiers

Imiquimod, an imidazoquinoline (Fig. 1), is the first in a novel class of immune-response modifiers developed by 3M Pharmaceuticals (St Paul, MN, USA). It is already licensed for the treatment of genital warts, which are caused by human papillomavirus (HPV). Unlike most other immunomodulatory drugs, which inhibit immune-related pathways, it stimulates the immune system by inducing the release of cytokines involved in both innate and cell-mediated immunity (Figs 2 and 3). These include IFN-α and γ, interleukin-12 and tumour necrosis factor

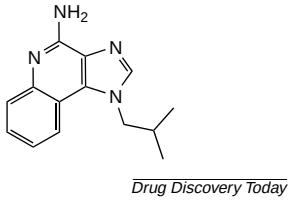

Figure 1. Imiquimod: 1-(2-methylpropyl)-1*H*-imidazo-[4,5-*c*]quinolin-4-amine.

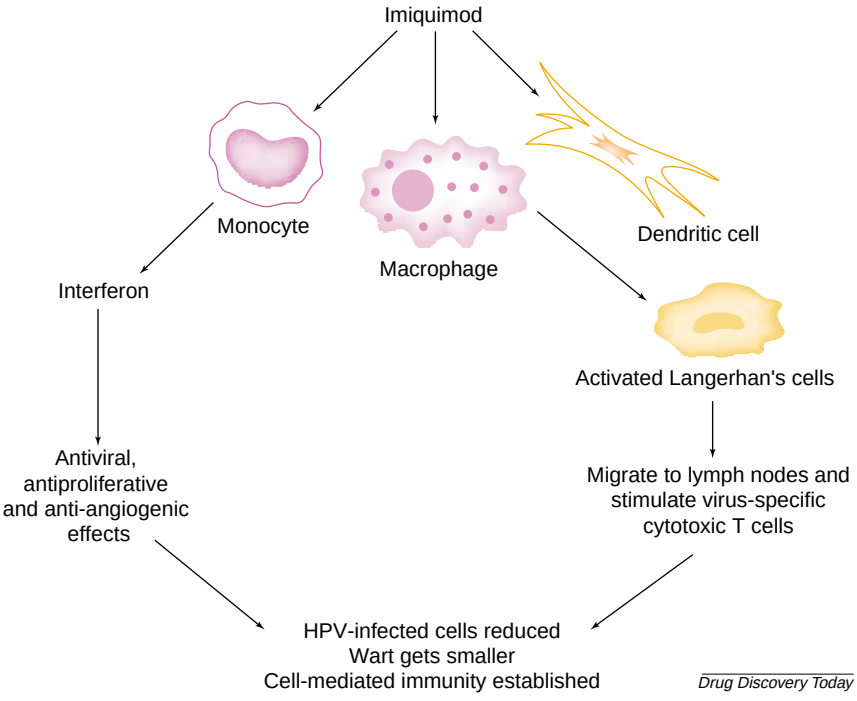

Figure 2. Possible mechanism of antiviral action of imiquimod. Adapted from 3M Pharmaceuticals.

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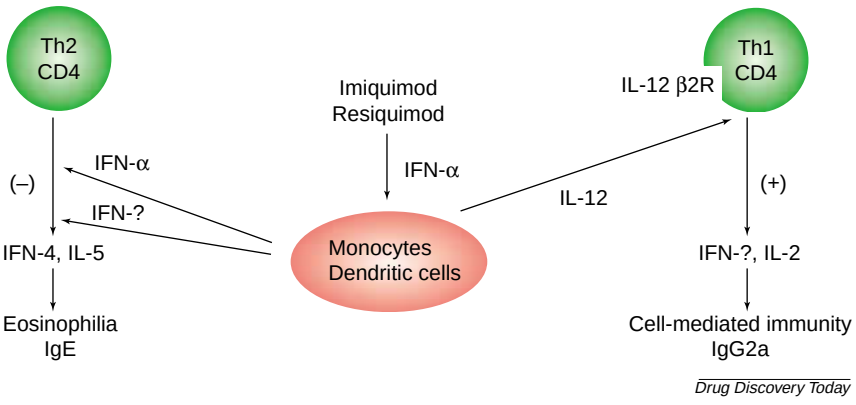

Figure 3. Immune-response modifier effects on Th1 and Th2 cells. Adapted from 3M Pharmaceuticals.

(TNF)[4], which give the drug both anti-viral and anti-tumour properties.

'The importance of the cell-mediated response is evidenced by the conditions that occur when you suppress it,' says Richard L. Miller of 3M. 'People who take cyclosporin to prevent rejection of transplants get viral infections and tumours of the skin.' He adds: 'With imiquimod, we think we are triggering a much more natural response than you get from using a single cytokine. We are inducing a broader range of cytokines, and even chemokines, that attract cells to the site and alert the body that there's something there to be dealt with.'

Clinical trials

In a multi-centre Phase II trial led by Robin Marks of St Vincent's Hospital (Melbourne, Australia), Aldara™ 5% imiquimod cream was tested on 99 patients with biopsy-proven sBCC. Patients were randomized to one of four dosage regimens, and treatment lasted for six weeks. Six weeks after treatment was completed, the tumour area was excised surgically and the tissue removed was carefully examined for the presence of tumour cells. Of the 33 patients on the once-daily regimen, 29 (87.9%) showed complete histological clearance of the tumour. Median tumour-area at the start of treatment was 0.7 cm^2. Most of the patients experienced local skin reactions, commonly redness or scabbing. Many of these reactions were moderate or severe, and 24% of patients reported pain. However, none discontinued treatment, perhaps in view of the pain and scarring associated with conventional treatments. The cosmetic outcome before excision was described as excellent: the only lasting mark was redness, which faded during the assessment period.

Phase III trials of imiquimod in sBCC are now under way. However, it has proved less effective than surgery in nodular BCC, which is more common and invasive than sBCC. The treatment is also being evaluated in Phase III trials against actinic keratosis, an ultraviolet radiation-induced skin lesion that can progress to squamous cell carcinoma (SCC). Some work has already been done on treating SCC itself, but this indication is not yet in formal development.

Resiquimod, a second-generation immune-response modifier, is also in Phase III trials. This compound is designed for application to moist lesions such as those characteristic of genital herpes caused by herpes simplex virus type 2 (HSV-2). HSV-2 is not eradicated by resiquimod but the interval between outbreaks is prolonged.

An expert in dermatology, Daniel Sauder (Director of Dermatology at Johns Hopkin's University, Baltimore, MD, USA) commented in a recent review[4] that: 'Increasing numbers of reports on the successful use of imiquimod as a convenient, patient-applied dermatological treatment reiterates the clinical potential of this family of immune-response modifiers.'

References

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2 Miller, S.J. *et al.*, eds (1997) *Cutaneous Oncology: Pathophysiology, Diagnosis and Management*. Blackwell Science

3 Wong, D.A. *et al.* (2000) Cytokine profiles in spontaneously regressing basal cell carcinomas. *Br. J. Dermatol.* 143, 91–98

4 Sauder, D.N. New immune therapies for skin disease: imiquimod and related compounds. *J. Cutaneous Med. Surgery* (in press)