Bowen's disease – a review of newer treatment options

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Abstract: Bowen's disease (squamous cell carcinoma in situ) has a 3%–5% risk to develop into invasive squamous cell carcinoma. Non-melanoma skin cancer is the most common cancer among Caucasians and its incidence has increased during the last decades dramatically. Multiple treatment options for Bowen's disease have been described and are established with advantages and disadvantages. Bowen's disease occurs more often in elderly patients (with a higher risk of comorbidities) and is frequently located on body sites with poor wound healing. Therefore there is need for non-invasive/non-destructive but effective treatment options.

We would like to give an overview of established therapies and more detailed information about the newer treatment options for Bowen's disease with topical diclofenac, topical imiquimod and photodynamic therapy.

Keywords: Bowen's disease, photodynamic therapy, imiquimod, diclofenac

Introduction

Bowen's disease (BD) is an in situ squamous cell carcinoma (SCC) which was first described in 1912 by JT Bowen.

Clinically a typical BD is a slowly enlarging erythematous patch or plaque which is well demarcated and has a scaling or crusted surface. In some cases it can be pigmented or verrucous. It is commonly located on the lower limbs and on the head and neck. But BD is also seen subungual or periungual, palmar, genital and perianal. Usually BD is a solitary lesion, but in 10% to 20% it occurs at multiple sites (Thestrup-Pedersen et al 1988; Cox et al 2007). The risk of progression into an invasive carcinoma is 3% to 5% in extragenital lesions and about 10% in genital lesions (Kao 1986; Cox et al 1999). BD is very common in the Caucasian population with an incidence of 1.42 per 1000 in some populations (Reizner et al 1994).

Several etiological factors of BD have been reported, such as irradiation (ultraviolet irradiation, radiotherapy, photochemotherapy), carcinogens (eg, arsenic), immunosuppression (eg, after organ transplantation, AIDS), viral (strong association of perianal and genital lesions with HPV; 47% of acral and 24% of nonacral extragenital BD contain HPV genome) and some others like chronic injury or dermatoses (Clavel et al 1999; Cox et al 2007).

Treatment options for Bowen's disease

Efficacy comparison and evaluation of different treatment options and treatment studies of Bowen's disease are difficult because there is a variety of different protocols and the success of a treatment modality is dependent on several factors (eg, body site, lesion size and thickness, different equipment).

The choice of treatment should be guided by efficacy, location and size of BD, number of lesions, availability of the therapy, the clinician's expertise, patient factors (age, immune status, concomitant medication, comorbidities and compliance), cosmetic outcome and the patient's preference.

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The different treatment options for BD are cryotherapy, curettage with cautery, excision, 5-fluorouracil (5-FU), radiotherapy, laser, photodynamic therapy (PDT), imiquimod and some other therapies that **were** described in some case reports or small numbers of patients. Up to now none of the treatment options has been unequivocally proven to be superior to any other.

This paper is focused on the newer treatment options for BD: topical diclofenac and imiquimod and photodynamic therapy.

Cryotherapy

The clearance and recurrence rates of cryotherapy vary between different studies. The reasons for this variety of results are different techniques and regimens (especially freezing time and number of freeze-thaw cycles (FTC)), lesion size and location of BD. In a retrospective study a clinical clearance of 61% was achieved (Bell and Rhodes 1999). Excellent results in combination with low recurrence rates were described for 30s freeze-thaw cycle liquid nitrogen cryotherapy (Plaza de Lanza et al 1980; Holt 1988). Lower recurrence rates were achieved by longer and repeated freezing cycles whereby problems like prolonged wound healing and poor cosmetic outcome (scaring, hypopigmentation) increased **(**Plaza de Lanza et al 1980; Holt 1988; Cox and Dyson 1995; Ball and Dawber 1998).

In comparative studies cryotherapy showed clearance rates from 50% to 100% by one to three 20s freeze-thaw cycles and recurrence rates from 10% (one 20s FTC, follow up 12 months) up to 36% (two 5 to 10s FTC, follow up 24 months) (Morton et al 1996; Ahmed et al 2000). Wound healing was faster with cryotherapy compared to radiotherapy, but slower than curettage and cautery regimen (Cox and Dyson 1995; Ahmed et al 2000). In comparison with PDT after cryotherapy ulceration was seen in 25% of the treated lesions (no ulceration in the PDT group) and the clearance rate of a single PDT was significantly higher than one 20s FTC (Morton et al 1996).

In conclusion cryotherapy with liquid nitrogen is an effective, commonly used option in the treatment of BD entailing only low costs. Especially for single and small BD located in well healing sites cryotherapy is a favorable treatment option.

Curettage with cautery

The reported cure rates and recurrence rates of this method differ due to different regimes, equipment used and skill of the clinician. Cure rates ranged from 81% for curettage up to 93% to 98% for curettage and cautery with a follow up of 2.5 to 4 years (Honeycutt and Jansen 1973; Thestrup-Pedersen et al 1988; Morton al 1996). In a comparative study with a follow up of 2 years there was a recurrence in the curettage and cautery group in 4 of 44 lesions and in the cryotherapy group (two 5 to 10 s FTC) in 13 of 36 lesions (Ahmed et al 2000). In this study curettage and cautery was associated with a better and faster wound healing, less discomfort and pain and a lower rate of complications. Additional anecdotal reports described a therapy regime that combined curettage and cryotherapy (Nordin 1999).

In summary curettage and cautery is a safe and effective therapy of BD with a very good cost-benefit analysis. It is suitable especially for small single BD.

Excision

Up to now no randomized, comparative studies have been published for surgery of BD. In 2 retrospective studies recurrence rates ranged from 4.6% up to 19% (Graham and Helwig 1961; Thestrup-Pedersen et al 1988). Higher rates were reported for perianal BD. Mohs micrographic surgery is especially performed in sites of the body where tissue-sparing surgery is necessary (eg, fingers and nail unit, penis). The recurrence rates differed from 6.3% up to 21%–28% (follow up 1 to 5 years) due to different body sites, viral etiology, large wound defects and lesion size. Perianal BD showed in a retrospective study of 47 cases a recurrence rate for wide excision of 23%, for local excision 53% and for laser therapy 80% (treatment with radiotherapy was not included)(Marchesa et al 1997). The most frequently used therapy for perianal BD is wide excision and the surgical treatment has been advocated as the treatment of choice (Cleary et al 2000; Cox et al 2007).

In conclusion surgical excision of BD is one of the standard treatments especially for small and single, digital and perianal BD. The main advantage is the securing of histological free excision margins. Possible limitations are cosmetic and functional outcome and prolonged or complicated wound healing in some body areas.

Fluorouracil

For the treatment with topical 5-FU the reported clearance and cure rates showed a wide range due to the use of different therapy regimens and concentrations. The commercially available and in most studies used concentration is a 5% 5-FU preparation. Once or twice daily application for variable periods of time (1 week to 2 months or even longer) is described, with preference for the twice daily usage and

longer treatment periods (8 weeks) with clearance rates up to 92% (Bargmann and Hochmann 2003).

Pulse therapies with 5-FU have been reported with a limited evidence base. A randomized trial for the treatment of BD with either PDT or 5-FU (1 or if required 2 cycles of once daily application for 1 week and twice daily for week 2–4) reported an initial clinical clearance for PDT in 88% and for 5-FU in 67%, with a clearance rate at follow up (12 months) of 82% (PDT) and 48% (5-FU) (Salim et al 2003).

Increasing effectiveness has been reported when 5-FU was combined with other therapeutic modalities like occlusive application, iontophoresis, pretreatment with erbium:YAG laser, cryotherapy, imiquimod and acitretin with response rates up to 96,2% (Heising 1979; Welch et al 1997; Khandpur and Sharma 2003; Wang et al 2004). The advantage of 5-FU cream is that it can be easily applied by the patients themselves accompanied by frequent clinical controls. The therapy with 5-FU is limited by local inflammation with erosion and ulceration which may last for several weeks.

In summary the commercially available 5% 5-FU preparation has shown its efficacy in short- and long-term studies and can be used for the treatment of BD in good or even bad healing sites and for special sites like fingers or penis.

Radiotherapy

Different radiotherapy techniques (external beam radiotherapy, Grenz rays, radioactive skin patches) have been used in the treatment of BD with reported cure rates between 94% and 100% (Stevens et al 1977; Lee et al 1997; Turpin 1999; Chung et al 2000; Lukas VanderSpek et al 2005). For BD located at poor healing sites (especially lower leg) radiotherapy should be avoided due to poor healing/failure-to-heal rates in 20% to 25 % of treated lesions (Cox and Dyson 1995; Dupree et al 2001). Severe toxicity of radiotherapy (eg, cartilage/bone necrosis) was reported for hypofractionated regimens after treatment of BD of the extremities (Lukas VanderSpek et al 2005).

To avoid some of the disadvantages and adverse effects of conventional radiotherapy skin patches equipped with the β-emitter holmium-166 were designed for the treatment of BD and other skin cancers (Lee et al 1997; Turpin 1999; Chung et al 2000). In 29 biopsy-confirmed BD histological clearance was reported at 5 month without any recurrence after 10–24 month (Chung et al 2000). In this study the functional and cosmetic outcome was good with no serious adverse effects (only desquamation, erythema and erosion were seen).

For anal/perianal BD radiotherapy has been reported as a reasonable treatment of choice particularly when other therapies (eg, surgery) are difficult to carry out (Cox et al 1999; Papillon and Chassard 1992; Lukas VanderSpek et al 2005. But there is no strong evidence supporting this point of view.

In conclusion radiotherapy should not be used for poor healing sites (especially not for the lower leg) but it can be an alternative with high efficacy when other treatment options (eg, surgery) are difficult or not possible (eg, very old patients with comorbidities and medication with anticoagulants, special sites like perianal or penile BD).

Laser

So far no randomized controlled trials to evaluate laser therapy in BD have been reported. The published data result from case reports and small series. Argon, CO_2 and Nd:YAG laser have been used for the treatment of BD.

Complete response of BD of the digits by CO_2 laser with no recurrence in the 0.5 to 7.7 years follow up was published in some studies with good functional and cosmetic outcome (Gordon et al 1994; Gordon et al 1996; Tantikun 2000), although others reported some failures (1 of 5 digital lesions) (Gordon et al 1994) or progression to invasive SCC of lower leg lesions after 100% healing at 2 months and complete response at 6 months (3/16 patients) (Dave et al 2003). Genital lesions showed complete response after treatment with argon, CO_2 and Nd:YAG laser (Landthaler et al 1986) with more recent data that reported a recurrence rate of 26% (van Bezooijen et al 2001). For perianal BD the results of laser therapy were poor (Cleary et al 2000), although a case report showed a clearance and no recurrence within 14 month after treatment with argon laser (Boynton and Bjorkman 1991).

In summary especially the CO_2 laser can be used for penile or digital BD with only limited data of recurrence rates.

Other therapies

As some of the most standard therapies for BD mentioned above are not evaluated by controlled randomized trials, data of other less commonly used therapies result from case reports or only small numbers of patients.

Local hyperthermia was tried by the use of chemical pocket warmers applied on the lesions under pressure with initial complete clinical clearance in six of eight patients but with histological clearance in only three of eight cases (Hiruma and Kawada 2000).

In 20 BD lesions (large and lower leg lesions included) an ultrasonic surgical aspirator was used with no recurrence during the follow up (12 to 26 months, mean 20 months)

(Otani et al 2001). After 10 months acitretin therapy in one of the two treated patients 90% of the multiple lesions cleared. The other patient did not tolerate the acitretin and no improvement was seen (Yerebakan et al 2002). In other reports for example, the use of topical (in combination with liquid nitrogen) and intralesional bleomycin (Dyall-Smith 1998; Ota et al 2002) and oral isotretinoin in combination with subcutaneous interferon-α (1 patient treated for 3 months for multiple BD, no recurrence 15 month after therapy) (Gordon et al 1997) was reported.

Newer treatment options

Diclofenac

Diclofenac inhibits cyclooxygenase enzymes and thereby downstream byproducts of arachidonic acid (AA) metabolism are decreased. In the promotion of epithelial tumor growth these metabolites of AA have shown to play an essential role by several mechanisms and pathways (eg, inhibition of apoptosis and immune surveillance, stimulation of angiogenesis, etc) (Gately 2000; Masferrer et al 2000).

Diclofenac 3% gel has been successfully used in the treatment of actinic keratosis (Wolf et al 2001; Smith et al 2006). Two cases of BD were treated with 3% diclofenac gel twice daily for 80 to 90 days with no residual disease clinically and histologically (Dawe et al 2005).

In another series of 5 patients the biopsy proven BD were treated once daily with diclofenac 3% gel for 8 weeks. The treatment was well tolerated with mild inflammation after 6 weeks and mild side effects like itching and dryness. Complete clinical and histological clearance was proven by biopsies taken 4 weeks after end of treatment (Pantel and Stockfleth 2007).

However these promising data have to be proven in randomized controlled trials and optimum regimens (eg, once vs twice daily application, duration of application) and recurrence rates in long-term follow-up have to be investigated.

Imiquimod

Imiquimod 5% cream is a topical immune response modifier with approval in most pharmaceutical markets for the treatment of anogenital warts, actinic keratoses and superficial basal cell carcinoma.

Imiquimod is heterocyclic imidazoquinoline amid with antiviral and antitumor effects. Imiquimod itself does not have antiviral or antiproliferative abilities, its efficacy is ascribed to the stimulation of innate and acquired immunity. Binding of imiquimod to toll-like receptor(TLR)-7 and -8 induces production of cytokines like interferon (IFN) alfa, tumor necrosis factor alfa, interleukin (IL)-1α, IL-1 receptor antagonist, IL-12 and IFN-γ resulting in a T-lymphocyte helper type 1 coordinated cell mediated immunity (Hengge et al 2001; Temmi et al 2002). During partial regression of BD a T-lymphocyte-rich infiltrate was seen in the dermis with epidermal apoptosis (Habetts et al 1989; Murata et al 1996). Furthermore resolution of BD was observed after treatments promoting cell-mediated immunity and apoptosis (Raaf et al 1967; Gordon et al 1997). Topical application on the skin results in a keratinocyte secretion of IL-6, Il-8, and IFN-α. The antiviral effects of imiquimod are mediated by IFN-α. IFN-α induces proteins that activate RNAses and are pivotal for antiviral activity. Furthermore Imiquimod induces maturation of Langerhans cells and migration to the regional lymph nodes and an increase of antigen presentation. Imiquimod has indirect effects on T-cells and T-cell cytokines (eg, IL-2, IL-4, IL-5) by the induction of IFN-γ that results in a production of these cytokines in peripheral mononuclear cells. These cytokines again increase cell-mediated immune responses. Imiquimod is able to induce antigen specific B-lymphocytes. Proliferation of B-cells is increased and the expression of MHC class II and B7.2 that are important for antigen presentation (Meykadeh and Hengge 2003).

Recently it has been reported that imiquimod can directly induce apoptosis in SCC cell lines, independently of inflammatory cells (Schön et al 2003). In this apoptotic reaction a cytosolic translocation of mitochondrial membrane protein cytochrome c by a Bcl-2-dependent pathway was observed. In the treatment of basal cell carcinoma with imiquimod this Bcl-2-depletion and a higher rate of apoptotic keratinocytes were seen (Urosevic et al 2003; Vidal et al 2004).

In a phase II open label study (16 patients with BD treated with imiquimod) the CD4/CD8 lymphocyte ratio in pre- and post-treatment biopsy specimens reversed from 2:1 to 1:2.2, indicating a recruitment of $CD8^+$ T lymphocytes (cytotoxic/suppressor T lymphocytes) in the lesion (Mackenzie-Wood et al 2001). In this study 16 BD (15 located an the legs, with 6 on the shin and one on the shoulder; maximum diameter 1 to 5.4 cm) were treated once daily up to 16 weeks (10 patients 16 weeks, 6 patients 4 to 8 weeks because of local side effects) with 93% (14 of 15 patients who completed the study) clinical and histological clearance. Local skin reactions appeared in 15 of the 16 patients. 6 patients stopped the treatment after 4–8 weeks due to marked skin reactions like superficial erosions with hemorrhagic crusts. All of these areas healed within 6 weeks after treatment

was stopped. In 4 other patients the treatment site healed without any residual crusting, although the treatment was not discontinued during the 16 weeks. In another 3 patients the treatment was discontinued for 6 to 13 days because of local reactions, but after the rest periods they completed the treatment without any flare up. In most of the patients the surrounding normal skin was not affected, but in patients with chronic sun damage satellite reactions were seen. During the study no remarkable changes in laboratory tests and no systemic side effects were seen.

In a randomized, double-blind, placebo-controlled trial (daily placebo/imiquimod for 16 weeks) 9 of 12 (75%) (11 of 15 resolved as per intention-to-treat analysis) patients in the imiquimod group and none in the placebo group had complete clearance of BD with no recurrence during the 9 months follow up. Three patients dropped out (1 was lost to follow-up, 1 patient with chronic photodamage had extended marked inflammatory reaction and a third patient had a localized *Staphylococcus aureus* infection, resolving after oral antibiotic therapy and stopping the imiquimod treatment). The local side effects (mild itching-edema with erosion) were similar to other studies (Patel et al 2006).

In another randomized, double-blind, placebo-controlled trial in high risk renal transplant recipients in the verum group imiquimod 5% cream was applied 3 times per week for 16 weeks with reduction of skin atypia in 7 of 14 cases (placebo group 1 of 6 cases) and a lower frequency of squamous skin tumors (Brown et al 2005).

Alternative regimens (application of imiquimod 5% cream 2 to 3 times per week for 6 weeks) with 87% clinical clearance (Sierra-Valenti 2003) and cyclic application (application of imiquimod 5% cream 3 times per week for 3 weeks, rest period of 4 weeks, second cycle if necessary) with maintaining good results (Chen and Shumack 2003) were assessed with a clear reduction of side effects and a better acceptance.

In a small series with 3 patients imiquimod 5% cream was applied occlusive with a 30% reduction of treatment duration but with systemic side effects like fever, flu-like symptoms, and psychic depression (suggesting significant imiquimod absorption under occlusion) (Muzio et al 2004).

Imiquimod 5% cream was used in combination with 5-fluorouracil in kidney transplant recipients (Smith et al 2001) and in combination with sulindac (COX-2 inhibitor) in immunosuppressed patients with chronic lymphocytic leukemia (Smith et al 2001).

In addition to the randomized, double-blind, placebo-controlled trial in high risk renal transplant recipients treated with 5% imiquimod cream and the combined therapy regimen (imiquimod and 5-FU) mentioned above, other publications showed efficacy of imiquimod 5% cream in transplant patients as well (Stockfleth et al 2003; Prinz et al 2004).

In other case reports successful treatment of genital BD/erythroplasia of Queyrat (Cook-Bolden and Weinberg 2002; Orengo et 2002; Schroeder and Sengelmann 2002; Thai and Sinclair 2002; Arlette 2003; Danielsen et al 2003; Mandekou-Lefaki et al 2003; Micali et al 2003), anal/perianal BD (Phoushek and Smith 2001; Gutzmer et al 2002; Kreuter et al 2004), large facial BD (Kossard 2003), and BD of the eyelid (Brannan et al 2005) was shown with good functional and cosmetic outcome.

Despite these good results, 2 cases have been published in which invasive SCC developed after the treatment of BD with imiquimod (Goh 2006).

A summarized overview of studies and some case reports is given in Table 1.

In conclusion topical imiquimod 5% cream is an effective alternative treatment option for patients and body sites that are unsuitable for other treatments like surgery. Nevertheless further large randomized, double-blind controlled-prospective studies with long-term follow-up are required to verify the results mentioned above and to figure out an optimal dosing scheme (duration of treatment, number of weekly applications) with high efficacy and decreased local side effects and an optimal cost-to-benefit analysis.

Photodynamic therapy

Photodynamic therapy (PDT) is a well established therapeutic option for actinic keratoses, basal cell carcinoma (superficial and nodular) and BD (Braathen et al 2007).

PDT is based on the combination of light and light sensitive agents (eg, porphyrins) in the presence of oxygen. The energy of photons is absorbed by porphyrins and then transferred to surrounding oxygen molecules. The formation of cytotoxic oxygen species (eg, singulet oxygen) and free radicals results in cell death (Szeimies et al 1995). Exact mechanisms of topical PDT in NMSC at cellular level are not completely known but apoptosis (Noodt et al 1996; Webber et al 1996; Gad et al 2001; Kuzelova et al 2004) as well as necrosis (Noodt et al 1996) have been described after PDT.

Currently used topical photosensitizer precursors are 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL). MAL-PDT is approved for the treatment of BD in 22 European countries. After topical application and accumulation in neoplastic lesions ALA and MAL are

Table 1 Summary of reviewed studies and case reports on topical imiquimod

Reference	Treatment groups	Number of lesions	Regimen	Results (at last follow-up)	Follow-up	Notes
Patel et al	Imiquimod 5% Placebo (vehicle)	15 16	Imiquimod 5% once daily for 16 weeks	75% (9/12) 0% CR	9 months	3 drop outs in the imiquimod group
Mackenzie-Wood et al	Imiquimod	16	Imiquimod 5% once daily for 16 weeks	93% CR (13/14)	6 months	2 patients died from unrelated illness
Smith et al	Imiquimod 5% + 5-FU	5	Alternating Imiquimod 3 × and 5-FU 4 × per week for 5–7 weeks	100% CR	3–15 months	Renal transplant recipients
Smith et al	Imiquimod 5% + sulindac + valacyclovir	5	Imiquimod 5% 3 ×/week + sulindac 200 mg 2 ×/d + valacyclovir 1000 mg/d for 16 weeks	100% CR	5–14 months	Patients with chronic lymphatic leukemia
Muzio et al	Imiquimod 5%	3	Imiquimod 5% under occlusive dressing (changed every 3 days) for 60–75 days	100% CR	267–423 days	Systemic side effects in 2 patients
Prinz et al	Imiquimod 5%	4	Imiquimod 5% 3 ×/week (daily application in case of no clinical response after 2 weeks)	75% CR (3/4)	6 months	Organ transplant recipients; 1 recurrence after 10 months

Abbreviations: CR, complete response; FU, 5-fluorouracil.

converted into photoactive porphyrins (protoporphyrin IX) with a higher selectivity for neoplastic lesions with MAL (Fritsch et al 1998; Sorensen et al 1998; Peng et al 2001). For the production and accumulation of these photoactive porphyins a sufficient period of time is necessary before the light activation (for MAL 3 hours, for ALA 4 hours up to 14 to 18 hours were stipulated by some authors) (Braathen et al 2007). With MAL-PDT no significant systemic uptake was detected (Sorensen et al 1998).

The light sources used for PDT should match one of the absorption peaks of the photoactive porphyrins. Visible blue light (405 nm), green light (540 nm) and red light (630 nm) from different light sources are used for PDT with a deeper light penetration in the skin for longer wavelengths. In a randomized comparison study red light was more effective than green light for ALA-PDT of BD (initial clearance 94% vs 72%, 12 month clearance 88% vs 48%) (Morton et al 2000).

Several studies provided evidence for the use of topical PDT in BD (summarized overview in Table 2) with initial clearance rates between 88% and 100% (Morton et al 1996; Morton et al 2000; Salim et al 2003).

The reported recurrence rates after 12 months were 15% for MAL-PDT (cryotherapy 21%, 5-FU 17%) (Morton et al 2004) and 0%–12% for ALA (cryotherapy 10%, 5-FU 18%) (Morton et al 1996; Morton et al 2000; Salim et al 2003). Reports about long-term clearance rates are rare. In a retrospective study (617 patients with BD) the recurrence rates after more than 5 years were 5% for surgery, 6% for radiotherapy, 14% for 5-FU, 19% for curettage and 34% for cryotherapy (Thestrup-Pedersen et al 1988). For PDT a relapse rate of 17% after 64 months was reported (Leman et al 2002) suggesting a comparable long-term efficacy of PDT and other established treatment options.

In the largest randomized, placebo-controlled, multicenter study the initial cure was 93% for MAL-PDT (5-FU 83%, cryotherapy 86%, 21% placebo-PDT) (Morton et al 2004). At the 24 months follow-up the complete response rate was 68% (5-FU 59%, cryotherapy 60%, 11% placebo-PDT). In this trial the percentage of an excellent or good cosmetic outcome at 3 months was 89% in the PDT group (cryotherapy 47%, 5-FU 76%) with an improvement after 12 month to 97% for PDT (cryotherpy 62%, 5-FU 94%). The tolerability of MAL-PDT was excellent and superior to cryotherapy and 5-FU (pain was experienced by most PDT patients, but the degree was less than in the cryotherapy group; 5-FU had a poor local tolerability because of eczematous reactions, erosion and ulceration) (Morton et al 2004). In the patients treated with MAL-PDT no serious adverse events were seen (in the cryotherapy group two therapy-related adverse events were reported: lymphangitis and necrosis).

Table 2 Summary of reviewed studies on photodynamic therapy

Reference	Treatment groups	Number of lesions	Regimen	Results (at last follow-up)	Follow-up
De Haas et al	SI	25	ALA-PDT SI with 75 J/cm^2	80% CR	12 months
	2FI	25	ALA-PDT 2FI with 20 and 80 J/cm^2	88% CR	
Morton et al	1. MAL-PDT	275 lesions 111 treated with MAL-PDT	2x MAL-PDT (red-light)	1. 68% CR	24 months
	2. Placebo-PDT			2. 11% CR	
	3. Cryotherapy			3. 59% CR	
	4. 5-FU			4. 60% CR	
Morton et al	ALA-PDT	20	1–2 × ALA-PDT	100% CR	12 months
	Cryotherapy	20	1–3 × 20s FTC	90% CR	
Salim et al	ALA-PDT	33	1 × ALA-PDT	82% CR	12 months
	5-FU	33	(red light)	48% CR	
Morton et al	ALA-PDT (green light)	29	green light (540 ± 15 nm, 62.6 J/cm^2)	48% CR	12 months
	ALA-PDT (red light)	32	red light (630 ± 15 nm, 125 J/cm^2)	88% CR	
Wong et al	ALA-PDT	4	Light-emitting diode 630 ± 40 nm, 240 J/cm^2	75% CR after 1 treatment, 1 recurrence after 8 months successful 2 treatment with CR after 20 months	16 months (20 months)
Dragieva et al	ALA-PDT in OTR	4	1–2 ALA-PDT, incoherent light source (75 J/cm^2)	50% CR	48 weeks
	ALA-PDT in non-OTR	4		not specified	

Abbreviations: ALA, 5-aminolevulinic acid; CR, complete response; FTC, freeze-thaw cycles; ORT, organ transplant recipients; PDT, photodynamic therapy; SI, single illumination; 2FI, 2-fold illumination.

Also in other comparative studies ALA-PDT was superior in efficacy with less adverse events compared with 5-FU (Salim et al 2003) and less painful compared to cryotherapy (Morton et al 1996; Ahmed et al 2000).

Successful treatment of digital BD with PDT was reported with good functional and cosmetic results (complete response in 4/4 patients with follow-up of 16 month, 1 recurrence after 8 months responding to retreatment (Wong et al 2001); complete response in 1/1 patient during 30 months follow-up (Usmani et al 2005).

In 2 cases after the treatment of anogenital BD with PDT a progression to SCC was reported (in both cases other treatments were performed either before or after the PDT) (Varma et al 2000; Heart et al 2006).

In immunosuppressed transplant recipients MAL-PDT was compared with 5-FU with complete resolution in 89% (8/9) after PDT and 13% in the 5-FU group (follow-up 6 months) (Perrett et al 2006). In another open trial ALA-PDT in immunosuppressed transplant recipients was compared with ALA-PDT in immunocompetent patients in the treatment of AK and BD. The four BD in the transplant recipients cleared 1 month after treatment with 2 recurrences during the follow-up (48 months) (Dragieva et al 2004).

In summary topical PDT in the treatment of BD is a therapy option with high efficacy and good cosmetic outcome. It is tissue-sparing and non-invasive and especially suited for poor-healing sites, patients with large and multiple lesions and patients with comorbidities (eg, diabetes, immunosupression, treatment with anticoagulants). The side effects (predominantly local phototoxic effects like burning, stinging and prickling sensations and pain) are mild-moderate, of short duration and easily managed. Rare side effects are erosions, ulceration, blisters, pustules, peeling, and hyper- or hypopigmentation (DeHaas al 2007). Topical PDT has been recommended as a first-line therapy for BD or even the best treatment option of BD (Salim et al 2003; Braathen et al 2007; Lehmann 2007).

In immunosuppressed transplant recipients (more than one million patients worldwide) with an incidence of cutaneous premalignant and malignant lesions from 40% to 60% after 20 years (Boyle et al 1984) and sometimes more than 100 NMSC in high risk patients with fatal outcome in 10% (Berg and Otley 2002) topical PDT is particularly useful because large areas can be treated and the treatment can and should be repeated frequently. Although the long-term cure rates are significantly lower than in immunocompetent

patients (Dragieva et al 2004), PDT is an excellent treatment option in transplant recipients because other standard therapies are limited in these patients as well.

Discussion

The conventional treatment options (cryotherapy, curettage with cautery, excision, 5-Fluorouracil, radiotherapy, laser) appear to have generally similar efficacy and recurrence rates with no single therapy being superior for all clinical situations. They all have their advantages and they all are connected with some certain side effects and adverse events (eg, ulceration, infection, scarring and hypopigmentation after cryotherapy; toxicity of radiotherapy and prolonged healing depending on the used technique; "fragile scalp syndrome" with atrophic epidermis and erosions after extensive carbon dioxide laser; inflammation with erosion and ulceration during 5-FU).

As BD is often located on the lower limb of an older person, there is need for non-invasive treatment options with only mild-moderate local side effects or adverse events even in poor-healing sites.

Diclofenac 3% gel is a non-destructive therapy that was already successfully used in the treatment of actinic keratosis (Wolf et al 2001; Smith et al 2006).

In the seven published cases of BD treated with diclofenac 3% gel mentioned above the therapy was very effective (100% complete clinical and histological clearance) and it was well tolerated with only mild side effects (inflammation, itching and dryness) (Pantel and Stockfleth 2007). However, these promising data have to be proven in randomized controlled trials and optimum regimens (once vs twice daily application, duration of application, etc) and recurrence rates in long-term follow-up have to be investigated. Diclofenac 3% gel is not yet licensed for BD.

The use of topical imiquimod is an effective alternative treatment option for patients and body sites that are unsuitable for other treatments like surgery.

As extragenital BD contains in about 47% of acral and in about 24% of nonacral lesions the HPV genome, imiquimod might have a double effect in these cases because of its antiviral and antitumor activity through stimulation of innate and acquired immunity.

Nevertheless further and larger prospective studies with long-term follow-up are required to verify the results mentioned above and to figure out an optimal dosing scheme (duration of treatment, number of weekly applications) with high efficacy and decreased local side effects (common local adverse effects: erythema, pruritus, erosion, ulceration vesicle formation). The risk of systemic side effects (eg, fever, flu-like symptoms, lymphopenia) due to absorption of imiquimod has to be considered when imiquimod is used under occlusion. Imiquimod is not yet licensed for BD.

In comparative studies topical PDT had a similar efficacy and less adverse events in comparison with cryotherapy and PDT was more effective with fewer adverse events when compared with 5-FU in the treatment of BD. The most common side effect during PDT is pain (reported by most of the patients as mild to moderate and by a minority as severe or even intolerable). Other common local side effects are erythema, edema and crust formation but in most of the studies no ulceration, infection or other more serious adverse events were seen.

Cosmetic outcome after PDT was typically superior compared to the existing standard therapies. PDT can be repeated easily if required and it is popular with patients.

PDT is especially suited for poor-healing sites, patients with large and multiple lesions and patients with comorbidities (eg, diabetes, immunosupression, treatment with anticoagulants).

Another special group of patients profiting from the (repetitive) treatment with PDT are immunosuppressed transplant recipients with their multiple premalignant and malignant cutaneous lesions and their higher risk to develop potentially fatal squamous cell carcinoma from AK and BD (although the evidence base in these patients is limited and the results showed a higher recurrence rate during follow-up compared with immunocompetent patients).

Thus there is no single definite "right way" for all patients with BD, the choice of treatment should be guided by its efficacy, location and size of BD, number of lesions, availability of the therapy, the clinicians expertise, patient factors (age, immune status, concomitant medication, comorbidities and compliance), cosmetic outcome and the patients preference. In consideration of a 10% recurrence rate for most treatment options a risk-adapted follow-up is recommended.

Disclosures

The authors declare no conflicts of interest.

References

Ahmed I, Berth-Jones J, Charles-Holmes S, et al. 2000. Comparison of cryotherapy with curettage in the treatment of Bowen's disease:a prospective study. *Br J Dermatol*, 143:759–66.

Arlette JP. 2003. Treatment of Bowen's disease and erythroplasia of Queyrat. *Br J Dermatol*, 149:43–7.

Ball SB, Dawber RP. 1998. Treatment of cutaneous Bowen's disease with particular emphasis on the problem of lower leg lesions. *Australas J Dermatol*, 39:63–8.

Bargmann H, Hochmann J. 2003. Topical treatment of Bowen's disease with 5-Fluorouracil. *J Cutan Med Surg*, 7:101–5.

Bell HK, Rhodes LE. 1999. Bowen's disease – a retrospective review of clinical management. *Clin Exp Dermatol*, 24:338–9.

Berg D, Otley CC. 2002. Skin cancer in organ transplant recipients:epidemiology, pathogenesis, and management. *J Am Acad Dermatol*, 47:1.

Boyle J, MacKie RM, Briggs JD. 1984. Cancer, warts, and sunshine in renal transplant patients. A case-control study. *Lancet*, 31:702.

Boynton KK, Bjorkman DJ. 1991. Argon laser therapy for perianal Bowen's disease:a case report. *Laser Surg Med*, 11:385–7.

Braathen LR, Szeimies RM, Basset-Seguin N, et al. 2007. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus. *J Am Acad Dermatol*, 56:125–43.

Brannan PA, Anderson HK, Kersten RC. 2005. Bowen disease of the eyelid successfully treated with imiquimod. *Ophthal Plast Reconstr Surg*, 21:321–2.

Brown VL, Atkins CL, Ghali L. 2005. Safety and efficacy of 5% imiquimod cream for the treatment of skin dysplasia in high risk renal transplant recepiens:randomized, double-blind, placebo-controlled trial. *Arch Dermatol*, 141:985–93.

Chen K, Shumack S. 2003. Treatment of Bowen's disease using a cycle regimen of imiquimod 5% cream. *Clin Exp Dermatol*, 28:10–2.

Chung YL, Lee JD, Bang D, et al. 2000. Treatment of Bowen's disease with a specially designed radioactive skin patch. *Eur J Nucl Med* 27:842–6.

Clavel C, Pham-Huu V, Durlach A, et al. 1999. Mucosal oncogenic human papillomaviruses and extragenital Bowen's disease. *Cancer*, 86:282.

Cleary RK, Schaldenbrand JD, Fowler JJ, et al. 2000. Treatment options for perianal Bowen's disease:survery of American Society of Colon and Rectal Surgeon Members. *Am Surg*, 66:686–8.

Cook-Bolden F, Weinberg JM. 2002. Topical imiquimod 5% cream in the treatment of Bowen's disease of the penis. *J Am Acad Dermatol*, 46:146–7.

Cox NH, Dyson P. 1995. Wound healing on the lower leg after radiotherapy or cryotherapy of Bowen's disease and other malignant skin lesions. *Br J Dermatol*, 133:60–5.

Cox NH, Eedy DJ, Morton CA. 1999. Guidelines for management of Bowen's disease. *Br J Dermatol*, 141:633–41.

Cox NH, Eedy DJ, Morton CA. 2007. Guidelines for management of Bowen's disease: 2006 update. *Br J Dermatol*, 156:11–21.

Danielsen AG, Sand C, Weismann K. 2003. Treatment of Bowen's disease of the penis with imiquimod 5% cream. *Clin Exp Dermatol*, 28:7–9.

Dave R, Monk B, Mahaffey P. 2003. Treatment of Bowen's disease with carbon dioxide laser. *Laser Surg Med*, 32:335.

Dawe SA, Salisbury JR, Higgins E. 2005. Two cases of Bowen's disease successfully treated topically with 3% diclofenac in 2.5% hyaluronan gel. *Clin Exp Dermatol*, 30:712–3.

DeHaas ERM, Sterenborg HJCM, Neumann HAM, et al. 2007. Response of Bowen Disease to ALA-PDT using a single and a 2-fold illumination scheme. *Arch Dermatol*, 143:264–5.

Dragieva G, Hafner J, Dummer R, et al. 2004. Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. *Transplantation*, 77:115–21.

Dupree MT, Kiteley RA, Weismantle K, et al. 2001. Radiation therapy for Bowen's disease:lessons for lesions of the lower extremity. *J Am Acad Dermatol*, 45:401–4.

Dyall-Smith D. 1998. Intralesional bleomycin. *Australas J Dermatol*, 39:123–4.

Fritsch C, Homey B, Stahl W, et al. 1998. Preferential relative porphyrin enrichment in solar keratoses upon topical application of delta-aminolevulinic acid methylester. *Photochem Photobiol*, 68:218–21.

Gad F, Viau G, Boushira M, et al. 2001. Photodynamic therapy with 5-aminolevulinic acid induces apoptosis and caspase activation in malignant T cells. *J Cutan Med Surg*, 5:8–13.

Gately S. 2000. The contributions of cyclooxygenase-2 to tumor angiogenesis. *Cancer Metastasis Rev*, 19:19–27.

Goh MSY. 2006. Invasive squamous cell carcinoma after treatment of carcinoma in situ with 5% imiquimod cream. *Australas J Dermatol*, 47:186–8.

Gordon KB, Garden JM, Robinson JK. 1996. Bowen's disease of the distal digit. Outcome of treatment with carbon dioxide laser vaporization. *Dermatol Surg*, 22:723–8.

Gordon KB, Robinson J. 1994. Carbon dioxide laser vaporization for Bowen's disease of the finger. *Arch Dermatol*, 130:1250–2.

Gordon KB, Roenigk HH, Gendleman M. 1997. Treatment of multiple lesions of Bowen disease with isotretinoin and interfon alfa. Efficacy of combination chemotherapy. *Arch Dermatol*, 133:691–3.

Graham JH, Helwig EB. 1961. Bowen's disease and its relationship to systemic cancer. *Arch Dermatol*, 83:76–96.

Gutzmer R, Kaspari M, Vogelbruch M, et al. 2002. Successful treatment of anogenital Bowen's disease with the immunomodulator imiquimod, and monitoring of therapy by DNA image cytometry. *Br J Dermatol*, 147:160–5.

Habetts JMW, Tank B, Van Joost T. 1989. Characterization of the mononuclear infiltrate in Bowen's disease (squamous cell carcinoma in situ):evidence of a T-cell-mediated anti-tumor response. *Virchows Arch*, 415:125–30.

Heising RA. 1979. Treatment of Bowen's disease of the ear by the combined use of cryosurgery and topical 5-fluorouracil. *Cutis*, 24:271–5.

Hengge UR, Benninghoff B, Ruzicka T, et al. 2001. Topical immunomodulators- progess treating inflammation, infection and cancer. *Lancet Inf Dis*, 1:189–98.

Herat A, Shirato K, Damian DL, et al. 2006. Invasive squamous cell carcinoma arising in refractory perianal Bowen's disease in a HIV-positive individual. *Australas J Dermatol*, 47:120–3.

Hiruma M, Kawada A. 2000. Hyperthermic treatment of Bowen's disease with disposable chemical pocket warmers:a report of 8 cases. *J Am Acad Dermatol*, 43:1070–5.

Holt PJ. 1988. Cryotherapy for skin cancer:results over a 5-year period using liquid nitrogen spray cryosurgery. *Br J Dermatol*, 119:231–40.

Honeycutt WM, Jansen GT. 1973. Treatment of squamous cell carcinoma of the skin. *Arch Dermatol*, 108:670–2.

Kao GF. 1986. Carcinoma arising in Bowen's disease. *Arch Dermatol*, 122:1124–6.

Khandpur S, Sharma VK 2003. Successful treatment of multiple pre-malignant and malignant lesions in arsenical keratosis with a combination of acitretin and intralesional 5-fluorouracil. *J Dermatol*, 30:730–4.

Kossard S. 2003. Treatment of large facial Bowen's disease:a case report. *Clin Exp Dermatol*, 28(Suppl 1):13–5.

Kreuter A, Hochdofer B, Stücker M, et al. 2004. Treatment of anal intraepithelial neoplasia in patients with acquired HIV with imiquimod 5% cream. *J Am Acad Dermatol*, 50:980–1.

Kuzelova K, Grebenova D, Pluskalova M, et al. 2004. Early apoptotic features of K562 cell death induced by 5-aminolaevulinic acid-based photodynamic therapy. *J Photochem Photobiol B*, 73:67–78.

Landthaler M, Haina D, Brunner R, et al. 1986. Laser therapy of bowenoid papulosis and Bowen's disease. *J Dermatol Surg Oncol*, 12:1253–7.

Lee JD, Park KK, Lee MG, et al. 1997. Radionuclide therapy of skin cancers and Bowen's disease using a specially designed radioactive skin patch. J Nucl Med 38:697–702.

Lehmann P. 2007. Nebenwirkungen der topischen photodynamischen Therapie. *Hautarzt*, 58:597–603.

Leman JA, Mackie RM, Morton CA. 2002. Recurrence rates following aminilaevulinic acid-photodynamic therapy for intraepidermal squamous cell carcinoma compare favourably with outcome following conventional modalities. *Br J Dermatol*, 147 (Suppl 62):35.

Lukas VanderSpek LA, Pond GR, Wells W, et al. 2005. Radiation therapy for Bowen's disease of the skin. *Int J Radiat Oncol Biol Phys*, 63:505–10.

Mackenzie-Wood A, Kossard S, de Launey J, et al. 2001. Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol*, 44:462–70.

Mandekou-Lefaki I, Delli F, Koussidou-Eremondi TH, et al. 2003. Treatment of Bowen's disease with imiquimod cream 5%. *J Eur Acad Dermatol Venereol*, 17:238–9.

Marchesa P, Fazio VW, Oliart S, et al. 1997. Perianal Bowen's disease: a clinicopathologica study of 47 patients. *Dis Colon Rectum*, 40:1286–93.

Masferrer JL, Leahy KM, Koki AT, et al. 2000. Antiangiogenetic and antitumor activities of cyclooxygenase-2 inhibitors. *Cancer Res*, 60:1306–11.

Meykadeh N, Hengge UR, 2003. Topische Immunmodulation in der Dermatologie. *Hautarzt*, 54:641–62.

Micali G, Nasca MR, Tedeschi A. 2003. Topical treatment of intraepithelial penile carcinoma with imiquimod. *Clin Exp Dermatol*, 28:4–6.

Morton CA, Horn M, Leman J, et al. 2004. A randomized, placebo-controlled, European study comparing MAL-PDT with cryotherapy and 5-fluorouracil in subjects with Bowen's disease. *J Eur Acad Dermatol Venereol*, 18 (Suppl 2):415.

Morton CA, Whitehurst C, Moore J, et al. 1996. Photodynamic therapy vs cryotherapy in the treatment of Bowen's disease. *Clin Exp Dermatol*, 21:79.

Morton CA, Whitehurst C, Moore JV, et al. 2000. Comparison of red and green light in the treatment of Bowen's disease by photodynamic therapy. *Br J Dermatol*, 143:767–72.

Morton CA, Whitehurst C, Moseley H, et al. 1996. Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease. *Br J Dermatol*, 135:766–71.

Murata Y, Kumano K, Sashikata T. 1996. Partial spontaneous regression of Bowen's disease. *Arch Dermatol*, 132:429–32.

Muzio G, Ciambellotti A, Rebora A. 2004. Occlusive medication with imiquimod in Bowen's disease. *Acta Derm Venereol*, 84:168–9.

Noodt BB, Berg K, Stokke T, et al. 1996. Apoptosis and necrosis induced with light and 5-aminolaevulinic acid-derived protoporphyrin IX. *Br J Cancer*, 74:22–9.

Nordin P. 1999. Curettage-cryosurgery for non-melanoma skin cancer o the external ear:excellent 5-year results. *Br J Dermatoo*, 140:291–3.

Orengo I, Rosen T, Guill CK. 2002. Treatment of squamous cell carcinoma in situ of the penis with 5% imiquimod cream: a case report. *J Am Acad Dermatol*, 47:225–8.

Ota M, Kawashima M, Mitsuishi T. 2002. Multiple Bowen's disease of the fingers. *Eur J Dermatol*, 12:275–7.

Otani K, Ito Y, Sumiya, et al. 2001. Treatment of Bowen's disease using the ultrasonic surgical aspirator. *Plast Reconstr Surg*, 108:68–72.

Pantel MJ, Stockfleth E. 2007. Does progession from actinic keratosis and Bowen's disease end with treatment:diclofenac gel, an old drug in a new environment? *Br J Dermatol*, 156(Suppl 3):53–6.

Papillon J, Chassard JL. 1992. Respective roles of radiotherapy and surgery in the management of epidermoid carcinoma of the anal margin. *Dis Colon Rectum*, 35:422–9.

Patel GK, Goodwin R, Chawla M, et al. 2006. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease):A randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol*, 54:1025–32.

Peng Q, Soler AM, Warloe T, et al. 2001. Selective distribution of porhpyrins in skin thick basal cell carcinoma after topical application of methyl 5-aminolevulinate. *J Photochem Photobiol B Biol*, 62:140–5.

Perrett CM, McGregor J, Proby C, et al. 2006. A comparative study of topical 5-fluorouracil and topical photodynamic therapy using methyl-aminolevulinate for actinic keratosis and Bowen's disease in organ transplant recipients [abstract]. *J Am Acad Dermatol*, 54:A7.

Phoushek J, Smith KJ. 2001. Imiquimod and 5% fluorouracil therapy for anal and perianal squamous cell carcinoma in situ in an HIV-1-positive man. *Arch Dermatol*, 137:14–6.

Plaza de Lanza M, Ralfs I, Dawber R. 1980. Cryosurgery for Bowen's disease of the skin. *Br J Dermatol*, 103:14.

Prinz BM, Hafner J, Dummer R, et al. 2004. Treatment of Bowen's disease with imiquimod 5% cream in transplant recipients. *Transplantation*, 77:790–1.

Raaf JH, Krown SE, Pinsky CM, et al. 1967. Treatment of Bowen's disease with topical dinitrochlorobenzene and 5-fluorouracil. Cancer, 37:1633–42.

Reizner GT, Chuang TY, Elpern DJ, et al. 1994. Bowen's disease (squamous cell carcinoma in situ) in Kaui, Hawaii: a population-based incidence report. *J Am Acad Dermatol*, 31:596–600.

Salim A, Leman JA, McColl JH, et al. 2003. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. *Br J Dermatol*, 148:539–43.

Schön M, Bong AB, Drewniok D, et al. 2003. Tumor-selective induction of apoptosis and the small-molecule immune response modifier imiquimod. *J Natl Cancer*, 95:1138–49.

Schroeder TL, Sengelmann RD. 2002. Squamous cell carcinoma in situ of the penis successfully treated with imiquimod 5% cream. *J Am Acad Dermatol*, 46:545–8.

Sierra-Valenti X. 2003. Efficacy of imiquimod 5% cream for the treatment of Bowen's disease and basal cell carcinoma. *J Eur Acad Dermatol Venereol*, 17:351.

Smith KJ, Germain M, Skelton H. 2001. Bowen's disease (squamous cell carcinoma insitu) in immunosuppressed patients treated with imiquimod 5% cream and a COX inhibitor, sulindac:potential applications for this combination of immunotherapy. *Dermatol Surg*, 27:143–6.

Smith KJ, Germain M, Skelton H. 2001. Squamous cell carcinoma in situ (Bowen's disease) in renal transplant patients treated with 5% imiquimod and 5% fluorouracil therapy. *Dermatol Surg*, 27:561–4.

Smith SR, Morhenn VB, Piacquadio DJ, et al. 2006. Bilateral comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% 5-fluorouracil cream in the treatment of actinic keratoses of the face and scalp. *J Drugs Dermatol*, 5:156–9.

Sorensen R, Juzenas P, Iani V, et al. 1998. Formation of protoporphyrin IX in mouse skin after topical application of 5-aminolevulinic acid and its methyl ester. *SPIE*, 3563:77–81.

Stevens DM, Kopf AW, Gladstein A, et al. 1977. Treatment of Bowen's disease with Grenz rays. *Int J Dermatol*, 16:329–39.

Stockfleth E, Ulrich C, Schmook T, et al. 2003. The therapeutic impact of immune-response-modifiers (IRM`s) in organ transplant patients. *J Eur Acad Dermatol Venereol*, 17:75–6.

Szeimies RM, Abels C, Fritsch C, et al. 1995. Wavelength dependency of photodynamic effects after sensitization with 5-aminolevulinic acid in vitro and in vivo. *J Invest Dermatol*, 105:672–7.

Tantikun N. 2000. Treatment of Bowen's disease of the digit with carbon dioxide laser. *J Am Acad Dermatol*, 43:1080–3.

Temmi H, Kaisho T, Takeuchi O, et al. 2002. Small antiviral compounds activate immune cells via the TLR7 MyD88-dependent pathway. *Nature Immunol*, 3:196–200.

Thai KE, Sinclair RD. 2002. Treatment of Bowen's disease of the penis with imiquimod. *J Am Acad Dermatol*, 46:470–1.

Thestrup-Pedersen K, Ravnborg L, Reymann F. 1988. Morbus Bowen. A description of the disease in 617 patients. *Acta Derm Venereol*, 68:236–9.

Turpin IM. 1999. Radionuclide therapy of skin cancers and Bowen's disease using a specially designed skin patch. *Plast Reconstr Surg*, 103:1333.

Urosevic M, Maier T, Benninghoff B, et a.l 2003. Mechanism underlying imiquimod-induced regression of basal cell carcinoma in vivo. *Arch Dermatol*, 139:1325–32.

Usmani N, Stables GI, Telfer NR, et al. 2005. Subungual Bowen's disease treated by topical aminolevulinic acid-photodynamic therapy. *J Am Acad Dermatol*, 53:273–6.

van Bezooijen BP, Horenblas S, Meinhardt W, et al. 2001. Laser therapy for carcinoma in situ of the penis. *J Urol*, 166:1670–1.

Varma S, Holt PJA, Anstey AV. 2000. Erythroplasia of Queyrat treated by topical aminolaevulinic acid photodynamic therapy:a cautionary tale. *Br J Dermatol*, 142:825–6.

Vidal D, Matias-Guiu X, Alomar A. 2004. Efficacy of imiquimod for the expression of Bcl-2, Ki67, p53 and basal cell carcinoma apoptosis. *Br J Dermatol*, 151:656–62.

Wang KH, Fang JY, Hu CH, et al. 2004. Erbium:YAG laser pretreatment accelerates the response of Bowen's disease treated by topical 5-fluorouracil. *Dermatol Surg*, 30:441–5.

Webber J, Luo Y, Crilly R, et al. 1996. An apoptotic response to photodynamic therapy with endogenous protoporphyrin in vivo. *J Photochem Photobiol B*, 35:209–11.

Welch ML, Grabski WJ, McCollough ML, et al. 1997. 5-Fluorouracil iontophoretic therapy for Bowen's disease. *J Am Acad Dermatol*, 36:956–8.

Wolf JE, Jr, Taylor JR, Tschen E, et al. 2001. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. *Int J Dermatol*, 40:709–13.

Wong TW, Sheu HM, Lee JY. 2001. Photodynamic therapy for Bowen's disease (squamous cell carcinoma in situ) of the digit. *Dermatol Surg*, 27:452–6.

Yerebakan O, Ermis O, Yilmaz E, et al. 2002. Treatment of arsenical keratosis and Bowen's disease with acitretin. *Int J Dermatol*, 41:84–7.