Hong Kong J. Dermatol. Venereol. (2005) **13**, 74-82

Review Article

A review of imiquimod in the treatment of non-lymphoma cutaneous malignancy

咪喹莫特用於治療皮膚非淋巴瘤惡性腫瘤的回顧

WK Tang 鄧偉祺

Imiquimod is a topical immune response modifier. It is licensed for genital warts, actinic keratosis, and recently basal cell carcinoma. Studies showed that it had potent anti-tumour activity by enhancing both innate and acquired immunity. A growing number of evidences are found to support the use of imiquimod in various kinds of cutaneous malignancies, especially in basal cell carcinoma. Imiquimod was also documented as a useful treatment option for squamous cell carcinomas, squamous cell carcinoma in-situ, lentigo maligna, and extramammary Paget's disease, in immunocompetent and immunosuppressed patients. Imiquimod may be a novel treatment option worthy of consideration for carefully selected patients in whom traditional therapy is not considered feasible. This article reviews the published articles in English literature with keywords-imiquimod, basal cell carcinoma, squamous cell carcinoma, squamous cell carcinoma in-situ, lentigo maligna, extramammary Paget's diseases. Lymphoma, lymphomatoid or lymphomatous malignancy/cies were excluded in the literature search.

咪喹莫特為局部應用的免疫調控劑。它經已被批准用於生殖器疣、光化性角化病及基底細胞癌。研究發現，它通過增強身體的固有及獲得性免疫而有強大的抗腫瘤活性。有愈來愈多証據支持咪喹莫特用於各種皮膚惡性腫瘤，特別是基底細胞癌。對於免疫力正常或低下的病人，亦有文獻報導咪喹莫特能有效治療鱗狀細胞癌、鱗狀細胞原位癌、惡性雀斑樣痣和乳腺外佩吉氏病。對未能應用傳統療法治療的個別患者，咪喹莫特不失為一個值得考慮的治療方法。

Keywords: Basal cell carcinoma, extramammary Paget's diseases, imiquimod, lentigo maligna, squamous cell carcinoma, squamous cell carcinoma in-situ

關鍵詞：基底細胞癌，乳腺外佩吉氏病，咪喹莫特，惡性雀斑樣痣，鱗狀細胞癌，鱗狀細胞原位癌

Social Hygiene Service, Department of Health, Hong Kong

WK Tang, MRCP(UK), FHKAM(Medicine)

Correspondence to: Dr. WK Tang

Yaumatei Dermatology Clinic, 12/F, Yaumatei Specialist Clinic, 143 Battery Street, Kowloon, Hong Kong

Introduction

Surgical treatment is the standard treatment in most cutaneous malignancies. However, the risk of scarring, loss of body function and unsightly cosmetic outcome is hard to eliminate. Topical immunomodulators is a potentially useful

alternative for patients who refuse surgery or when surgery is deemed difficult. This article reviews the current data regarding the use of 5% imiquimod cream (imiquimod thereafter in this article) in the treatment of different cutaneous malignancies including basal and squamous cell carcinomas (BCC and SCC), squamous cell carcinoma in-situ (SCC-is), lentigo maligna (LM), and extramammary Paget's disease (EMPD). As there are more scientific evidences to support the use of imiquimod in basal cell carcinoma, more emphasis will be put on this area.

What is imiquimod?

Imiquimod (Aldara™, 3M Pharmaceuticals Ltd) is a member of immune response modifiers (IRM). It is primarily used to treat external genital and perianal warts in individuals 12 years old and above.

Imiquimod itself does not have direct antiviral or anti-tumour properties. It works by boosting local immunity. Although the exact mechanism is still unknown, it works by using the toll-like receptor (TLR)-7. TLRs represent a major component of the innate immune response and consist of 10 human pathogen-recognition receptors (TLR-1-10). These receptors can be detected on human neutrophils, macrophages, dendritic cells, dermal endothelial cells, mucosal epithelial cells, B cells and T cells. Activation of TLRs allows cytokine synthesis in response to various classes of microbial products. Imiquimod acts as TLR-7 agonist, which induces the expression of different cytokines like interleukin (IL)-1, IL-6, IL-12, interferon (IFN)-α and tumour necrosis factor (TNF)-α, they in turn stimulate or enhance both the innate immune system and the cell-mediated immune response.[1,2]

The innate immune system depends on the ability of phagocytic cells to recognise pathogens either through complement fixation or by binding to specific receptor-recognition molecules and then activating systems, including natural killer (NK) cells, capable of eliminating the pathogens. On the other hand, the cytokines induced by imiquimod stimulate the Th1 pathway and inhibit the Th2 pathway via stimulation of monocytes and dendritic cells, which produce IFN-α. Th1 CD4 cells also produce IL-12β2 receptor, which stimulates CD4 cells themselves to produce IFN-γ and IL-2 (cytokines that activate CD8 cells to become cytotoxic T cells that kill virus-infected and tumour cells), and provides the immune memory needed for future protection.[3]

Induction of apoptosis via Fas receptor[4] and down regulation of Bcl-2 expression by imiquimod is observed in human epithelial cell and keratinocytes, as well as BCC tumour cells.[5] These findings suggest that the mode of action of imiquimod to eliminate virus-infected, dysplastic or neoplastic epithelial cells may also include the induction of apoptotic processes (Figure 1).[6]

Basal cell carcinoma

BCC is a common cutaneous malignancy. A wide variety of treatment choices are possible for BCC with response rates varying from 80% to 99% depending on the tumour type, site, treatment modality selected, and the skill of the operator performing the procedure.[7] Traditionally, BCC is treated by surgical excision. Alternative treatment including cryotherapy or radiotherapy is also used. Early in this millennium, investigators have successfully used imiquimod to treat BCC. And imiquimod is gaining popularity in treating BCC in the United States.

There are different types of BCC, but the phase II and phase III studies of imiquimod mainly addressed its use in the two main subtypes, nodular (nBCC) and superficial BCC (sBCC).

Imiquimod has been shown to promote histological clearance of BCC. Beutner et al first

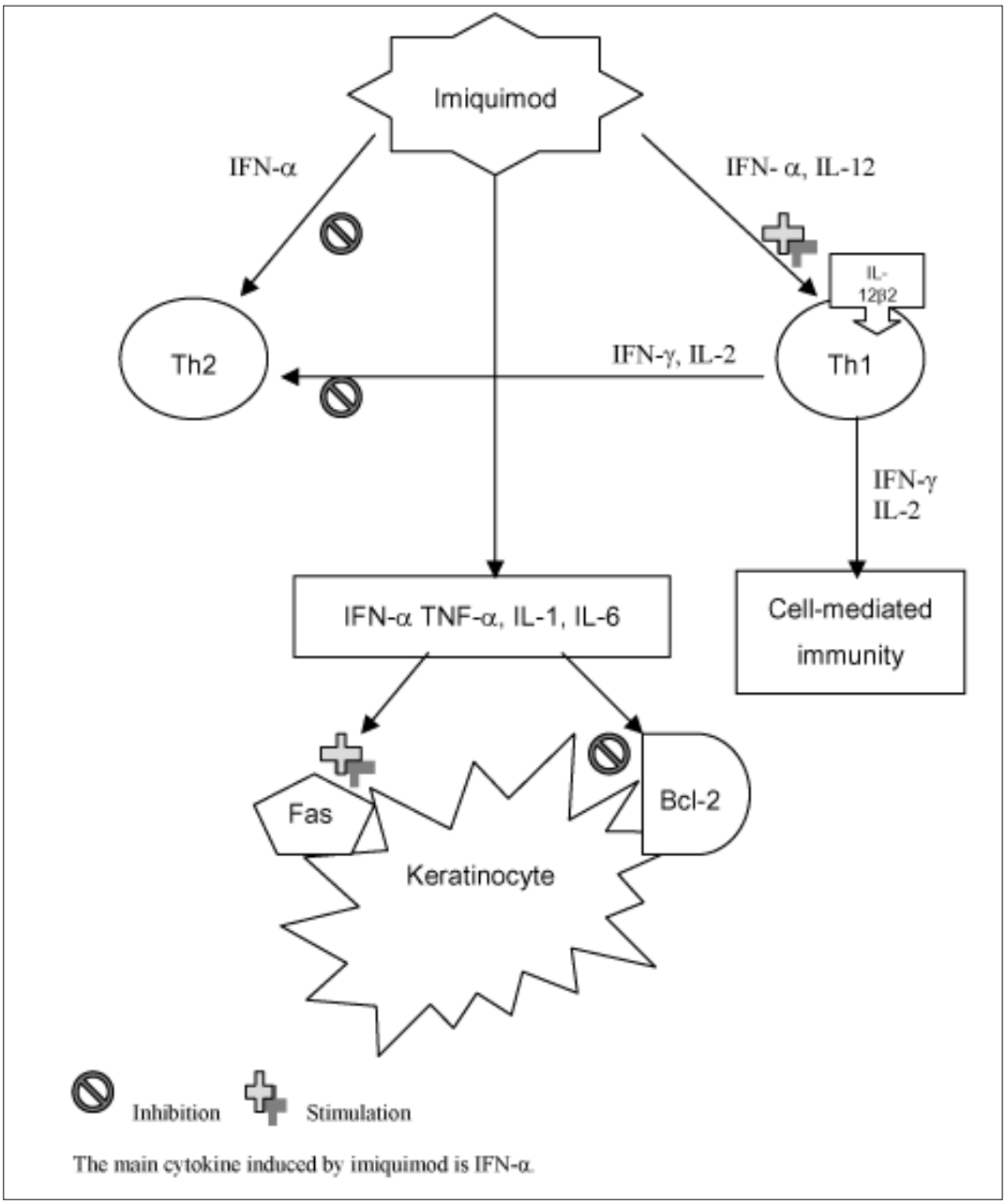

Figure 1. Immunomodulatory effect of imiquimod.

reported on the efficacy of imiquimod in the treatment of solitary BCC of the superficial and nodular type in 1999.[8] Imiquimod was found to be more effective for superficial lesions. Thereafter, clinical trials mainly focused on the efficacy and safety in treating sBCC with different dosing of imiquimod.

A phase II, dose-response, open-label trial conducted by Marks et al enrolling 99 patients revealed 100% cure rate of sBCC could be achieved by twice daily dosing for six weeks. Almost 90% (89.7% in per-protocol analysis, 87.9% in intention-to-treat analysis) histologic clearance of sBCC was seen for a once daily

treatment at the same treatment period.[9] A recent study carried out by Geisse et al[10] also demonstrated that the daily application of imiquimod was better than alternating day regime (87.1% cure vs. 51.7%). Interestingly, similar response rate was found at a lower dosing regime in another phase II trial, which assessed the response of superficial and nodular BCCs to imiquimod under the influence of occlusion with three times per week dosing for six weeks. Histologic cure was achieved in 87% and 76% with and without occlusion in sBCC respectively, 65% and 50% with and without occlusion in nodular BCCs respectively. Although the absolute response rates were apparently higher with occlusion, no statistical significant advantage with occlusion was found.[11]

Current evidences seem favour that the efficacy of imiquimod in treating BCC is dose-related. Nevertheless, optimal dosing to minimise cutaneous side-effects and maximise efficacy is still controversial. The latest phase III clinical trial demonstrated that imiquimod applied five times a week for six weeks could achieve 82% histological clearance in sBCC.[11]

When imiquimod is used in clinical practice, clinical clearance is practically used to assess the response of the patient. Thus concordance between clinical and histological assessments of the post-treatment lesion is important. Results from two randomised, double-blind, vehicle-controlled phase III studies showed that the positive predictive value was 36% (i.e., the probability of a positive clinical assessment confirmed to be positive histologically); of 98 lesions that were clinically assessed as being positive for sBCC 12 weeks post-treatment, 35 were histologically confirmed to be positive for sBCC. The negative predictive value was 93% for the pooled imiquimod groups (i.e., the probability of a negative clinical assessment confirmed as being negative histologically); of the 250 lesions that were considered to be clinically clear of sBCC post-treatment, 232 were histologically confirmed to be clear. The sensitivity and specificity of the clinical assessments were 66% and 79%, respectively.[12] In another word, it is clinically more reliable to rule out responders. However, if the patients have pre-existing skin condition which makes clinical judgement difficult, post-treatment biopsy is needed. Moreover, it should be aware that local treatment effects, particularly persistent erythema, may linger beyond 12 weeks after treatment, so longer follow-up period is warranted before re-biopsy for low-risk patients. But this guideline may not be applicable to high-risk BCC types or other cutaneous malignancies.

It should be noted that patients recruited in large clinical studies were those with superficial type of BCC and with diameter less than 2 cm^2. Furthermore, lesions localised on high-risk areas were excluded from the studies. It is interesting to know whether imiquimod also works well in large and aggressive BCC types. Eklind et al reported the first case of high-risk and aggressive growth pattern BCC (sclerodermiform type and localisation in the face) that was successfully treated with topical imiquimod.[13] The largest imiquimod treated lesion reported to date is by Chen et al[14] The lesions affected the entire forearm. Clinical and histological clearance was achieved with 12 weeks of imiquimod three times weekly. And the patient remained disease free in the ensuing 10 months follow-up.

For patients with a number of lesions as in basal cell naevus syndrome, imiquimod may save multiple surgical procedures and the attendant scarring. Future studies should evaluate the role of imiquimod as an adjunctive therapy with other treatment modalities, and its effect on larger BCCs and other BCC subtypes.

Squamous cell carcinomas

SCC bears the potential of metastasis and rapid progression; surgical removal is the

standard treatment. Placebo-controlled trial is ethically difficult. Studies of imiquimod in this area are scanty.[15,16] However, successful outcomes in immunosuppressed patients are encouraging.

Two immunosuppressed renal transplant patients with invasive SCC were successfully treated with imiquimod three times a week for 12 weeks. Interestingly, systemic immunosuppression did not adversely affect the response to therapy.[13] No recurrence was detected up to 9-month follow-up. Hengge et al reported a case of invasive SCC successfully treated with topical imiquimod in a severely compromised patient with chronic renal failure and prostate cancer. The patient remained recurrence-free up to 16 months after treatment.[17] However, larger number of patients and longer follow up is needed in order to determine the risk of recurrence after imiquimod treatment in SCC. Nevertheless, the success in these cases might reflect intact quality of the skin-derived immune system is still present even in immunocompromised patients.

Others

Clinical evidences for other indications of imiquimod in skin malignancies are weak. Only small clinical trials or anecdotal case reports are available.

Bowen's disease, erythroplasia of Queyrat and Bowenoid papulosis

Bowen's disease, its counterpart on the penis erythroplasia of Queyrat, and Bowenoid papulosis are all SCC-is. Surgical excision and primary closure is primarily aimed for. However, imiquimod is useful for tumours occurring on sites such as on the foot, ankle, lower leg and penis, where morbidity risk is higher and surgical excision is technically difficult.

In an open-label study of imiquimod treatment of large SCC-is (with one cm or larger in diameter) on the limbs in 16 patients, 93% demonstrated biopsy-proven cure after 16 weeks of treatment.[18]

Bowen's disease is seen more frequently in immunosuppressed patients.[19] Five patients with chronic lymphocytic leukaemia and head and neck SCC-is were treated with imiquimod and the oral cyclooxygenase inhibitor twice daily. All patients demonstrated clinical resolution and histological clearing of tumours after 16 weeks of imiquimod applications three times per week.[20] Five renal-transplant patients with SCC-is on the lower limbs had clearing of their lesions with the application of imiquimod and 5-fluorouracil 5% cream topically, in an alternating regimen for 7-9 weeks.[21] Imiquimod has also been successful in treating anogenital SCC-is in an HIV-positive man.[22]

Imiquimod has also been effective in treating SCC-is of the penis, both on the shaft and on the glans.[23] Arlette reported to success with imiquimod every second day for 12 to 16 weeks in five patients with SCC-is on the penis. The only adverse effects were swelling, erythema and irritation. All patients tolerated the treatment well.[24] Patients with human papillomavirus (HPV) associated Bowenoid papulosis on the vulva responded to imiquimod. Interestingly, HPV was not detected after treatment and 18 months afterwards in the follow-up.[25,26]

Although HPV DNA have been associated with SCC-is in epidermodysplasia verruciformis,[27] erythroplasia of Queyrat,[28] and found in 31% of extra-genital Bowen's disease lesions.[29] It is still unknown whether imiquimod works mainly by cell-mediated antiviral immunity response. But because BCC and SCC are not always associated with HPV, other mechanism such as direct apoptosis of tumour cells may also contribute to the cure.

Genital area is a sensitive area. Severe local inflammatory reactions have been reported even when low dosing of imiquimod, three times weekly,

was used.[30] Physicians should monitor their patients closely when imiquimod is used in this area.

Lentigo maligna

Lentigo maligna (LM) is melanoma in situ. It most commonly occurs in elderly individuals, on the head and neck. Surgical excision is the treatment of choice whenever possible. Unfortunately, recurrence can occur because histological changes commonly extend beyond the clinical margins of the lesion. Since IFN-α is a major cytokine induced by imiquimod and intralesional administration of IFN-α has been shown to induce remission of LM,[31] imiquimod may thus have a role in LM. Moreover, imiquimod was also recently found to be able to induce apoptosis in malignant melanoma cells both *in vitro* and *in vivo* independent of various death receptors: Fas/APO-1 (CD95), TRAIL, and TNF.[32] So it is expected that imiquimod can be used in LM, and will be particularly useful for large lesions at cosmetically sensitive sites. The largest clinical study noted at the time of writing reported a 93% curative rate in an open-label clinical trial of 30 LM cases.[33] In a more recent study, twelve patients with facial LM were treated with topical imiquimod, three times a week for four to 20 weeks. Seven of 12 patients had their lesions disappeared, 10 patients showed histological clearance. And there was no relapse in a median follow-up of six months.[34]

Transformation of invasive melanoma developed from LM following imiquimod treatment has been reported.[35] But interestingly, topical imiquimod had been used as palliative therapy in metastatic melanoma. Complete clinical and histopathologic remission had been achieved in patients with locoregional cutaneous metastases of malignant melanoma.[36-38] Even so regional lymphatic spread of melanoma still occurred after treatment.[39] Imiquimod might have a role in the palliative treatment of metastatic melanoma, but its use in LM is still not widely accepted. Should imiquimod be used in cases without other surgical options, close follow up is mandatory.

Cutaneous extramammary Paget's diseases (EMPD)

EMPD is an infrequent epidermal malignancy, occurring most commonly in the anogenital and vulvar regions. Surgical treatment in these areas is usually difficult. In addition, the multifocal nature of the disease and the fact that clinically inapparent extensions of the disease may be present makes recurrences very frequent.

Zampogna et al first reported two cases of perineal and genital EMPD, who were treated successfully with imiquimod on alternating days of the week for 7.5 to 12 weeks.[40] Berman et al treated a case of cutaneous scrotal EMPD with imiquimod once-daily, over a period of 6 weeks. Though local erythema developed in the treatment area, no systemic symptoms were noted and clinical resolution occurred by week-4 of treatment, with no remaining pathology at 6-month follow-up.[41] Although the treatment was non-invasive, systemic symptoms including flu-like symptoms (malaise, fatigue, and low-grade fever), nausea and vomiting were noted in the reported cases.

Is imiquimod safe to use?

In general, imiquimod is well-tolerated. There is no detectable systemic absorption of imiquimod and there is a low potential for sensitisation. Based on the carcinogenicity studies done in animal models, the maximum recommended human dose (MRHD) is set at two packets per treatment of Aldara Cream (25 mg imiquimod).

As imiquimod works by inducing local immune response, local inflammation is expected to occur. It has been shown that increasing severity of erythema, erosion, and scabbing/crusting was associated with higher clearance rates.[11] Reported side-effects include erosion, excoriation, flaking, oedema, and erythema, with erythema occurring most commonly and ranged from 33% to 80% of patients.[42] The local adverse reactions are dose

related. Vesicle and ulceration become more common at a higher dose.[7,8] Intolerable local reactions occur in subjects dosing with very high frequency (i.e., 2×/day, 7×/week) and with occlusion. Topical imiquimod may have systemic side effects via the cytokine induction. The most frequently reported subjective systemic adverse events were fatigue, headache, fever, malaise, pain, nausea, diarrhoea, and arthralgia.[7] If intolerable adverse reactions occur, the patient should rest until the side effects subside and restart at a lower dose. Interruption of treatment with resting period did not appear to affect the efficacy of complete response.[8]

The only contraindication associated with imiquimod is in the case of hypersensitivity. Preliminary safety studies suggest that imiquimod does not possess a detectable photosensitising potential in humans, and furthermore, does not enhance ultraviolet radiation-induced damage to epidermal cells or DNA.[43] Even though treatment with imiquimod usually with a better cosmetic outcome, superficial scarring does occur; a side effect that is not usually observed in the treatment of viral infection.

Conclusion

The choice of therapy requires consideration of the location of the lesion, and a desire for a high cure rate without causing loss of form, function or cosmesis. Imiquimod, as an immune modifier offers a topical alternative to surgical intervention. It may serve as an adjunct to de-bulk the tumour before surgery and reduce relapse after operation.

The potential for non-surgical, patient-administered treatment of cutaneous malignancies in selected patients is great. However, patients are needed to be highly motivated and compliant. And since a major disadvantage of topical therapy is the lack of a histological specimen confirming complete clearance, extreme care should be executed in clinical and histologic follow-up.

Furthermore, carefully designed studies are necessary to establish the usefulness of topical immunomodulatory therapy for SCC, multiple BCCs, and BCCs with more aggressive growth patterns and particularly locations such as the face. Moreover, comparative trials should establish the cost-effectiveness of non-surgical compared with surgical therapy.

Upon the time of writing this article, imiquimod is only licensed in the United States for external genital and perianal warts in individuals 12 years old and above, and for clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults, and recently sBCC. Nevertheless, the extensive array of cutaneous malignancies treated successfully with imiquimod warrants further study of this novel and valuable drug.

References

1. Hemmi H, Kaisho T, Takeuchi O, Sato S, Sanjo H, Hoshino K, et al. Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. Nat Immunol 2002; 3:196-200.
2. Gibson SJ, Lindh JM, Riter TR, Gleason RM, Rogers LM, Fuller AE, et al. Plasmacytoid dendritic cells produce cytokines and mature in response to the TLR7 agonists, imiquimod and resiquimod. Cell Immunol 2002;218:74-86.
3. Miller RL, Tomai MA, Harrison CJ, Bernstein DI. Immunomodulation as a treatment strategy for genital herpes: review of the evidence. Int Immunopharmacol 2002;2:443-51.
4. Berman B, Sullivan T, De Araujo T, Nadji M. Expression of Fas-receptor on basal cell carcinomas after treatment with imiquimod 5% cream or vehicle. Br J Dermatol 2003;149 Suppl 66:59-61.
5. Vidal D, Matias-Guiu X, Alomar A. Efficacy of imiquimod for the expression of Bcl-2, Ki67, p53 and basal cell carcinoma apoptosis. Br J Dermatol 2004;151:656-62.
6. Meyer T, Nindl I, Schmook T, Ulrich C, Sterry W, Stockfleth E. Induction of apoptosis by Toll-like receptor-7 agonist in tissue cultures. Br J Dermatol 2003;149 Suppl 66:9-14.
7. Ratner D, Skouge JW. Surgical management of local disease. In: Miller SJ, Maloney ME, editors.

Cutaneous oncology: pathophysiology, diagnosis and management. Malden (MA): Blackwell Science; 1997:664-71.
8. Beutner KR, Geisse JK, Helman D, Fox TL, Ginkel A, Owens ML. Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. J Am Acad Dermatol 1999;41:1002-7.
9. Marks R, Gebauer K, Shumack S, Amies M, Bryden J, Fox TL, et al. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multicenter 6-week dose-response trial. J Am Acad Dermatol 2001; 44:807-13.
10. Geisse JK, Rich P, Pandya A, Gross K, Andres K, Ginkel A, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: a double-blind, randomized, vehicle-controlled study. J Am Acad Dermatol 2002;47:390-8.
11. Sterry W, Ruzicka T, Herrera E, Takwale A, Bichel J, Andres K, et al. Imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinoma: randomized studies comparing low-frequency dosing with and without occlusion. Br J Dermatol 2002;147: 1227-36.
12. Geisse J, Caro I, Lindholm J, Golitz L, Stampone P, Owens M. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatol 2004;50:722-33.
13. Eklind J, Tartler U, Maschke J, Lidbrink P, Hengge UR. Imiquimod to treat different cancers of the epidermis. Dermatol Surg 2003;29:890-6.
14. Chen TM, Rosen T, Orengo I. Treatment of a large superficial basal cell carcinoma with 5% imiquimod: a case report and review of the literature. Dermatol Surg 2002;28:344-6.
15. Florez A, Feal C, de la Torre C, Cruces M. Invasive squamous cell carcinoma treated with imiquimod 5% cream. Acta Derm Venereol 2004;84:227-8.
16. Oster-Schmidt C. Two cases of squamous cell carcinoma treated with topical imiquimod 5%. J Eur Acad Dermatol Venereol 2004;18:93-5.
17. Hengge UR, Schaller J. Successful treatment of invasive squamous cell carcinoma using topical imiquimod. Arch Dermatol 2004;140:404-6.
18. Mackenzie-Wood A, Kossard S, de Launey J, Wilkinson B, Owens ML. Imiquimod 5% cream in the treatment of Bowen's disease. J Am Acad Dermatol 2001;44: 462-70.
19. Euvrard S, Kanitakis J, Pouteil-Noble C, Dureau G, Touraine JL, Faure M, et al. Comparative epidemiologic study of premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. J Am Acad Dermatol 1995;33(2 Pt 1): 222-9.
20. Smith KJ, Germain M, Skelton H. Bowen's disease (squamous cell carcinoma in situ) in immunosuppressed patients treated with imiquimod 5% cream and a cox inhibitor, sulindac: potential applications for this combination of immunotherapy. Dermatol Surg 2001; 27:143-6.
21. Smith KJ, Germain M, Skelton H. Squamous cell carcinoma in situ (Bowen's disease) in renal transplant patients treated with 5% imiquimod and 5% 5-fluorouracil therapy. Dermatol Surg 2001;27: 561-4.
22. Pehoushek J, Smith KJ. Imiquimod and 5% fluorouracil therapy for anal and perianal squamous cell carcinoma in situ in an HIV-1-positive man. Arch Dermatol 2001; 137:14-6.
23. Cook-Bolden F, Weinberg JM. Topical imiquimod 5% cream in the treatment of Bowen's disease of the penis. J Am Acad Dermatol 2002;46:146-7.
24. Arlette JP. Treatment of Bowen's disease and erythroplasia of Queyrat. Br J Dermatol 2003;149 Suppl 66:43-9.
25. Richter ON, Petrow W, Wardelmann E, Dorn C, Kupka M, Ulrich U. Bowenoid papulosis of the vulva-immunotherapeutical approach with topical imiquimod. Arch Gynecol Obstet 2003;268:333-6.
26. Petrow W, Gerdsen R, Uerlich M, Richter O, Bieber T. Successful topical immunotherapy of bowenoid papulosis with imiquimod. Br J Dermatol 2001;145: 1022-3.
27. Padlewska K, Ramoz N, Cassonnet P, Riou G, Barrois M, Majewski S, et al. Mutation and abnormal expression of the p53 gene in the viral skin carcinogenesis of epidermodysplasia verruciformis. J Invest Dermatol 2001;117:935-42.
28. Wieland U, Jurk S, Weissenborn S, Krieg T, Pfister H, Ritzkowsky A. Erythroplasia of queyrat: coinfection with cutaneous carcinogenic human papillomavirus type 8 and genital papillomaviruses in a carcinoma in situ. J Invest Dermatol 2000;115:396-401.
29. Meyer T, Arndt R, Christophers E, Nindl I, Stockfleth E. Importance of human papillomaviruses for the development of skin cancer. Cancer Detect Prev 2001; 25:533-47.
30. Thai KE, Sinclair RD. Treatment of Bowen's disease of the penis with imiquimod. J Am Acad Dermatol 2002; 46:470-1.
31. Cornejo P, Vanaclocha F, Polimon I, Del Rio R. Intralesional interferon treatment of lentigo maligna. Arch Dermatol 2000;136:428-30.
32. Schon MP, Wienrich BG, Drewniok C, Bong AB, Eberle J, Geilen CC, et al. Death receptor-independent apoptosis in malignant melanoma induced by the small-molecule immune response modifier imiquimod. J Invest Dermatol 2004;122:1266-76.
33. Naylor MF, Crowson N, Kuwahara R, Teague K, Garcia C, Mackinnis C, et al. Treatment of lentigo maligna with topical imiquimod. Br J Dermatol 2003;149 Suppl 66:66-70.
34. Powell AM, Russell-Jones R, Barlow RJ. Topical imiquimod immunotherapy in the management of

lentigo maligna. Clin Exp Dermatol 2004;29:15-21.
35. Fisher GH, Lang PG. Treatment of melanoma in situ on sun-damaged skin with topical 5% imiquimod cream complicated by the development of invasive disease. Arch Dermatol 2003;139:945-7.
36. Wolf IH, Richtig E, Kopera D, Kerl H. Locoregional cutaneous metastases of malignant melanoma and their management. Dermatol Surg 2004;30(2 Pt 2): 244-7.
37. Wolf IH, Smolle J, Binder B, Cerroni L, Richtig E, Kerl H. Topical imiquimod in the treatment of metastatic melanoma to skin. Arch Dermatol 2003; 139:273-6.
38. Steinmann A, Funk JO, Schuler G, von den Driesch P. Topical imiquimod treatment of a cutaneous melanoma metastasis. J Am Acad Dermatol 2000;43:555-6.
39. Ugurel S, Wagner A, Pfohler C, Tilgen W, Reinhold U. Topical imiquimod eradicates skin metastases of malignant melanoma but fails to prevent rapid lymphogenous metastatic spread. Br J Dermatol 2002; 147:621-4.
40. Zampogna JC, Flowers FP, Roth WI, Hassenein AM. Treatment of primary limited cutaneous extramammary Paget's disease with topical imiquimod monotherapy: two case reports. J Am Acad Dermatol 2002;47(4 Suppl):S229-35.
41. Berman B, Spencer J, Villa A, Poochareon V, Elgart G. Successful treatment of extramammary Paget's disease of the scrotum with imiquimod 5% cream. Clin Exp Dermatol 2003;28 Suppl 1:36-8.
42. Rudy SJ. Imiquimod (Aldara): modifying the immune response. Dermatol Nurs 2002;14:268-70.
43. Kaidbey K, Owens M, Liberda M, Smith M. Safety studies of topical imiquimod 5% cream on normal skin exposed to ultraviolet radiation. Toxicology 2002;178: 175-82.