REVIEW ARTICLE

Drugs 2007; 67 (6): 915-934
0012-6667/07/0006-0915/$49.95/0

Pharmacological Treatments for Basal Cell Carcinoma

Seongmu Lee,[1] *Dinesh Selva*,[2,3] *Shyamala C. Huilgol*,[4] *Robert A. Goldberg*[1] and *Igal Leibovitch*[1,2]

1 Division of Orbital and Ophthalmic Plastic and Reconstructive Surgery, and the Department of Ophthalmology, David Geffen School of Medicine at UCLA, Jules Stein Eye Institute, Los Angeles, California, USA
2 Department of Ophthalmology and Visual Sciences, University of Adelaide, South Australia, Australia
3 South Australian Institute of Ophthalmology, Adelaide, South Australia, Australia
4 Department of Dermatology, Royal Adelaide Hospital, University of Adelaide, South Australia, Australia

Contents

Abstract

Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer, and its incidence continues to rise. Current management options are numerous and focus on tumour eradication while maximising cosmetic and functional capacity. Although surgery continues to be considered the main treatment modality, new pharmacological agents, such as immunomodulators, topical chemotherapeutic agents and photodynamic therapy, have emerged and show promising results. Pharmacological agents offer the potential for lower morbidity and improved tissue preservation compared with surgery and radiotherapy. However, pharmacological treatments possess higher failure rates when compared with surgery, and most studies have investigated only low-risk lesions. Several prospective, randomised, double-blind, vehicle-controlled studies have established the efficacy of imiquimod for superficial BCC.

This review summarises the evidence regarding the mechanism, efficacy and safety of pharmacological agents based on the literature from the past 10 years. Experimental treatments that have been successfully utilised in the treatment of BCC are also discussed. Treatment of BCC with other agents, such as tazarotene, glycoalkaloid (BEC-5) cream, cidofovir and calcium dobesilate have been reported, but further studies are needed to ascertain the efficacy and adverse-effect profiles of these treatments.

Non-melanoma skin cancer is the most common form of cancer in the US, Canada, and Australia.[1-3] Of these cancers, basal cell carcinomas (BCCs) constitute the majority, with an estimated annual incidence ranging from 200 to 400 per 100 000.[1,2] Geographic variablitiy exists and incidence rates of >2% per year have been reported in population-based studies from Australia.[4-6] Additionally, studies have demonstrated an increase in the incidence of BCC worldwide over the past several decades.[7-10] Of even greater concern is evidence that this trend may include aggressive-growth histological subtypes (table I, table II) and involve patients <40 years of age.[11,12]

The majority of BCCs develop on the face, and while typically slow growing and confined to the area of origin, these cancers can be considerably destructive. Given the continued increase in the incidence of BCC and the potential for damage to sensitive areas, treatment modalities that provide effective tumour eradication while optimising cosmetic and functional outcomes are particularly important.

Conventional treatments for BCC typically consist of simple excision, cryosurgery, or curettage and electrodesiccation for low-risk lesions, and surgical excision with frozen section control or Mohs' micrographic surgery (MMS) for high-risk lesions. Surgical excision and MMS offer the advantage of histological evaluation and are associated with excellent long-term cure rates. Five-year efficacy rates exceeding 95% have been reported for primary BCCs treated with surgical excision with frozen section control, although these data are derived primarily from retrospective studies.[16-20] High 5-year recurrence rates of up to 26% have been reported for tumours with margin involvement.[21] MMS is a technique of tumour excision using 'en face' frozen section assessment of the margins. This allows for exceptionally high cure rates and maximal preservation of tissue. The technique is widely used for high-risk tumours, with reported recurrence rates ranging from 1% to 3% for primary tumours and 5–6% for recurrent tumours.[20,22,23]

Radiotherapy utilises ionising radiation, typically high energy photons and charged particles, to induce cell death in target cells, and has been shown to be an effective treatment for BCC. This approach may be particularly useful in elderly patients with tumours in difficult-to-treat locations and in those individuals for whom surgical treatment may not be appropriate. The biological effects of radiation are manifested chiefly by the loss of cellular regenerative capacity as a result of single- and double-strand-

Table I. Histological subtypes of basal cell carcinoma[13,14]

Subtype	Comments
Nodular	Most common (70%) and least invasive subtype
Superficial	10–15% of cases
Microdnodular	More aggressive than the nodular type
Morpheaform/morphoeic	Aggressive subtype
Infiltrative	Aggressive subtype
Basosquamous	Aggressive subtype
Mixed subtypes	

Table II. Features of high risk basal cell carcinoma[15]

Histological
Subtype: morpheaform, basosquamous, infiltrative, micronodular, mixed
Deep and perineural invasion
Clinical
High-risk location (mask areas): central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, temple, ears, hands, or feet
Size: >5–10mm in high-risk locations; >10mm in other areas of face (cheeks, forehead, scalp, neck); >20mm in other areas (trunk, extremities)
Poorly defined borders
Recurrent or incompletely excised tumours
Tumour at site of prior irradiation
Immunosuppression

ed breaks in DNA and indirect damage caused by generation of free radicals.[24] Cure rates of 86–97% have been reported for radiotherapy, with greatest efficacy in smaller, primary BCCs.[25,26] Studies have also suggested that tumour control and recurrence risk are related primarily to tumour size and stage, with higher efficacy rates being reported for stage I and II carcinomas (American Joint Committee on Cancer staging system)[27] and a diameter of <1cm.[28-32] Disadvantages of radiotherapy, however, include lack of tumour margin control, the potential for carcinogenesis, and inferior long-term cosmesis compared with surgery.[33]

Although effective therapies for BCC, these modalities may result in significant scarring, functional deficits, tissue loss and altered pigmentation. Pharmacological agents offer the potential for lower morbidity and improved tissue preservation compared with surgery and radiotherapy. While first-line therapy for BCC often involves surgical intervention, numerous nonsurgical treatments exist, and it is of great interest to ascertain whether these modalities can serve as viable alternatives or adjunctive options for maximising the treatment aims of complete tumour removal with preservation of function and cosmesis. The purpose of this study is to review the evidence regarding the mechanism, efficacy and safety of the wide range of pharmacological treatment modalities for BCC, including topical immunomodulators and chemotherapeutic agents, injection therapies and photodynamic therapy (PDT).

1. Literature Review

We reviewed the relevant medical literature by searching MEDLINE (1995 to February 2006) using the key words 'basal cell carcinoma' and 'treatment' in combination with the following terms: 'immunomodulator', 'imiquimod', 'interferon', 'radiotherapy', '5-fluorouracil', 'aminolevulinic acid', 'photodynamic therapy', 'retinoid', 'tazarotene', 'BEC cream', 'chemotherapy', 'bleomycin', 'paclitaxel', 'cisplatin', 'methotrexate', 'NSAID', 'dobesilate' and 'cidofovir'. Searches focused mainly on human studies published in peer-reviewed English language journals. Manual searches were conducted for cited references from identified trials, recent review articles and major medical textbooks. From these studies, 5424 abstracts were identified and reviewed, and those pertinent to our discussion were selected. Clinical studies were chosen if they were prospective, double-blind, randomised trials investigating the efficacy of a pharmacological agent versus placebo or other treatment modality. For pharmacological agents without studies meeting such criteria, nonrandomised open-label studies involving a larger number of patients with longer-term follow-up and/or histological analysis of lesion site for recurrent or residual disease following treatment were reviewed. Case series and reports that investigated experimental treatments were also included.

2. Pharmacological Agents for the Treatment of Basal Cell Carcinoma

2.1 Topical Immunomodulators

2.1.1 Imiquimod

Mechanism of Action

Imiquimod {1-(2-methylpropyl)-1*H*-imidzo[4,5-C]quinolin-4-amine} is an imidazoquinoline immunomodulator that has been utilised to treat a number of common dermatological conditions, including actinic keratosis and external anogenital warts.[34,35] Its precise mechanism of action, while

not fully understood, involves stimulation of innate and cell-mediated immunity. Studies have shown that imiquimod promotes rapid development of intratumoral inflammatory cell infiltration and Langerhans cell migration from the skin to draining lymph nodes, thereby enhancing antigen presentation.[36,37]

The effects of imiquimod may be mediated in part through the activation of toll-like receptor 7 (TLR7). Toll-like receptors, a family of transmembrane receptors located on the surface of antigen-presenting cells, affect the transcription of pro-inflammatory genes through the recognition of specific microbial structures.[38,39] Activation of TLR7 by imiquimod ligand results in a subsequent upregulation via nuclear factor-κB of various cytokines, including interferon-α, tumour necrosis factor-α, and interleukins (IL) 1, 6 and 12, thereby upregulating the T helper-1 (T_h1) immune response.[39-41]

Imiquimod has been shown to have apoptotic effects *in vitro*.[42,43] One study showed that imiquimod induced apoptosis in squamous cell cancer lines through the activation of caspase and Bcl-2-dependent cytosolic translocation of cytochrome c.[43] Additionally, levels of the anti-apoptotic protein Bcl-2 have been shown to decrease following administration of imiquimod.[36,42] However, studies investigating the expression of Fas and Fas ligand (FasL), which play important roles in programmed cell death, have shown inconsistent results.[43,44] The various actions of imiquimod as an immune response modifier may contribute to its antiviral and antineoplastic properties.

Efficacy

Several randomised, double-blind, vehicle-controlled studies have investigated the short-term therapeutic efficacy of imiquimod 5% cream for the treatment of superficial BCC (table III).[45-47] In a report of two multicentre studies, 724 patients with histologically confirmed superficial BCC were randomised to receive imiquimod once daily five or seven times weekly versus vehicle alone for 6 weeks.[45] Histological clearance rates at 12 weeks post-treatment for the five- and seven-day treatment groups were 82% and 79%, respectively, versus 3% for the vehicle group. A third study of 166 patients treated daily for 6 weeks showed similar results, with histological clearance rates of 80% for the treatment group and 6% for the vehicle group.[46] In another study, treatment for 12 weeks at varying dosages (twice daily, once daily, five times weekly, three times weekly) demonstrated a dose-response gradient, with histological clearance rates of 100% (10/10), 87.1% (27/31), 80.8% (21/26) and 51.7% (15/29), respectively.[47] Negative predictive values ranged from 91% to 93%, suggesting accurate clinical assessment of tumour absence.[45,46]

Lower cure rates for nodular BCC have been reported for imiquimod.[49,50,52-54] For example, a randomised, double-blind, vehicle-controlled trial in 92 patients investigated the efficacy of imiquimod at varied dose administration schedules for the treatment of nodular BCC.[49] Histological response rates 6 weeks following treatment were 59–76%. Sterry et al.[50] conducted a randomised, open-label study seeking to examine the effect of occlusion following application of imiquimod. Six-week post-treatment results demonstrated lower clearance rates for nodular BCC compared with superficial BCC, with occlusion offering no statistically significant improvement in efficacy. Higher cure rates of 90–94% were reported with curettage followed by imiquimod administration.[52,53]

Two ongoing open-label, multicentre studies are currently investigating the long-term safety and efficacy of imiquimod 5% cream for the treatment of superficial BCC.[55,56] In both studies, patients with evidence of clinical clearance 12 weeks post-treatment were enrolled for long-term follow-up. In one study, following a 6-week treatment with imiquimod five times weekly, 89.6% (163/182) were clinically clear at 12 weeks post-treatment, and 162 patients were enrolled for long-term follow-up of 5 years.[55] At 24-month follow-up, 14 patients who were clinically clear at 12 weeks post-treatment demonstrated clinical evidence of superficial BCC recurrence, and a total of 26 patients were reported to have discontinued from the study for reasons other than recurrence. In the second study, of 157 patients entering the long-term follow-up period, 14

Table III. Comparison of studies investigating imiquimod for the treatment of basal cell carcinoma (BCC)

Study (year)	Design	Subjects	Intervention	Outcome measures	Results	Adverse effects
Geisse et al. (2004)[45]	Prospective, randomised, double-blind, vehicle-controlled	724 patients, sBCC, min 0.5cm^2 area, max 2cm diameter	5% imiquimod cream: 1) 5 × per wk for 6wk 2) 7 × per wk for 6wk	Clinical and histological evidence of BCC 12wk post-treatment	Clinical + histological clearance rate: 1) 5 × per wk: 75% (139/185) 2) 7 × per wk: 73% (130/179) 3) vehicle: 2% (6/360) Histological clearance rate: 1) 5 × per wk: 82% (152/185) 2) 7 × per wk: 79% (142/179) 3) vehicle: 3% (11/360)	At least one adverse event in 58% of 5 × per wk for 6wk group; 64% of 7 × per wk for 6wk group; 36% in vehicle group. Application site reactions most common, including itching, burning and pain
Schulze et al. (2005)[46]	Prospective, randomised, double-blind, vehicle-controlled	166 patients, sBCC, min 0.5cm^2, max 2cm diameter	5% imiquimod cream daily for 6wk	Clinical and histological evidence of BCC 12wk post-treatment	Clinical + histological clearance rate: 77% for treatment group vs 6% for vehicle group Histological clearance rate: 80% for treatment group vs 6% for vehicle group	At least one adverse event in 52% of treatment group; 18% of vehicle group. Application site reactions most common, including itching and burning
Beutner et al. (1999)[48]	Prospective, randomised, double-blind, vehicle-controlled	35 patients, sBCC (28 patients, 0.5–2cm^2), nBCC (7 patients, 0.5–1.5cm^2)	5% imiquimod cream in one of five dosage regimens (24/35) vs vehicle (11/35) Administration 2wk after clinical clearance or up to 16wk	Clinical and histological evidence of BCC 6wk post-treatment	Clearance rates: overall 83% (20/24) 1) bid, 10wk: 100% (7/7) 2) od, 13wk: 100% (4/4) 3) 3 × per wk, 14.5wk: 100% (4/4) 4) 2 × per wk, 16wk: 80% (3/5) 5) 1 × per wk, 16wk: 50% (2/4) 6) vehicle, 16wk: 9% (1/11)	Application site reactions in 92% (22/24) of treatment group, 64% (7/11) in vehicle group, including itching, erythema, papular rash and discharge. Severe local reactions (erosion, induration, ulceration) observed only in bid and od groups
Geisse et al. (2002)[47]	Prospective, randomised, double-blind, vehicle-controlled	128 patients, sBCC (0.5–2cm^2) 24 patients withdrew from treatment portion of study	5% imiquimod cream in one of four dosage regimens for 12wk	Clinical and histological evidence of BCC 6wk post-treatment	Clearance rates: 1) bid: 100% (10/10) 2) od: 87% (27/31) 3) 5 × per wk: 81% (21/26) 4) 3 × per wk: 52% (15/29) 5) vehicle: 19% (6/32)	118/128 reported at least one adverse event. Most frequently reported application site reactions included itching, pain and tenderness at application site

Continued next page

Table III. Contd

Study (year)	Design	Subjects	Intervention	Outcome measures	Results	Adverse effects
Schumack et al. (2002)[49]	Prospective, randomised, double-blind, vehicle-controlled	92 patients, nBCC (0.5–1.5cm^2)	5% imiquimod cream in one of three dosage regimens for 12wk	Clinical and histological evidence of BCC 6wk post-treatment	Clearance rates: 1) daily for 7 days/wk: 76% (16/21) 2) daily for 5 days/wk: 70% (16/23) 3) daily for 3 days/wk: 60% (12/20) 4) vehicle: 13% (3/24)	Local skin reactions in all treatment groups, mild to moderate in intensity. Eight patients discontinued because of local skin reactions. Application site reactions most common, including itching, tenderness and burning
Sterry et al. (2002)[50]	Two prospective, randomised, open-label	Study 1: 93 patients, sBCC (0.5–2cm^2) Study 2: 90 patients, nBCC (0.25–1.5cm^2)	Four groups: 5% imiquimod cream 2 × per wk or 3 × per wk with and without occlusion	Clinical and histological evidence of BCC 6wk post-treatment	Clearance rates: 1) 3 days/wk, occlusion: 87% (sBCC, 20/23) / 65% (nBCC, 15/23) 2) 3 days/wk, no occlusion: 76% (sBCC, 19/25) / 50% (nBCC, 12/24) 3) 2 days/wk, occlusion: 43% (sBCC, 9/21) / 50% (nBCC, 11/22) 4) 2 days/wk, no occlusion: 50% (sBCC, 12/24) / 57% (nBCC, 12/21)	Application site reactions in all treatment groups. Four with severe adverse events. Most frequently reported adverse events included itching, burning and hypopigmentation
Shumack et al. (2004)[51]	Prospective, nonrandomised, open-label	66 patients, sBCC >2cm in one dimension (median 4.3cm^2)	5% imiquimod cream 5 × per wk for 6wk	Clinical and histological evidence of BCC in punch biopsy specimens 12 wks post-treatment	83% overall clearance of all treated tumours: 1) 2–5.9 cm^2 (n = 45): 89% 2) 6–9.9 cm^2 (n = 16): 81% 3) 10–13.9 cm^2 (n = 3): 33% 4) >14 cm^2 (n = 2): 50%	Not specifically discussed
Wu et al. (2006)[52]	Prospective, nonrandomised, open-label	17 patients (34 lesions), nBCC	Curettage without electrodesiccation + 5% imiquimod cream daily for 6–10wk; (6 lesions with 30 applications, 1 lesion with 28 applications)	Clinical and histological evidence of BCC 12wk post-treatment	32/34 lesions histologically cleared of BCC	Local skin reactions at tumour site and surrounding area: erythema 74%, scabbing/crusting 47%, flaking/scaling 44% and erosion 44%
Spencer (2006)[53]	Prospective, randomised, double- blind, vehicle-controlled	20 patients, histologically confirmed nBCC	Curettage with electrodesiccation + 5% imiquimod cream (n = 10) or vehicle daily (n = 10) for 4wk	Clinical and histological evidence of BCC 8wk post-treatment	Residual tumour in 10% of treatment group vs 40% of vehicle group	Painless inflammation and crusting beyond the borders of the curettage and electrodesiccation wound

bid = twice daily; **max** = maximum; **min** = minimum; **nBCC** = nodular basal cell carcinoma; **od** = once daily; **sBCC** = superficial basal cell carcinoma.

subjects displayed clinical evidence of BCC recurrence at 24-month follow-up. Histological results of these 14 individuals were available for 11, all of whom had histological evidence of superficial BCC.[56]

Safety

Imiquimod is administered topically and, while its effects are localised primarily to the site of treatment, systemic absorption has been observed in pharmacokinetic studies.[57] In a study of 58 patients with actinic keratosis who were treated with imiquimod 5% cream three times weekly for 16 weeks, mean peak serum concentrations at the end of the treatment period were found to be 0.1, 0.2 and 3.5 ng/mL for the face (dose 12.5mg), scalp (dose 25mg) and hands/arms (dose 75mg), respectively.[58] Systemic absorption increased with dose, but this increase was not proportional. The mean half-life was approximately 24 hours, and urinary excretion was minimal, with mean recoveries of the estimated applied dose ranging from 0.1–2.4%.[57-59]

In all studies, local reactions such as itching, burning and tenderness at the application site were common, with up to 50–60% of individuals reporting at least one adverse event. Other local adverse effects included erythema, erosion, oedema and ulceration, most of which were mild to moderate and well tolerated. Some patients required a temporary cessation of treatment because of the severity of the local site reaction. In addition, a dose-response gradient has been reported, with increases in the incidence and severity of reactions being linked to increased application frequency.[47] While systemic adverse effects were minimal, flu-like symptoms, angioedema and exacerbation of psoriasis have been reported in patients using topical imiquimod.[60-64]

Summary

Imiquimod 5% cream has been shown to be superior to placebo in the treatment of BCC in several randomised, double-blind, vehicle-controlled studies. Adverse effects consisted primarily of local site reactions and were well tolerated. However, these series typically included only smaller superficial BCCs and nodular BCCs, and as such, their results cannot be extrapolated to larger BCCs or those with more aggressive growth patterns. Moreover, studies have suggested less successful cure rates for nodular BCCs than for superficial BCCs. Smaller, open-label studies have suggested similar cure rates for larger BCCs measuring ≥2cm in at least one dimension (treated tumours ranged in size from 2 to 48 cm^2; median 4.3 cm^2) (range 2–48 cm^2; median 4.3 cm^2) but lower rates of 47–58% for multiple BCCs, particularly for lesions located in the lower extremities.[51,65] Furthermore, histological examination was utilised as a surrogate for long-term follow-up in these studies, which could have resulted in residual nests of BCC being missed. Studies investigating long-term cure rates with imiquimod are currently underway.

Imiquimod may be useful for the treatment of primary superficial BCCs in low-risk sites where recurrence is unlikely to result in substantial morbidity, particularly while further studies with long-term follow-up, inclusion of other subtypes of BCC, and head-to-head comparison of imiquimod with other conventional treatment modalities are completed. Adjuvant treatment with imiquimod prior to MMS may diminish tumour size and allow for a smaller cosmetic defect.[66] Higher cure rates are attainable with twice-daily treatment, although local site reactions exhibit a dose-response gradient and may be limiting. Treatment durations of 6 and 12 weeks have been associated with similar cure rates, although longer treatment durations may be required for nodular BCC, and once-daily regimens may provide a balance between an acceptably high cure rate and fewer adverse effects.

2.2 Intralesional Chemotherapy

2.2.1 Interferon

Mechanism of Action

Interferons are a family of naturally occurring glycoproteins that exhibit a broad spectrum of antiviral, immunomodulatory and antiproliferative activities. Three major classes of human interferons exist, classified as type I (interferon-α, interferon-β) and type II (interferon-γ).[67] Binding of specific cell-surface receptors by interferon initiates a series

of intracellular events via the Janus kinase-signal transducer and activator of transcription (Jak/STAT) signalling pathway.[68] Specifically, binding of interferon initiates the activation of two receptor-associated tyrosine kinases, Jak1 and Tyk2, which phosphorylate receptor subunits and transcription factors, including cytosolic STAT proteins. These transcription factors translocate into the nucleus and initiate the transcription of specific target genes within immune cells.[69,70] The effects of interferon include stimulation of macrophage and natural killer cell activity, augmentation of lymphocyte cytotoxicity, promotion of cell differentiation and increased expression of major histocompatibility antigens.[71-75]

Studies have shown that the mechanism by which interferon promotes regression of BCC may be mediated in part through increased expression of Fas, an important component of interferon-induced apoptosis in BCC. In a study of 15 patients with nodular BCC, Buechner et al.[76,77] found that while specimens from untreated patients were strongly positive for FasL, Fas was not detectable. Specimens from interferon-α-treated patients, however, exhibited expression of both Fas and FasL, as well as the presence of a dense dermal lymphoid infiltrate of CD4+ T cells surrounding BCC nests. Elevated levels of Fas and apoptosis have been shown to result from interferon-α-induced inhibition of the sonic hedgehog pathway-induced mitogen-activated Erk-regulating kinase.[78]

Efficacy

The short-term efficacy of recombinant forms of interferon, including interferon-α-2a and interferon-α-2b, have been investigated in multiple studies (table IV). In these, efficacy rates ranging from 67% to 86% with good cosmesis have been reported, although few large, double-blind studies have been conducted.[79-83] A randomised, double-blind, vehicle-controlled trial of 172 patients compared the efficacy of intralesional injections of interferon-α-2b versus vehicle.[83] At 20 weeks, a treatment failure rate of 14% (17/120) was reported for the interferon group versus 71% (30/42) for the placebo group. The cure rate was independent of tumour type and size. Another randomised, open-label study of 45 patients compared the efficacy of intralesional interferon-α-2a, -α-2b and the combination of α-2a and -α-2b in the treatment of superficial, nodular and morphoeic BCC.[82] No increase in effectiveness with combination therapy at 8 weeks post-treatment was seen, with treatment failures of 33.3%, 33.3% and 26.6% being observed on cytological examination for the three types of BCC, respectively. Edwards et al.[81] evaluated the differential effects of different dose administration schedules of intralesional interferon-α-2b, comparing a single dose of 10 million IU versus the same dose once weekly for 3 weeks, in a randomised study of 65 patients. A significant difference was found in favour of weekly injection for 3 weeks, with early treatment failure rates of 48% (16/33) versus 20% (6/30) at 16 weeks post-treatment in the single injection group being documented. The long-term efficacy of perilesional interferon-α-2b was studied in 50 patients with biopsy-proven superficial or nodular BCC.[84] Clinical cures were noted in 95/98 lesions, with a mean follow-up of 10.5 years (range 9 months to 18.5 years; 31% had <10 years' follow-up).

Safety

The most frequently reported adverse effects of interferon consisted of local reactions at the site of injection, which included erythema, oedema and tenderness. Local inflammatory reactions were typically graded as moderate.[79] However, injections of interferon were also associated with flu-like symptoms of fever, chills, headache, myalgia, nausea and vomiting, particularly within the first few weeks following treatment initiation.[85] In one study, 82% of patients experienced at least one severe adverse reaction, defined as necessitating an interruption in daily activities.[81] Fever, rigors and myalgia were relatively common, with 83%, 82% and 75%, respectively, reporting such adverse reactions in the same study. In a randomised, open-label study of 45 patients, Alpsoy[82] reported reversible leukopenia in four patients and thrombocytopenia with increased liver function enzymes in two patients receiving interferon therapy. Adverse effects were usually

Table IV. Comparison of studies investigating interferon (IFN) for the treatment of basal cell carcinoma (BCC)

Study (year)	Design	Subjects	Intervention	Outcome measures	Results	Adverse effects
Cornell et al.[83] (1990)	Prospective, randomised, double- blind, vehicle-controlled	165 patients, sBCC, nodulo-ulcerative, mean lesion 83mm^2	IFNα-2b 1.5MU 3 $\times$ per wk for 3wk (n = 130) vs placebo (n = 42)	1) histological evidence of BCC at 20wk 2) cosmetic outcome at 1 year	Response rate: 1) IFNα-2b: 86% (103/120) 2) placebo: 29% (12/42) 3) 83% of patients and 61% of physicians rated cosmetic outcome as excellent for IFN group	Adverse reactions in 75% of IFN group vs 50% of placebo group. Mainly local reactions at injection site and flu-like symptoms, mild or moderate in severity, occurring during treatment period
Alpsoy (1996)[82]	Prospective, randomised, open-label	45 patients, sBCC, nBCC, morphoeic, 0.5-8.9cm^2	IFNα-2a, IFNα-2b, or combination of both in doses of 15 (lesion size <2 cm^2) or 30MU (lesion size >2 cm^2) 3 $\times$ per wk (total 10 injections)	Clinical and cytological evidence of BCC 8wk post-treatment	Response rate: 1) IFNα-2a: 66.6% (10/15): 8/12 nBCC, 0/1 sBCC, 2/2 morphoeic 2) IFNα-2b: 66.6% (10/15): 7/11 nBCC, 1/2 sBCC, 2/2 morphoeic 3) α-2a plus α-2b: 73.3% (11/15), 9/11 nBCC, 1/2 sBCC, 1/2 morphoeic	Local discomfort at the treatment site in all patients during injection. Almost every patient reported flu-like symptoms, including fever, chills, headache, fatigue and myalgia, especially within first 2wk of treatment
Edwards et al. (1990)[81]	Prospective, randomised, open-label	65 patients, sBCC (2cm largest diameter), nBCC (0.5–1.5cm)	IFNα-2b protamine zinc chelate sustained-release single-dose 10MU vs same dose wkly for 3wk	1) histological evidence of BCC at 16wk 2) cosmetic outcome, independent ratings by patient and investigator	Response rate: 1) single injection: 52% (17/33) 2) 3 $\times$ weekly: 80% (24/30) Cosmetic outcome: 51% excellent, 22% very good, 14% good, 10% satisfactory, 3% poor	All patients with at least one adverse reaction, particularly flu-like symptoms (fever, rigor, myalgia, headache, nausea). Reactions began on day of treatment, generally lasting 5–8h
Kowalzick et al. (2002)[79]	Prospective, nonrandomised, open-label	139 patients, problematic BCC (i.e. location, patient refusal to undergo surgery or radiotherapy)	Intratumoral rIFNα-1a 3 $\times$ per wk for 3wk, (total dose = 9.0MU)	1) clinical and histological evidence of BCC 16wk post-treatment initiation 2) cosmetic outcome, patient rating	1) response rate: 66.9% 2) cosmetic result: 83% rated as good or very good	Local reactions, erythema most commonly reported symptom, 48% moderate, 35% intense, 6% very intense. 81 systemic adverse reactions in 32 patients
Tucker et al. (2006)[84]	Retrospective, nonrandomised	50 patients (98 lesions), sBCC, nBCC treated during 1985-1992	Nine total perilesional and intradermal injections of 5 million units of IFNα-2b over 3–6wk	Clinical evidence of BCC	95/98 lesions clinically free of tumour at final follow-up visit (mean 10.5y, range 9 months to 18.5y, 31% with <10y follow-up)	Flu-like symptoms in all patients, well tolerated

nBCC = nodular basal cell carcinoma; **rIFN** = recombinant interferon; **sBCC** = superficial basal cell carcinoma.

transient and were typically successfully moderated with paracetamol (acetaminophen).

Summary

Interferon has been shown to be superior to placebo in a randomised, double-blind, vehicle-controlled study for the treatment of BCC.[83] However, studies have suggested high failure rates for aggressive subtypes of BCC, with only 4 of 15 patients exhibiting a complete response to intralesional injections of interferon-α-2b in one study.[86] Additional randomised, double-blind, vehicle-controlled studies with long-term follow-up are needed to better characterise the efficacy and safety profile of interferon for the treatment of BCC, particularly with respect to more aggressive subtypes.

The major limitation of interferon is the high incidence of systemic adverse effects that can disrupt the daily activities of patients during treatment. This may prevent interferons from being commonly utilised as a treatment modality for BCC, given that similarly effective but better tolerated alternatives are available.[87]

2.2.2 Fluorouracil

Mechanism of Action

Fluorouracil is a pyrimidine antimetabolite that exerts its cytotoxic effect primarily by blocking DNA formation through inhibition of thymidylate synthetase. Specifically, fluorouracil is converted through a series of steps into fluorodeoxyuridine monophosphate, which, through its covalent interaction with thymidylate synthetase, inhibits the formation of thymidylate from uracil. This results in a deficiency of thymidylate, a precursor of thymidine phosphate, one of four deoxyribonucleotides necessary for DNA synthesis. Additional effects of fluorouracil include misincorporation into DNA leading to single strand breaks and aberrant incorporation into RNA, with subsequent interference with normal RNA function.[88,89] Rapidly multiplying tumour cells, which require more DNA and RNA because of their proliferative activities, are therefore most sensitive to the cytotoxic effects of fluorouracil.

Efficacy

Many studies have investigated the efficacy of fluorouracil for the treatment of BCC over the past 40 years (table V), although well designed, randomised, double-blind, vehicle-controlled trials are limited. While clinical resolution of up to 90% of superficial BCCs has been reported with fluorouracil, treatment of other BCCs – including non-superficial, nodular and recurrent lesions – has been associated with lower reported cure rates, and one study reported a 5-year recurrence rate of 21%.[89-91] The efficacy of six treatment regimens of fluorouracil/epinephrine gel was investigated in an open-label, randomised study of 122 patients with biopsy-proven superficial and nodular BCCs.[92] At 12 weeks post-treatment, analysis of excision specimens revealed an overall efficacy rate of 91%, with no statistically significant difference among regimens. A double-blind, randomised pilot study of 13 patients suggested that use of a phosphatidyl choline-based cream versus a petrolatum-based cream may improve cure rates.[93] Relatively high recurrence rates have been reported with longer-term follow-up, ranging from 21% to as high as 72%, with higher rates for non-superficial and recurrent BCCs.[89-91] Reports have suggested that combination therapy with cryotherapy may improve cure rates.[94] Furthermore, studies have shown that treatment with fluorouracil may result in an apparent clinical cure despite persistent dermal disease, which may account for higher rates of recurrence for non-superficial BCCs.[95,96]

Safety

Adverse effects of fluorouracil are typically confined to the site of treatment and include transient, moderate to severe stinging, erythema, oedema, ulceration and erosions.[92,93] Romagosa et al.[93] reported a high occurrence of hyperpigmentation (83%) and ulceration (43%) at the site of treatment. Although a rapid inflammatory reaction is thought to be an indication of treatment efficacy, reactions may be severe, with serous oozing and secondary infections. Rare cases of contact dermatitis have been reported, as well as photosensitivity during treatment periods. Uncommon adverse effects re-

Table V. Comparison of studies investigating fluorouracil (FU) for the treatment of basal cell carcinoma (BCC)

Study (year)	Design	Subjects	Intervention	Outcome measures	Results	Adverse effects
Romagosa et al.[93] (2000)	Prospective, randomised, double-blind	13 patients (17 lesions), nonsuperficial BCC ≥0.7cm in diameter	FU in phosphatidyl choline vs FU in petrolatum bid for 4wk	Histological evidence of BCC at 16wk	Response rate: 1) FU in phosphatidyl choline: 90% (9/10) 2) FU in petrolatum: 57% (3/7)	Local irritation, erythema, ulceration and tenderness; well tolerated. Minimal itching and discomfort reported
Miller et al.[92] (1997)	Prospective, randomised, open-label	122 patients, size 6–15mm largest diameter, median 80 mm^2	FU/epinephrine gel, six treatment regimens	Histological evidence of BCC 12wk post-treatment	Overall efficacy: 91% 1) 1.0mL 1 × per wk for 6wk: 90% (18/20) 2) 0.5mL 1 × per wk for 3wk: 95% (20/21) 3) 1mL 2 × per wk for 3wk: 94% (17/18) 4) 0.5mL 2× per wk for 3 wk: 79% (15/19) 5) 0.5mL 2 × per wk for 4wk: 90% (19/21) 6) 0.5mL 3 × per wk for 2wk: 100% (17/17)	Transient, moderate to severe stinging, burning and pain at time of injection. Erythema, swelling, desquamation and erosions. Hyperpigmentation (83%) and ulceration (47%)

ported following topical fluorouracil administration include myocardial ischaemia, systemic toxicity, hypertrophic scarring and bullous pemphigoid.[89,97,98]

Summary

Topical fluorouracil has been shown to be an effective treatment modality for superficial BCC, particularly for multiple superficial BCCs at low-risk locations, such as may be found in patients with basal cell nevus syndrome.[89,99] However, high recurrence rates have been reported with longer-term follow-up, particularly with high-risk BCCs, and well designed trials are scarce. Adverse effects are typically moderate to severe and localised to the site of treatment, although severe adverse events may occur uncommonly. An important limitation of fluorouracil is evidence suggesting incomplete destruction of tumour in deeper cells. Post-treatment biopsies of lesions with clinical appearance of cure have demonstrated persistent dermal disease.[95,96] On the basis of these findings, the role of fluorouracil may be limited to treatment of superficial BCCs in low-risk locations.

2.2.3 Other Chemotherapeutic Agents

Chemotherapeutic agents, including bleomycin and cisplatin, have been investigated for the treatment of BCC, particularly in studies utilising adjunctive electric pulses to enhance entry of drug into target cells.[100-103] Glass et al.[102] treated 20 patients (54 lesions) with intralesional bleomycin and electric pulses delivered through needle electrodes. A response rate of 98% (53/54 lesions) was reported 6 weeks after treatment, with no evidence of tumour on histopathology. Adverse effects included erythema, crusting and ulceration. Studies utilising intravenous chemotherapy for metastatic BCC have shown relative unresponsiveness, although some studies have reported limited success.[104-108]

2.3 Photodynamic Therapy (PDT)

PDT utilises the combination of light, a photosensitiser and oxygen to selectively damage and destroy pathological cells. Following the uptake of administered photosensitiser into the target tissue,

exposure to light of a specific wavelength activates a cascade of reactive oxygen species, resulting in cell death.[109-111] In addition to direct cytotoxicity, vascular damage resulting in tissue infarction, apoptosis through stimulation of multiple signal transduction reactions, and upregulation of immune mediators, such as IL-1 and IL-6, have been shown to further promote tumour destruction.[112-115]

Porfimer sodium, a haematoporphyrin derivative, was among the earlier photosensitisers utilised in PDT. While effective and widely used for the treatment of non-dermatological tumours such as oesophageal and lung cancers, its limitations of prolonged photosensitivity associated with systemic administration, low initial selectivity between neoplastic and normal tissue, and long duration requirement between administration of the photosensitiser and exposure to light have led to a general preference for topical photosensitisers for the treatment of superficial lesions.[116,117]

2.3.1 Topical PDT

Mechanism of Action

Topical PDT involves the application of the prodrug aminolaevulinic acid or its derivatives, such as methyl aminolaevulinate, which are metabolised intracellularly by the intrinsic haem biosynthetic pathway into photoactive porphyrins, particularly protoporphyrin IX.[109,118,119] Selective accumulation of protoporphyrin IX in neoplastic tissue compared with normal tissue occurs after administration of aminolaevulinic acid and is thought to be due, in part, to abnormal architectural changes and diminished integrity in the epidermal layers of diseased tissue, subsequently resulting in increased permeability and penetration of aminolaevulinic acid through cellular membranes.[120,121] Additional factors contributing to preferential accumulation of protoporphyrin IX in neoplastic cells may involve variations in specific transport systems, altered activities of enzymes in the haem biosynthetic pathway, and disparities in iron availability and uptake.[122]

Efficacy

Multiple studies have investigated the short-term efficacy of topical PDT for the treatment of BCC (table VI), although well designed studies with randomisation, double-blind analysis, post-treatment histopathology, and long-term follow-up are limited. Moreover, many studies lack specific endpoints and instead utilise clinical observations to assess efficacy. While response rates for superficial BCC range from 79% to 100% with good cosmesis, lower rates of <50% have been reported for pigmented and morphoeic BCCs, and recurrence rates of up to 63% have been reported.[110,123-136] However, another study has suggested longer-term maintenance of cure rates at 1 year post-treatment.[137] Postulated reasons for lower efficacy rates for other subtypes when compared with superficial BCCs include inability to administer light to deeper tumour depths and absorption of photoactivating light by melanin.[138,139] It has also been suggested that tumour thickness and subsequent depth of photosensitiser penetration may be an important determinant of efficacy.[140]

The effectiveness of aminolaevulinic acid-PDT and cryotherapy in the treatment of superficial and nodular BCC was compared in a non-blinded, phase III clinical trial of 88 patients.[132] Histologically verified recurrence rates at 1 year were statistically comparable between the two modalities: 25% (11/44) for the PDT group and 15% (6/39) for the cryosurgery group. Cosmetic outcome, including scarring and pigmentation defects, was superior in the PDT group. Rhodes et al.[141] conducted a randomised study comparing methyl aminolaevulinate-PDT versus standard excision surgery for the treatment of histologically confirmed nodular BCC in 101 patients. Lesions with an incomplete response to PDT received an additional treatment cycle. Complete response rates assessed clinically at 3 months post-treatment were 98% for the surgical group and 91% for the PDT group. There was higher recurrence in the PDT group than the surgical group, with 85% versus 60% of patients being free of tumour at 2 years' follow-up, respectively. A third randomised study investigated the short-term efficacy of methyl aminolaevulinate-PDT compared with

Table VI. Comparison of studies investigating topical photodynamic therapy (PDT) for the treatment of basal cell carcinoma (BCC)

Study (year)	Design	Subjects	Intervention	Outcome measures	Results	Adverse effects
Wang et al.[132] (2001)	Prospective, randomised, open-label	88 pts, sBCC, nBCC	ALA-PDT (47 lesions, 22 sBCC, 25 nBCC) or cryosurgery, two freeze-thaw cycles (41 lesions, 17 sBCC, 24 nBCC); re-treatment (13 pts) for partial responses	1) Clinical and histological evidence of BCC in punch biopsy specimens 12 months post-treatment 2) Cosmetic outcome (scarring, tissue defects, pigmentation) 12 months post-treatment, grading by physician and two non-medical scientists	Histological recurrence rate at 12 months: 1) PDT group: 25% (11/44; 8/21 sBCC, 3/23 nBCC) Cryotherapy group: 15% (6/39; 1/15 sBCC, 5/24 nBCC) 2) Cosmetic outcomes significantly better with PDT	Trend towards increased pain and discomfort during and after treatment with PDT than cryotherapy. Other adverse effects included leakage, oedema and crusting
Rhodes et al.[141] (2004)	Prospective, randomised, open-label	101 pts, nBCC	MAL-PDT (52 pts), simple surgical excision (49 pts)	1) Clinical inspection for evidence of lesion 3 months post-treatment 2) Cosmetic outcome, investigator- and patient-rated, 4 point scale at 3, 12 and 24 months	Complete clinical response rate: 1) PDT group: 91% (48/53) Surgery group: 98% (51/52) 2) Cosmetic result favourable in PDT group vs surgery group	Adverse events reported by 52% (27/52) in PDT group vs 29% (14/49) in surgery group. Most transient and local, included burning, pain and erythema
Foley[142] (2003)	Prospective, randomised, double-blind, vehicle-controlled	66 pts, nBCC	MAL-PDT vs placebo cream; re-treatment of lesions with partial response at 3 months	Histological evidence of BCC 6 months post-treatment	Response rate: PDT group: 68% Placebo group: 19%	Transient local reactions, mild to moderate, without systemic or serious adverse events
Thissen et al.[143] (2000)	Prospective, nonrandomised, open-label	23 pts (24 lesions), nBCC	ALA-PDT 3wk after prior debulking	1) Clinical and histological evidence of BCC 12wk post-treatment 2) Cosmetic results, investigator- and patient-rated	1) Complete response in 92% (22/24) 2) Cosmesis good (1/22 cured BCCs), excellent (21/22 cured BCCs)	Erythema, oedema in all treated lesions. No other serious adverse effects reported
Haller et al.[136] (2000)	Prospective, nonrandomised, open-label	6 pts (26 lesions), sBCC	ALA-PDT, double treatment, 7-day interval between treatment sessions	Clinical evidence of BCC	4% recurrence rate, median follow-up 27 months (range: 15–45 months)	Not discussed

ALA = aminolaevulinic acid; **MAL** = methyl aminolaevulinate; **nBCC** = nodular basal cell carcinoma; **pts** = patients; **sBCC** = superficial basal cell carcinoma.

placebo cream in 66 patients with nodular BCC. Lesions were prepared prior to PDT with debridement/debulking, and patients with partial responses at 3 months were re-treated. Histologically confirmed response rates at 6 months post-treatment were 68% for methyl aminolaevinulate-PDT versus 19% for placebo, with higher response rates seen for lesions of the face compared with the extremities or trunk.[142]

Attempts to reduce recurrence, enhance tissue absorption, and improve efficacy through multiple treatment sessions, curettage of lesions prior to treatment, and adjunctive dimethylsulfoxide or deferoxamine, have resulted in increased response rates, although well designed, randomised, double-blind studies specifically investigating these methods are lacking.[136,143-146] Thissen et al.[143] conducted a nonrandomised open-label study of 23 patients who were treated with aminolaevulinic acid-PDT for 3 weeks following prior curettage; the histological clearance rate 3 months post-treatment was 92%. Haller et al.[136] treated six patients with 26 histologically confirmed superficial BCCs with a second treatment of aminolaevulinic acid-PDT 1 week following initial treatment. The clinical response rate was 100% at 1 month, with a 4% relapse rate at a median follow-up of 27 months (range 15–45 months). These findings suggest the possibility of heterogeneous accumulation of photosensitiser with initial administration that may be ameliorated with a second treatment. Ester derivatives of aminolaevulinic acid have also been developed to enhance lipophilicity and improve tissue penetration.[147]

Safety

Adverse events after topical photodynamic therapy most commonly consist of local site reactions, including burning, stinging, crusting, erythema, and transient pigmentary changes at the treatment site. Local reactions, transient and mild in severity, were reported in as many as 79% of patients that underwent photodynamic therapy.[148] Higher pain scores have been reported for 5-aminolaevulinic acid compared with 5-aminolaevulinic methylester.[149] Systemic administration is associated with prolonged photosensitivity and adverse effects such as hyperthermia, nausea, vomiting, headache and myalgias.[117] Hence, following administration of photosensitiser, exposure to sunlight or bright indoor light should be avoided. Wang et al.[132] reported a shorter healing time with aminolaevulinic acid-PDT than with cryotherapy, as manifested by less leakage and oedema. Rarely, allergic reactions to the porphyrin component may occur, and caution must be exercised in patients with known photosensitivity disorders, porphyria or porphyrin allergies.

Summary

Topical PDT has shown promising results with good cosmesis in the treatment of BCC in a prospective, randomised, double-blind, vehicle-controlled study, although most studies investigating PDT were nonrandomised and relied on clinical observations for efficacy analysis.[142] However, high recurrence rates (up to 63%) have been reported with longer-term follow-up. PDT may be useful in the treatment of superficial BCCs, particularly in those patients who are not amenable to surgery because of large lesion size or multiple lesions, although treatment of larger skin areas may result in increased pain.[150] Adverse events are typically local site reactions and generally mild in severity. Additional studies with randomised, double-blind design and long-term follow-up are needed to better characterise the efficacy and safety profile of photodynamic therapy for BCC, particularly with respect to aggressive subtypes, adjunctive methods seeking to enhance tissue penetration, optimal number of treatments, and best time interval between drug and exposure to light. Standardised investigation of time intervals may prove important, given that studies have shown that a short interval promotes accumulation of sensitiser primarily in the intravascular compartment, resulting in thrombus formation and indirect killing.[151,152] A longer duration, on the other hand, may promote localisation to the extravascular compartment via vascular leakage and interstitial diffusion. Until these considerations are addressed in further studies, PDT should be considered investigational and limited to the treatment of superficial BCCs in low-risk areas where recurrence is unlikely to result in significant morbidity.

2.4 Other Agents

The continued increase in the incidence of BCC worldwide has prompted many studies evaluating the efficacy of various other treatment modalities seeking to eradicate tumour effectively while maximising cosmetic and functional outcomes. Experimental treatments reported to have achieved successful results include tazarotene, glycoalkaloid (BEC-5) cream, cidofovir and calcium dobesilate.

Retinoids, as modulators of epithelial cell differentiation, have been investigated as chemopreventive treatments for a number of conditions, including liver and lung malignancies, psoriasis and actinic keratosis.[153] The efficacy of tazarotene, a topical retinoid, was studied in an open-label pilot study of 20 patients with 30 lesions: a 53% (16/30) response rate was reported.[154] Despite a lower cure rate compared with other modalities, studies have suggested a potential utility of retinoids as a viable treatment for BCC by showing decreased expression of retinoid-induced tumour suppressor in skin cancer and inhibition of BCC formation in mouse models by tazarotene.[155,156] BEC-5 cream, a mixture of glycoalkaloid derived from a plant source, was compared with vehicle and revealed a 1-year cure rate of 52% (32/62) versus 16% (5/32), respectively, without major adverse effects.[157]

Aspirin (acetylsalicylic acid) and other NSAIDs have been shown to inhibit BCC tumour growth *in vitro*.[158] In addition, Buckman et al.[159] demonstrated an increase in the expression of cyclo-oxygenase-2 (COX-2) in response to UVB irradiation, and several studies have shown COX-2 upregulation in epithelial tumours, including colorectal, breast and lung cancers. Administration of the COX-2 inhibitor celecoxib has been shown to prevent new tumour formation following photocarcinogenesis in a murine model, although there was no regression of established tumours.[158] These studies suggest a protective effect of NSAIDs, although a large, long-term trial reported that alternate-day use of aspirin did not lower the risk of total (nonmelanoma skin cancer excluded), breast and colorectal cancer.[160] However, another recent study has suggested a weak protective effect of NSAIDs against BCC.[161]

Cidofovir, a purine nucleoside analogue of deoxycytidine, has been reported as a treatment for recurrent respiratory papillomatosis, a disease characterised by benign epithelial tumours of the airway.[162] A pilot study of four patients with BCC investigated the efficacy of topical 1% cidofovir and revealed regression of tumour on histological assessment in three of four patients.[163] In addition, Cuevas and Arrazola[164] reported successful treatment of a case of nodular BCC with calcium dobesilate (dihydroxy-2,5 benzenesulfonate), an agent reported to block fibroblast growth factor and to possess antioxidant and angioprotective properties.[165-167]

3. Conclusions

There are numerous treatment modalities for BCC, and various factors need to be considered in treatment selection, including tumour type, location, size, prior recurrence and patient preference. Surgery and radiotherapy appear to offer the highest long-term efficacy rates, but pharmacological treatments are particularly attractive as they offer the potential for lower morbidity and improved cosmesis. However, pharmacological agents possess higher failure rates when compared with surgery, and most studies of pharmacological treatment have investigated only low-risk lesions. Accurate assessment of the different modalities is difficult, because of the relative lack of comparative studies evaluating various treatments and other subtypes of BCC. Many studies are without long-term follow-up and lack specific endpoints such as histological evidence of clearance, but instead rely on clinical observations for efficacy analysis.

However, several prospective, randomised, double-blind, vehicle-controlled studies have established the efficacy of imiquimod for superficial BCC, and this approach is associated with an acceptable adverse effect profile and the additional advantage of simple self application. Interferons, while effective, possess a high incidence of systemic adverse effects that can disrupt the daily activities of patients during treatment. Fluorouracil has been shown to be an effective treatment for superficial BCC, but high recurrence rates have been reported

with long-term follow-up, and well designed trials are lacking. PDT has shown promising results and may be particularly useful for patients with large lesion size or multiple lesions, although most studies investigating PDT were nonrandomised, open-label trials and utilised clinical observation for efficacy analysis.

Additional long-term studies are needed to better establish the efficacy and safety profile of other promising pharmacological agents, particularly with respect to high-risk BCCs. Until these studies are completed, pharmacological modalities may be limited to the treatment of low-risk superficial BCCs for which surgery or radiation may be difficult or contraindicated.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. American Cancer Society. Cancer facts and figures [online]. Available from URL: http://www.cancer.org/docroot/STT/stt_0.asp [Accessed 2006 April]
2. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med 2005; 353 (21): 2262-9
3. Canadian Cancer Society. Canadian cancer statistics 2006 [online]. Available from URL: http://129.33.170.32/ccs/internet/standard/0,3182,3172_14279__langId-en,00.html [Accessed 2007 Feb]
4. Green A, Battistutta D, Hart V, et al. Skin cancer in a subtropical Australian population: incidence and lack of association with occupation. Am J Epidemiol 1996; 144 (11): 1034-40
5. Buettner PG, Raasch BA. Incidence rates of skin cancer in Townsville, Australia. Int J Cancer 1998; 78 (5): 587-93
6. Diepgen TL, Mahler V. The epidemiology of skin cancer. Br J Dermatol 2002; 146 Suppl. 61: 1-6
7. Wong CSM, Strange RC, Lear JT. Basal cell carcinoma. BMJ 2003; 327 (7418): 794-8
8. de Vries E, Louwman M, Bastiaens M, et al. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. J Invest Dermatol 2004; 123 (4): 634-8
9. Holme SA, Malinovszky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales, 1988-98. Br J Dermatol 2000; 143 (6): 1224-9
10. Preston DS, Stern, RS: Nonmelanoma cancers of the skin. N Engl J Med 1992; 327 (23): 1649-62
11. Christenson LJ, Borrowman TA, Vachon CM, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA 2005; 294 (6): 681-90
12. Wrone DA, Swetter SM, Egbert BM, et al. Increased proportion of aggressive-growth basal cell carcinoma in the Veterans Affairs population of Palo Alto, California. J Am Acad Dermatol 1996; 35 (6): 907-10
13. Saldanha G, Fletcher A, Slater DN. Basal cell carcinoma: a dermatopathological and molecular biological update. Br J Dermatol 2003; 148 (2): 195-202
14. Rippey JJ. Why classify basal cell carcinomas? Histopathology 1998; 32 (5): 393-8
15. National Comprehensive Cancer Network. Clinical practice guidelines in oncology v.1.2007. Basal cell skin cancer [online]. Available from URL: http://www.nccn.org/professionals/physician_gls/PDF/nmsc.pdf [Accessed 2007 Feb 5]
16. Silverman MK, Kopf AW, Bart RS, et al. Recurrence rates of treated basal cell carcinomas: part 3. Surgical excision. J Dermatol Surg Oncol 1992; 18 (6): 471-6
17. Griffiths RW, Suvarna SK, Stone J. Do basal cell carcinomas recur after complete conventional surgical excision? Br J Plast Surg 2005; 58 (6): 795-805
18. Smeets NW, Krekels GA, Ostertag JU, et al. Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial. Lancet 2004; 364 (9447): 1766-72
19. Bart RS, Schrager D, Kopf AW, et al. Scalpel excision of basal cell carcinomas. Arch Dermatol 1978; 114 (5): 739-42
20. Rowe DE, Carroll RJ, Day CL Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. J Dermatol Surg Oncol 1989; 15 (3): 315-28
21. Nagore E, Grau C, Molinero J, et al. Positive margins in basal cell carcinoma: relationship to clinical features and recurrence risk: a retrospective study of 248 patients. J Eur Acad Dermatol Venereol 2003; 17 (2): 167-70
22. Leibovitch I, Huilgol SC, Selva D, et al. Basal cell carcinoma treated with Mohs surgery in Australia: II. Outcome at 5-year follow-up. J Am Acad Dermatol 2005; 53 (3): 452-7
23. Smeets NW, Kuijpers DI, Nelemans P, et al. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face: results of a retrospective study and review of the literature. Br J Dermatol 2004; 151 (1): 141-7
24. Mundt AJ, Roeske JC, Weichelbaum RR. Principles of radiation oncology. In Bast RC Jr, Kuff DW, Pollock RE, et al., editors. Cancer Medicine, 5th ed. Hamilton, ON: BC Decker Inc., 2000
25. Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. Int J Radiat Oncol Biol Phys 2004; 60 (2): 406-11
26. Locke J, Karimpour S, Young G, et al. Radiotherapy for epithelial skin cancer. Int J Radiat Oncol Biol Phys 2001; 51 (3): 748-55
27. Carcinoma of the skin. In: American Joint Committee on Cancer. AJCC Cancer Staging Manual, 6th ed. New York (NY): Springer, 2002: 203-8
28. Wilder RB, Kittelson JM, Shimm DS. Basal cell carcinoma treated with radiation therapy. Cancer 1991; 68 (10): 2134-7
29. Wilder RB, Shimm DS, Kittelson JM, et al. Recurrent basal cell carcinoma treated with radiation therapy. Arch Dermatol 1991; 127 (11): 1668-72
30. Silverman MK, Kopf AW, Gladstein AH, et al. Recurrence rates of treated basal cell carcinomas: part 4. X-ray therapy. J Dermatol Surg Oncol 1992; 18 (7): 549-54
31. Lovett RD, Perez CA, Shapiro SJ, et al. External irradiation of epithelial skin cancer. Int J Radiat Oncol Biol Phys 1990; 19 (2): 235-42
32. Griep C, Davelaar J, Scholten AN, et al. Electron beam therapy is not inferior to superficial x-ray therapy in the treatment of

skin carcinoma. Int J Radiat Oncol Biol Phys 1995; 32 (5): 1347-50
33. Petit JY, Avril MF, Margulis A, et al. Evaluation of cosmetic results of a randomized trial comparing surgery and radiotherapy in the treatment of basal cell carcinoma of the face. Plast Reconstr Surg 2000; 105 (7): 2544-51
34. Sauder DN. Immunomodulatory and pharmacologic properties of imiquimod. J Am Acad Dermatol 2000; 43 (1 Pt 2): S6-11
35. Imiquimod 5% cream [online]. Available from URL: http://www. fda.gov/medwatch/safety/2005/aug_PI/Aldara_PI.pdf [Accessed 2006 April]
36. Urosevic M, Maier T, Benninghoff B, et al. Mechanisms underlying imiquimod-induced regression of basal cell carcinoma in vivo. Arch Dermatol 2003; 139 (10): 1325-32
37. Suzuki H, Wang B, Shivji GM, et al. Imiquimod, a topical immune response modifier, induces migration of Langerhans cells. J Invest Dermatol 2000; 114 (1): 135-41
38. Medzhitov R. Toll-like receptors and innate immunity. Nat Rev Immunol 2001; 1 (2): 135-45
39. Hemmi H, Kaisho T, Takeuchi O, et al. Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. Nat Immunol 2002; 3 (2): 196-200
40. Arany I, Tyring SK, Stanley MA, et al. Enhancement of the innate and cellular immune response in patients with genital warts treated with topical imiquimod cream 5%. Antiviral Res 1999; 43 (1): 55-63
41. Stanley MA. Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential. Clin Exp Dermatol 2002; 27 (7): 571-7
42. 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 (3): 656-62
43. Schon M, Bong AB, Drewiniok C. Tumor-selective induction of apoptosis and the small-molecule immune modifier imiquimod. J Natl Cancer Inst 2003; 95 (15): 1138-49
44. Berman B, Sullivan T, De Araujo T, et al. 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
45. Geisse J, Caro I, Lindholm J, et al. 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 (5): 722-33
46. Schulze HJ, Cribier B, Requena L, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. Br J Dermatol 2005; 152 (5): 939-47
47. Geisse JK, Rich P, Pandya 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 (3): 390-8
48. Beutner KR, Geisse JK, Helman D, et al. Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. J Am Acad Dermatol 1999; 41 (6): 1002-7
49. Shumack S, Robinson J, Kossard S, et al. Efficacy of topical 5% imiquimod cream for the treatment of nodular basal cell carcinoma: comparison of dosing regimens. Arch Dermatol 2002; 138 (9): 1165-71
50. Sterry W, Ruzicka T, Herrera E, 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 (6): 1227-36
51. Shumack S, Gebauer K, Quirk C, et al. 5% Imiquimod cream for the treatment of large superficial basal cell carcinoma. Arch Dermatol 2004; 140 (10): 1286-7
52. Wu JK, Oh C, Strutton G, et al. An open-label, pilot study examining the efficacy of curettage followed by imiquimod 5% cream for the treatment of primary nodular basal cell carcinoma. Australas J Dermatol 2006; 47 (1): 46-8
53. Spencer JM. Pilot study of imiquimod 5% cream as adjunctive therapy to curettage and electrodesiccation for nodular basal cell carcinoma. Dermatol Surg 2006; 32 (1): 63-9
54. Peris K, Campione E, Micantonio T, et al. Imiquimod treatment of superficial and nodular basal cell carcinoma: 12-week open-label trial. Dermatol Surg 2005; 31 (3): 318-23
55. Gollnick H, Barona CG, Frank RG, et al. Recurrence rate of superficial basal cell carcinoma following successful treatment with imiquimod 5% cream: interim 2-year results from an ongoing 5-year follow-up study in Europe. Eur J Dermatol 2005; 15 (5): 374-81
56. Quirk C, Gebauer K, Owens M, et al. Two-year interim results from a 5-year study evaluating clinical recurrence of superficial basal cell carcinoma after treatment with imiquimod 5% cream daily for 6 weeks. Aust J Dermatol 2006; 47 (4): 258-65
57. Aldara prescribing insert. 3M Pharmaceuticals, August 2005
58. Harrison LI, Skinner SL, Marbury TC, et al. Pharmacokinetics and safety of imiquimod 5% cream in the treatment of actinic keratoses of the face, scalp, or hands and arms. Arch Dermatol Res 2004; 296 (1): 6-11
59. Owens ML, Bridson WE, Smith SL, et al. Percutaneous penetration of Aldara cream, 5% during the topical treatment of genital and perianal warts [abstract]. Prim Care Update Obs Gyn 1998; 5 (4): 151
60. Hanger C, Dalrymple J, Hepburn D. Systemic side effects from topical imiquimod. N Z Med J 2005; 118 (1223): U1682
61. Systemic reactions to imiquimod (Aldara). Med Lett Drugs Ther 2004; 46 (1195): 92
62. Barton JC. Angioedema associated with imiquimod. J Am Acad Dermatol 2004; 51 (3): 477-8
63. Gilliet M, Conrad C, Geiges M, et al. Psoriasis triggered by toll-like receptor 7 agonist imiquimod in the presence of dermal plasmacytoid dendritic cell precursors. Arch Dermatol 2004; 140 (12): 1490-5
64. Rajan N, Langtry JA. Generalized exacerbation of psoriasis associated with imiquimod cream treatment of superficial basal cell carcinomas. Clin Exp Dermatol 2006; 31 (1): 140-1
65. Marks R, Owens M, Walters SA, et al. Efficacy and safety of 5% imiquimod cream in treating patients with multiple superficial basal cell carcinomas. Arch Dermatol 2004; 140 (10): 1284-5
66. Torres A, Niemeyer A, Berkes B, et al. 5% imiquimod cream and reflectance-mode confocal microscopy as adjunct modalities to Mohs micrographic surgery for treatment of basal cell carcinoma. Dermatol Surg 2004; 30 (12 Pt 1): 1462-9
67. Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2001
68. Ransohoff RM. Cellular responses to interferons and other cytokines: the JAK-STAT paradigm. N Engl J Med 1998; 338 (9): 616-8
69. Eisenbeis CF, Lesinski GB, Anghelina M, et al. Phase I study of the sequential combination of interleukin-12 and interferon alfa-2b in advanced cancer: evidence for modulation of interferon signaling pathways by interleukin-12. J Clin Oncol 2005; 23 (34): 8835-44

70. Liu KD, Gaffen SL, Goldsmith MA. JAK/STAT signaling by cytokine receptors. Curr Opin Immunol 1998; 10 (3): 271-8
71. Orange JS, Biron CA. Characterization of early IL-12, IFN-alphabeta, and TNF effects on antiviral state and NK cell responses during murine cytomegalovirus infection. J Immunol 1996; 156 (12): 4746-56
72. Biron C. Interferons alpha and beta as immune regulators: a new look. Immunity 2001; 14 (6): 661-4
73. Samuel CE. Antiviral actions of interferons. Clin Microbiol Rev 2001; 14 (4): 778-809
74. Der SD, Zhou A, Williams BR, et al. Identification of genes differentially regulated by interferon alpha, beta, or gamma using oligonucleotide arrays. Proc Natl Acad Sci U S A 1998; 95 (26): 15623-8
75. Tompkins WA. Immunomodulation and therapeutic effects of the oral use of interferon-alpha: mechanism of action. J Interferon Cytokine Res 1999; 19 (8): 817-28
76. Buechner S, Wernli M, Bachmann F, et al. Intralesional interferon in basal cell carcinoma: how does it work? Recent Results Cancer Res 2002; 160: 246-50
77. Buechner SA, Wernli M, Harr T, et al. Regression of basal cell carcinoma by intralesional interferon-alpha treatment is mediated by CD95 (Apo-1/Fas)-CD95 ligand-induced suicide. J Clin Invest 1997; 100 (11): 2691-6
78. Li C, Chi S, He N, et al. IFNalpha induces Fas expression and apoptosis in hedgehog pathway activated BCC cells through inhibiting Ras-Erk signaling. Oncogene 2004; 23 (8): 1608-17
79. Kowalzick L, Rogozinski T, Wimheuer R, et al. Intralesional recombinant interferon beta-1a in the treatment of basal cell carcinoma: results of an open-label multicentre study. Eur J Dermatol 2002; 12 (6): 558-61
80. Chimenti S, Peris K, Di Cristofaro S, et al. Use of recombinant interferon alfa-2b in the treatment of basal cell carcinoma. Dermatology 1995; 190 (3): 214-7
81. Edwards L, Tucker SB, Perednia D, et al. The effect of an intralesional sustained-release formulation of interferon alfa-2b on basal cell carcinomas. Arch Dermatol 1990; 126 (8): 1029-32
82. Alpsoy E. Comparison of the effects of intralesional interferon alfa-2a, 2b and the combination of 2a and 2b in the treatment of basal cell carcinoma. J Dermatol 1996; 23 (6): 394-6
83. Cornell RC, Greenway HT, Tucker SB, et al. Intralesional interferon therapy for basal cell carcinoma. J Am Acad Dermatol 1990; 23 (4 Pt 1): 694-700
84. Tucker SB, Polasek JW, Perri AJ, et al. Long-term follow-up of basal cell carcinomas treated with perilesional interferon alfa 2b as monotherapy. J Am Acad Dermatol 2006; 54 (6): 1033-8
85. Dusheiko G. Side effects of alpha interferon in chronic hepatitis C. Hepatology 1997; 26: 112-21S
86. Stenquist B, Wennberg AM, Gisslen H, et al. Treatment of aggressive basal cell carcinoma with intralesional interferon: evaluation of efficacy by Mohs surgery. J Am Acad Dermatol 1992; 27 (1): 65-9
87. Hurd DS, Conte ET. Practical uses of the interferons in dermatology. Int J Dermatol 1998; 37 (12): 881-96
88. Danenberg PV, Shea LC, Danenberg K. Effect of 5-fluorouracil substitution on the self-splicing activity of Tetrahymena ribosomal RNA. Cancer Res 1990; 50 (6): 1757-63
89. Goette DK. Topical chemotherapy with 5-flurouracil. J Am Acad Dermatol 1981; 4 (6): 633-49
90. Reymann F. Treatment of basal cell carcinoma of the skin with 5-fluorouracil ointment: a 10-year follow-up study. Dermatologica 1979; 158 (5): 368-72
91. Epstein E. Fluorouracil paste treatment of thin basal cell carcinomas. Arch Dermatol 1985; 121 (2): 207-13
92. Miller BH, Shavin JS, Cognetta A, et al. Nonsurgical treatment of basal cell carcinomas with intralesional 5-fluorouracil/epinephrine injectable gel. J Am Acad Dermatol 1997; 36 (1): 72-7
93. Romagosa R, Saap L, Givens M, et al. A pilot study to evaluate the treatment of basal cell carcinoma with 5-fluorouracil using phosphatidyl choline as a transepidermal carrier. Dermatol Surg 2000; 26 (4): 338-40
94. Tsuji T, Otake N, Nishimura M. Cryosurgery and topical fluorouracil: a treatment method for widespread basal cell epithelioma in basal cell nevus syndrome. J Dermatol 1993; 20 (8): 507-13
95. Klostermann GF. Effects of 5-fluorouracil (5-FU) ointment on normal and diseased skin: histologic findings and deep action. Dermatologica 1970; 140 Suppl. 1: 47-54
96. Mohs FE, Jones DL, Bloom RF. Tendency of fluorouracil to conceal deep foci of invasive basal cell carcinoma. Arch Dermatol 1978; 114: 1021-2
97. Rozenman Y, Gurewich J, Gotsman MS. Myocardial ischemia induced by topical use of 5-fluorouracil. Int J Cardiol 1995; 49: 282-3
98. Johnson MR, Hageboutros A, Wang K, et al. Life-threatening toxicity in a dihydropyrimidine dehydrogenase-deficient patient after treatment with topical 5-fluorouracil. Clin Cancer Res 1999; 5: 2006
99. Telfer NR, Colver GB, Bowers PW. Guidelines for the management of basal cell carcinoma. British Association of Dermatologists. Br J Dermatol 1999; 141 (3): 415-23
100. Rodriguez-Cuevas S, Barroso-Bravo S, Almanza-Estrada J, et al. Electrochemotherapy in primary and metastatic skin tumors: phase II trial using intralesional bleomycin. Arch Med Res 2001; 32 (4): 273-6
101. Denic S. Preoperative treatment of advanced skin carcinoma with cisplatin and bleomycin. Am J Clin Oncol 1999; 22 (1): 32-4
102. Glass LF, Jaroszeski M, Gilbert R, et al. Intralesional bleomycin-mediated electrochemotherapy in 20 patients with basal cell carcinoma. J Am Acad Dermatol 1997; 37 (4): 596-9
103. Morley M, Finger PT, Perlin M, et al. Cis-platinum chemotherapy for ocular basal cell carcinoma. Br J Ophthalmol 1991; 75 (7): 407-10
104. Guthrie TH Jr, Porubsky ES, Luxenberg MN, et al. Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: results in 28 patients including 13 patients receiving multimodality therapy. J Clin Oncol 1990; 8 (2): 342-6
105. Khandekar JD. Complete response of metastatic basal cell carcinoma to cisplatin chemotherapy: a report on two patients. Arch Dermatol 1990; 126 (12): 1660
106. Baxter DL Jr, Joyce AP, Feldman BD, et al. Cisplatin chemotherapy for basal cell carcinoma: the need for posttreatment biopsy -report of a case. J Am Acad Dermatol 1990; 23 (6 Pt 1): 1167-8
107. Coker DD, Elias EG, Viravathana T, et al. Chemotherapy for metastatic basal cell carcinoma. Arch Dermatol 1983; 119 (1): 44-50
108. Bason MM, Grant-Kels JM, Govil M. Metastatic basal cell carcinoma: response to chemotherapy. J Am Acad Dermatol 1990; 22 (5 Pt 2): 905-8
109. Henderson BW, Dougherty TJ. How does photodynamic therapy work? Photochem Photobiol 1992; 55 (1): 145-57

110. Kalka K, Merk H, Mukhtar H. Photodynamic therapy in dermatology. J Am Acad Dermatol 2000; 42 (3): 389-413
111. Pass HI. Photodynamic therapy in oncology: mechanisms and clinical use. J Natl Cancer Inst 1993; 85 (6): 443-56
112. Engbrecht BW, Menon C, Kachur AV, et al. Photofrin-mediated photodynamic therapy induces vascular occlusion and apoptosis in a human sarcoma xenograft model. Cancer Res 1999; 59 (17): 4334-42
113. Oleinick NL, Morris RL, Belichenko I. The role of apoptosis in response to photodynamic therapy: what, why and how. Photochem Photobiol Sci 2002; 1 (1): 1-21
114. Gollnick SO, Liu X, Owczarczak B, et al. Altered expression of interleukin 6 and interleukin 10 as a result of photodynamic therapy in vivo. Cancer Res 1997; 57 (18): 3904-9
115. de Vree WJ, Essers MC, de Bruijn HS, et al. Evidence for an important role of neutrophils in the efficacy of photodynamic therapy in vivo. Cancer Res 1996; 56 (13): 2908-11
116. Dougherty TJ, Cooper MT, Mang TS. Cutaneous phototoxic occurrences in patients receiving photofrin. Lasers Surg Med 1990; 10 (5): 485-8
117. Brown SB, Brown EA, Walker I. The present and future role of photodynamic therapy in cancer treatment. Lancet Oncol 2004; 5 (8): 497-508
118. Peng Q, Warloe T, Berg K, et al. 5-Aminolevulinic acid-based photodynamic therapy. Clinical research and future challenges. Cancer 1997; 79 (12): 2282-308
119. Dougherty TJ, Gomer CJ, Henderson BW, et al. Photodynamic therapy. J Natl Cancer Inst 1998; 90 (12): 889-905
120. Svanberg K, Anderson T, Killander D, et al. Photodynamic therapy of non-melanoma malignant tumours of the skin using topical 5-aminolaevulinic acid sensitisation and laser irradiation. Br J Dermatol 1994; 130 (6): 743-51
121. Fritsch C, Lehmann P, Stahl W, et al. Optimum porphyrin accumulation in epithelial skin tumours and psoriatic lesions after topical application of delta-aminolaevulinic acid. Br J Cancer 1999; 79 (9-10): 1603-8
122. Collaud S, Juzeniene A, Moan J, et al. On the selectivity of 5-aminolevulinic acid-induced protoporphyrin IX formation. Curr Med Chem Anticancer Agents 2004; 4 (3): 301-16
123. Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. J Photochem Photobiol B 1990; 6 (1-2): 143-8
124. Roberts DJH, Cairnduff F. Photodynamic therapy of primary skin cancer: a review. Br J Plast Surg 1995; 48 (6): 360-70
125. Wilson BD, Mang TS, Stoll H, et al. Photodynamic therapy for the treatment of basal cell carcinoma. Arch Dermatol 1992; 128 (12): 1597-601
126. Wolf P, Rieger E, Kerl H. Topical photodynamic therapy with endogenous porphyrins after application of 5-aminolevulinic acid: an alternative treatment modality for solar keratoses, superficial squamous cell carcinomas, and basal cell carcinomas? [Published erratum appears in J Am Acad Dermatol 1993; 29 (1): 41]. J Am Acad Dermatol 1993; 28 (1): 17-21
127. Calzavara-Pinton PG. Repetitive photodynamic therapy with topical delta-aminolaevulinic acid as an appropriate approach to the routine treatment of superficial non-melanoma skin tumours. J Photochem Photobiol B 1995; 29 (1): 53-7
128. Fink-Puches R, Soyer HP, Hofer A, et al. Long-term follow-up and histological changes of superficial nonmelanoma skin cancers treated with topical delta-aminolevulinic acid photodynamic therapy. Arch Dermatol 1998; 134: 821-6
129. Peng Q, Warloe T, Berg K, et al. 5-ALA based photodynamic therapy. Cancer 1997; 79 (12): 2282-308
130. Morton CA, Brown SB, Collins S, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. Br J Dermatol 2002; 146 (4): 552-67
131. Langmack K, Mehta R, Twyman P, et al. Topical photodynamic therapy at low fluence rates: theory and practice. J Photochem Photobiol B Biol 2001; 60: 37-43
132. Wang I, Bendsoe N, Klinteberg CAF, et al. Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. Br J Dermatol 2001; 144: 832-40
133. Horn M, Wolf P, Wulf HC, et al. Topical methyl aminolevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional treatment. Br J Dermatol 2003; 149 (6): 1242-9
134. Pennington DG, Waner M, Knox A. Photodynamic therapy for multiple skin cancers. Plast Reconstr Surg 1988; 82 (6): 1067-71
135. Cairnduff F, Stringer MR, Hudson EJ, et al. Superficial photodynamic therapy with topical 5-aminolaevulinic acid for superficial primary and secondary skin cancer. Br J Cancer 1994; 69 (3): 605-8
136. Haller JC, Cairnduff F, Slack G, et al. Routine double treatments of superficial basal cell carcinomas using aminolevulinic acid-based photodynamic therapy. Br J Dermatol 2000; 143 (6): 1270-5
137. Soler AM, Warloe T, Tausjo J, et al. Photodynamic therapy by topical aminolevulinic acid, dimethylsulphoxide and curettage in nodular basal cell carcinoma: a one-year follow-up study. Acta Derm Venereol 1999; 79 (3): 204-6
138. Itoh Y, Henta T, Ninomiya Y, et al. Repeated 5-aminolevulinic acid-based photodynamic therapy following electro-curettage for pigmented basal cell carcinoma. J Dermatol 2000; 27 (1): 10-5
139. Lui H, Salasche S, Kollias N, et al. Photodynamic therapy and nonmelanoma skin cancer with topical aminolevulinc acid: a clinical and histologic study. Arch Dermatol 1995; 131 (6): 737-8
140. Morton CA, MacKie RM, Whitehurst C, et al. Photodynamic therapy for basal cell carcinoma: effect of tumor thickness and duration of photosensitizer application on response. Arch Dermatol 1998; 134 (2): 248-9
141. Rhodes LE, de Rie M, Enstrom Y, et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol 2004; 140 (1): 17-23
142. Foley P. Clinical efficacy of methyl aminolevulinate (Metvix) photodynamic therapy. J Dermatolog Treat 2003; 14 Suppl. 3: 15-22
143. Thissen MR, Schroeter CA, Neumann HA. Photodynamic therapy with delta-aminolaevulinic acid for nodular basal cell carcinomas using a prior debulking technique. Br J Dermatol 2000; 142 (2): 338-9
144. Soler AM, Angell-Petersen E, Warloe T, et al. Photodynamic therapy of superficial basal cell carcinoma with 5-aminolevulinic acid with dimethylsulfoxide and ethylendiaminetetraacetic acid: a comparison of two light sources. Photochem Photobiol 2000; 71 (6): 724-9
145. Fijan S, Honigsmann H, Ortel B. Photodynamic therapy of epithelial skin tumours using delta-aminolevulinic acid and desferrioxamine. Br J Dermatol 1995; 133 (2): 282-8

146. De Rosa FS, Marchetti JM, Thomazini JA, et al. A vehicle for photodynamic therapy of skin cancer: influence of dimethylsulphoxide on 5-aminolevulinic acid in vitro cutaneous permeation and in vivo protoporphyrin IX accumulation determined by confocal microscopy. J Control Release 2000; 65 (3): 359-66

147. Uehlinger P, Zellweger M, Wagnieres G, et al. 5-Aminolevulinic acid and its derivatives: physical chemical properties and protoporphyrin IX formation in cultured cells. J Photochem Photobiol B 2000; 54 (1): 72-80

148. Vinciullo C, Elliott T, Francis D, et al. Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. Br J Dermatol 2005; 152 (4): 765-72

149. Wiegell SR, Stender IM, Na R, et al. Pain associated with photodynamic therapy using 5-aminolevulinic acid or 5-aminolevulinic acid methylester on tape-stripped normal skin. Arch Dermatol 2003; 139 (9): 1173-7

150. Grapengiesser S, Ericson M, Gudmundsson F, et al. Pain caused by photodynamic therapy of skin cancer. Clin Exp Dermatol 2002; 27 (6): 493-7

151. Dolmans DE, Kadambi A, Hill JS, et al. Vascular accumulation of a novel photosensitizer MV6401 causes selective thrombosis in tumor vessels after photodynamic therapy. Cancer Res 2002; 62 (7): 2151-6

152. Dolmans DE, Kadambi A, Hill JS, et al. Targeting tumor vasculature and cancer cells in orthotopic breast tumor by fractionated photosensitizer dosing photodynamic therapy. Cancer Res 2002; 62 (15): 4289-94

153. Smith W, Saba N. Retinoids as chemoprevention for head and neck cancer: where do we go from here? Crit Rev Oncol Hematol 2005; 55 (2): 143-52

154. Peris K, Fargnoli MC, Chimenti S. Preliminary observations on the use of topical tazarotene to treat basal-cell carcinoma. N Engl J Med 1999; 341 (23): 1767-8

155. So PL, Lee K, Hebert J, et al. Topical tazarotene chemoprevention reduces basal cell carcinoma number and size in Ptch1+/- mice exposed to ultraviolet or ionizing radiation. Cancer Res 2004; 64 (13): 4385-9

156. Duvic M, Helekar B, Schulz C, et al. Expression of a retinoid-inducible tumor suppressor, tazarotene-inducible gene-3, is decreased in psoriasis and skin cancer. Clin Cancer Res 2000; 6 (8): 3249-59

157. Punjabi S, Cook LJ, Kersey P, et al. A double-blind, multicentre parallel group study of BEC-5 cream in basal cell carcinoma. Eur Acad Dermatol Venereol 2000; 14 Suppl. 1: 47-60

158. Wilgus TA, Koki AT, Zweifel BS, et al. Chemotherapeutic efficacy of topical celecoxib in a murine model of ultraviolet light B-induced skin cancer. Mol Carcinog 2003; 38 (1): 33-9

159. Buckman SY, Gresham A, Hale P, et al. COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer. Carcinogenesis 1998; 19 (5): 723-9

160. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005; 294 (1): 47-55

161. Grau MV, Baron JA, Langholz B, et al. Effect of NSAIDs on the recurrence of nonmelanoma skin cancer. Int J Cancer 2006; 119 (3): 682-6

162. Snoeck R. Papillomavirus and treatment. Antiviral Res 2006; 71 (2-3): 181-91. Epub 2006 Jun 23

163. Calista D. Topical 1% cidofovir for the treatment of basal cell carcinoma. Eur J Dermatol 2002; 12 (6): 562-4

164. Cuevas P, Arrazola JM. Treatment of basal cell carcinoma with dobesilate. J Am Acad Dermatol 2005; 53 (3): 526-7

165. Angulo J, Cuevas P, Fernandez A, et al. Calcium dobesilate potentiates endothelium-derived hyperpolarizing factor-mediated relaxation of human penile resistance arteries. Br J Pharmacol 2003; 139 (4): 854-62

166. Tejerina T, Ruiz E. Calcium dobesilate: pharmacology and future approaches. Gen Pharmacol 1998; 31 (3): 357-60

167. Suschek C, Kolb H, Kolb-Bachofen V. Dobesilate enhances endothelial nitric oxide synthase-activity in macro- and microvascular endothelial cells. Br J Pharmacol 1997; 122 (7): 1502-8

Correspondence: Dr *Igal Leibovitch*, Division of Orbital and Ophthalmic Plastic and Reconstructive Surgery, and the Department of Ophthalmology, David Geffen School of Medicine at UCLA, Jules Stein Eye Institute, 100 Stein Plaza #2-267, Los Angeles, CA 90095-7006, USA.
E-mail: leibovitch@gmail.com