Review of photodynamic therapy in actinic keratosis and basal cell carcinoma

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Abstract: The number of non-melanoma skin cancers is increasing worldwide, and so also the demand for effective treatment modalities. Topical photodynamic therapy (PDT) using aminolaevulinic acid or its methyl ester has recently become good treatment options for actinic keratosis and basal cell carcinoma; especielly when treating large areas and areas with field cancerization. The cure rates are usually good, and the cosmetic outcomes excellent. The only major side effect reported is the pain experienced by the patients during treatment. This review covers the fundamental aspects of topical PDT and its application for treatment of actinic keratosis and basal cell carcinoma. Both potentials and limitations will be reviewed, as well as some recent development within the field.

Keywords: photodynamic therapy, actinic keratosis, basal cell carcinoma

Introduction

The number of skin cancers has increased annually for many years (Marks 1995). One of the most important etiologic factors is considered to be sun exposure. Staying out in the sun during a prolonged time and repeated sun burns are clear risk factors for the development of different types of skin cancer. This is especially applicable on persons having lighter complexion (skin type I-II).

There are mainly three forms of malignant tumors of the skin. These are malignant melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC and SCC belong to the group of non-melanoma skin cancer (NMSC), which is the most common skin malignancy worldwide (Miller 1991; Green 1992). Actinic keratosis (AK) and squamous cell carcinoma in situ (SCCIS), also called Morbus Bowen, are precursors of SCC and therefore also normally are ascribed the NMSCs. The incidence of NMSC is increasing steadily (Green 1992), and the association between skin type, solar habits and NMSC is well known. Furthermore, once a patient has had a NMSC, additional lesions are common (Frankel et al 1992). Also, organ transplant recipients (OTR) run an extremely high risk of contracting NMSC (Adami et al 2003; Bouwes Bavinck et al 2007). Consequently, an increasing number of patients seek care with sun damaged skin and skin tumors and the patients must be taken care of in an effective manner.

During recent years, several therapeutic modalities have been available for superficial skin cancer. One of those is photodynamic therapy (PDT), which involves the activation of a photosensitizer using visible light (Henderson and Dougherty 1992). This results in the formation of reactive and cytotoxic singlet oxygen. PDT is a relatively new therapeutic method and it has become a good complement in this respect to already established treatments of skin cancer of non-melanoma type, particularly because of the good cosmetic outcome which is increasingly important, as recently reviewed by other authors (Morton 2004; Marmur et al 2004; Kormeili et al 2004; Lehmann 2007; Braathen et al 2007). The current review will address PDT of BCC and AK, which

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are the most common applications of topical-PDT within dermatology today. Also the fundamental aspects and recent developments of the treatment will be covered.

Actinic keratosis (AK)

SCC and AK represent the same disease process at different stages of evolution (Cockerell 2000), ie, AKs are proliferations of transformed, neoplastic keratinocytes confined to the epidermis, whereas SCC extend more deeply including dermis. Thus AK lesions are considered as pre-cancerous or pre-malignant, and a few of the lesions progress to SCCIS or SCC. AKs are extremely prevalent and strongly related to sun exposure. The lesions occur on the dorsum of the hands, the face, scalp and other sun exposed sites. AKs are often multiple and recently the concept of 'field cancerization' has been discussed, meaning that the clinically normal appearing skin around AKs provides the basis for clonal expansion of genetically altered neoplastic cells (Braakhuis et al 2003). This means that an entire area has undergone solar damage with precancerous and cancerous lesions. Field cancerization can, for example, occur in the face. It is clinically difficult to distinguish between a proliferative AK and an early invasive SCC. As field cancerization often occurs, it is necessary with a treatment that not only involves overt AK, but also treats subclinical lesions nearby. For this reason, topical PDT which is a non-invasive method, has become an important treatment modality.

Basal cell carcinoma

Of the NMSCs, BCCs are the most common (Miller 1991). Of all BCCs, 85% appear in the head and neck region. BCCs almost never metastasize but can destroy the tissue locally and thus have to be treated. Particularly this has to be kept in mind when located in the H-zone. The BCCs can be divided into three variants according to histopathological pattern and degree of aggressiveness (Miller 1991; Champion et al 1998). The most common is nodular BCC, which grows in large, normally well delineated, rounded, nests pushing into dermis. Nodular BCC accounts for approximately 60% of the BCCs, and is most frequently observed in the face. Superficial BCC has a growth pattern where the tumor nests are restricted to epidermis or superficial parts of hair follicles. The most common location of the superficial BCCs is on the trunk. The third and most aggressive type is morpheic BCC, which has an infiltrative growth pattern. The tumor nests are diffuse and irregularly spread, and are often found in subcutis. This type of BCC is often located on the central face, ie, on the nose, lips, ears and around the eyes, with a higher risk of recurrence after treatment compared to other locations. Transitions between the different types of BCC may occur. Regarding therapy, the H-zone location is very important to keep in mind concerning the high recurrence risk, while, usually, superficial BCC outside this area run a low risk. Topical PDT is today an accepted treatment for superficial BCC.

Non-melanoma skin cancer in organ transplant recipients(OTRs)

OTRs have been reported to run a more than fifty times increased risk of contracting SCC because of their immunosuppressive therapy (Adami et al 2003). Many of these patients obtain widespread AK. Heart transplant patients are particularly susceptible because of their older mean age and the requirement for more aggressive immunosuppressive therapy. Therefore, efficient treatment modalities are required to be able to treat these patients, and topical-PDT has recently become an interesting treatment option.

Basic aspects of PDT

The fundamental approach of PDT is initial photosensitization of the treatment site, followed by irradiation with visible light, which initiates a tissue-toxic photochemical reaction (Henderson and Dougherty 1992). The first attempts at PDT were reported by Tappeiner and Jesionek as early as in 1903 (Tappeiner and Jesionek 1903). But it was not until in 1972, Diamond and co-workers found that tumor cells were destroyed by visible light after sensitization using hematoporphyrin derivative (Diamond et al 1972). Thereafter Dougherty et al (1978) initiated clinical studies of PDT of various malignant tumors with promising results. Today, most commonly, the photosensitization for PDT of superficial skin lesions is obtained by topical application of δ-5-aminolaevulinic acid (ALA) or its methyl ester (MAL) (Peng et al 1997; Salva 2002; Braathen et al 2007). The main advantages of topical PDT are that the method is non-invasive and effective, and generally gives a good cosmetic outcome. The application of ALA or MAL enhances the formation of protoporphyrin IX (PpIX) in the skin. The tumor is irradiated with light matching the absorption of PpIX, which initiates the photochemical reaction, in which reactive singlet oxygen is formed. The singlet oxygen is generally believed to be one of the key factors for the desired therapeutic effect of PDT (Weishaupt et al 1976; Moan and Sommer 1985). Consequently, the presence of appropriate concentration of sensitizer, light matching the absorption of

the sensitizer and molecular oxygen in the tissue, is crucial for the efficiency of PDT.

Photosensitizing drugs for topical PDT

The early photosensitisers for PDT were based on hematoporphyrin derivatives, which were directly injected into the tumors (Peng et al 1997). The main drawback however was prolonged and systemic photosensitivity, persisting around 4–6 weeks. Kennedy et al investigated the possibility to use endogenously formed PpIX obtained after application of ALA, a precursor in the haem synthesis (Kennedy et al 1990; Kennedy and Pottier 1992). The results were promising, and the drawbacks of systemic and prolonged photosensitization were eliminated. Instead, a local photosensitization of the application site was found up to 48 hours. Since then, topical ALA-PDT has been widely investigated for treatment of superficial skin lesions, eg, BCCs and AK. In addition to ALA, a number of ALA esters have been investigated (Lopez et al 2004). The methyl-ester, ie, 16% MAL, has gained drug approval and is the sole commercially available drug for topical PDT in Europe with the trade name Metvix® (Galderma & Photocure ASA). While in the USA, 20% ALA in ethanol solution is the approved drug, ie, Levulan® (DUSA Pharmaceuticals, Inc.).

It has been known for a long time that certain abnormalities in the haem synthesis, ie, porphyria, lead to extensive photosensitization because of the accumulation of porphyrins particularly PpIX (Bottomley and Muller-Eberhard 1988). But the group of Pottier et al (1986) was the first to demonstrate the accumulation of PpIX after injection of exogenous ALA in mice. The formation of haem takes place in the mitochondrial and the cytosolic compartments of the cells. The primary substrates in the production of haem are glycine and succinyl CoA, from which ALA is formed. This is the rate-limiting step in the pathway, due to negative feedback control by haem. By applying exogenous ALA this step is bypassed leading to an accumulation of PpIX in the tissue. Two enzymes have been reported to be of particular importance for the accumulation of PpIX in tissue after topical application of ALA. These enzymes are porphobilinogen deaminase (PBGD) and ferrochelatase (FC). Increased activity of PBGD, in connection with decreased FC activity in neoplastic tissue, have been reported to be possible factors behind the selective accumulation of PpIX (Dailey and Smith 1984; Leibovici et al 1988; Kondo et al 1993; Hinnen et al 1998; Gibson et al 1998). The metabolic pathway of MAL is generally believed to be the same as ALA, but the transportmechanism into the cells have been shown to differ (Rud et al 2000; Gederaas et al 2001; Rodriguez et al 2006). In addition, the the methyl-ester must be dehydrolyzed at some stage, but it is not clear in which step the ester hydrolysis is undertaken.

Selective accumulation between tumor and normal tissue has been observed using ALA-induced PpIX sensitization (El-Far et al 1990; Kennedy and Pottier 1994; Abels et al 1994; Andersson-Engels et al 1995). When ALA is applied systemically, the selectivity is most likely explained by altered enzymatic activity in the tumor cells, as described above. Although, the stratum corneum, ie, the outer skin barrier, seems to be the factor of major importance for the selectivity, since it has a large impact on the penetration of ALA through the skin (Moan et al 2001). The abnormal keratin layer that is produced by BCCs or SCCs is rapidly penetrated by ALA, while the adjacent normal skin with intact stratum corneum is less permeable. This has been verified in vivo, where the ALA penetration was found to be higher in BCC compared to the surrounding normal skin by microdialysis studies (Wennberg et al 2000). Consequently, higher concentrations of ALA will result in higher amounts of PpIX in the tumor. The fluorescence contrast after application of ALA has been found to be time dependent with an optimum around 3 hours in BCCs (Ericson et al 2003). There are indications that MAL is more selective towards neoplastic tissue compared to ALA (Angell-Petersen et al 2006), although there is a lack of comparing studies verifying this relationship.

When ALA or MAL is applied topically, sufficient amounts of drug have been found to be present in both epidermis and dermis, although the dermal cells do not develop significant PpIX levels to become photosensitized (Divaris et al 1990). Hence, only epidermis becomes sensitized. This makes it possible to treat epidermal cancers without damaging dermis, which might be the reason why scarring is uncommon in topical ALA-PDT. It has been shown that the cellular localization of PpIX after ALA application is restricted to the mitochondria (Peng et al 1992; Iinuma et al 1994; Malik et al 1996). Hence, the initial photodynamic damage will be localized to this organelle. The subsequent apoptosis of the cells has been reported to occur within 10 hours (Webber et al 1996).

In order to improve topical drug delivery of ALA or MAL, some attempts have been made. Soler et al (2000) used a formulation including DMSO for delivery of 20% ALA. Other recent publications report on the use of cubic-lipid-systems (Bender et al 2005), and a bioadhesive patch (McCarron et al 2006). However, so far there is a

lack of studies verifying the clinical response using these methods.

Light sources and dosimetry

Whatever the choice of light source for PDT, two criteria have to be fulfilled. Firstly, the wavelength must match the absorption of the sensitizer in order to induce the desired photochemical reaction. The second criterion is that the light must be able to penetrate the tissue, so that the depth of the tumor can be treated. Due to the presence of melanin, hemoglobin, oxyhemoglobin and water, the absorption of visible light is high in biological tissue (Tuchin 2000). But the absorption has a minimum in the wavelength region 600–1000 nm, ie, the "optical window" of tissue (Richards-Kortum and Sevick-Muraca 1996). In this region, the light propagation is dominated by scattering, and the penetration depth is around 8–10 mm. Therefore, normally red light centered around 635 nm is used to ensure therapeutic fluence rates for topical PDT (Peng et al 1997; Salva 2002; Braathen et al 2007), even though the maximum absorption of PpIX is around 400 nm. But successful treatment of AK with ALA-PDT and blue light has been reported (Jeffes et al 2001; Zelickson et al 2005).

Both coherent and incoherent light sources have been applied for PDT of various diseases. Lasers offer significant advantages whenever fibre optics are needed. In addition lasers have the advantage of producing monochromatic light, exactly matching the absorption band of the sensitizer. In this way excessive heating is avoided. Various lasers have been applied in PDT, eg, Svanberg et al (1994), but the major drawbacks are their bulkiness and the fact that they are expensive. Moreover, the area of irradiation is limited, so the beam has to be scanned in order to treat larger areas.

Filtered broadband lamps have proven to be very useful for the treatment of superficial lesions (Wennberg et al 1996; Varma et al 2001). The main advantages are that they are relatively inexpensive, but the wavelength bands are usually quite broad, 50–130 nm, and they can be quite bulky. The wavelengths outside the absorption spectrum of the photosensitiser were earlier thought to have no therapeutic effect, other than hyperthermia. On the other hand, it has been discussed that the excitation of photoproducts absorbing around 670 nm might actually contribute to the photodynamic reaction (Peng et al 1997); but the results are contradictory (Soler et al 2000; Clark et al 2003). Recently, so-called intense pulsed light (IPL) has been evaluated for PDT (Kim et al 2005; Gold et al 2006), although there is a report on dramatically decreased PDT reaction using IPL compared to broad-band light source (Strasswimmer and Grande 2006).

Light-emitting diodes (LED) can also be used as light sources for PDT (Thompson et al 2001; Yang et al 2003). The wavelength band is narrower compared with filtered lamps. The earlier problem with LEDs has been their relatively low intensity, although the recent generation of LEDs seems to provide sufficient intensities for PDT of superficial skin lesions. These light sources are very compact and cheap, which is of great preference for clinical practice.

Light dosimetry and oxygen depletion

Despite the fact that PDT is a rather well accepted treatment modality for treatment of NMSC, there exists no common light dosimetry guide. Because of the wide variety of light sources, the reported light doses and fluence rates used for PDT have a broad span, ranging from 50 to 500 J/cm^2 and 50 to 200 mW/cm^2 respectively (Dougherty et al 1998; Radakovic-Fijan et al 2005). Fluence rates below 150 mW/cm^2 should be used to avoid hyperthermia (Peng et al 1997). In addition, oxygen depletion is of concern at fluence rates above 50 mW/cm^2 for PDT of AK (Ericson et al 2004). This is verified by experimental studies in rodents (Sitnik et al 1998; Robinson et al 1999; Iinuma et al 1999; Bissonnette et al 2004), cell spheroids (Foster et al 1993), and mathematical modeling (Foster et al 1991), showing significantly better results when low fluence rates are applied. These results are most likely related to oxygen depletion at high fluence rates (Tromberg et al 1990).

Since the presence of singlet oxygen is crucial for the photodynamic reaction, it would be desirable to be able to monitor its formation in vivo. Unfortunately, there exists no simple method of direct detection of singlet oxygen in biological tissue (Gorman and Rodgers 1992), but there have been attempts with some success in keratinocytes (Bilski et al 1998). Different oxygen sensors have been investigated in pre-clinical studies for monitoring the oxygen tension during PDT (Curnow et al 2000), although this has so far not been investigated in patients. Another possibility is in vivo monitoring of the photobleaching of the sensitizer. In the clinical study presented by Ericson et al (2004) it was reported that the treatment outcome indeed was found to be fluence-rate-dependent and correlated to the rate of photobleaching, where low fluence rates were found preferable.

Light fractionation

It has been suggested that light fractionation should be performed to minimize the effect of hypoxia during PDT.

Splitting up the light dose in minor fractions would allow oxygen to diffuse back into the cells, increasing the efficiency of the treatment. Theoretical calculations have predicted that effective reoxygenation takes place already after 45 s (Foster et al 1991). In vivo studies in rodents state that dark interval of 150 s is required (Curnow et al 2000). Other reports with 2 hours' dark period show similar results (Robinson et al 2000; Robinson et al 2003). For this reason, various illumination schemes have been suggested. For example, de Haas et al (2006) suggest that 20 + 80 J/cm^2 given at a fluence rate of 50 mW/cm^2 is more effective than a single treatment of 75 J/cm^2 when treating superficial BCCs. Earlier reports based on results from an animal model recommend 5 + 95 J/cm^2 (Robinson et al 2000; Robinson et al 2003). Other investigators have failed to show an effect when using fractionated PDT (Babilas et al 2003), which implies that the choice of illumination scheme is important in order to obtain an effect of the fractionation minimizing hypoxia during PDT.

Clinical studies with PDT of AK

AK typically appears as field cancerization of large areas in the head and face region. Thus PDT has proven to be an excellent treatment modality for this subgroup of patients, because of the ability to treat large areas and preferable cosmetic outcome. Both ALA and MAL have been applied as photosensitizisers for PDT of AK. No comparable study currently exists, although the cure rates seem to be similar by reviewing the literature.

The long-term cure rate for PDT using 20% ALA solution (14–18 hours application), blue light (10 mW/cm^2, 10 J/ cm^2), and two treatments was reported to be 78% after 12 months follow up (Tschen et al 2006). Another study reports on 89% cure rate at 3 month follow up using a similar treatment protocol (Piacquadio et al 2004). In a light-dose ranging study complete response using 20% ALA cream (3 hours application), red light (30 mW/cm^2, 100 J/cm^2), and single treatment was found to be 89% at two months follow up in the low fluence rate group (Ericson et al 2004). Similar treatment protocol, but two treatments and red light (70 mW/cm^2, 70 J/cm^2), resulted in 85% complete response (Sandberg et al 2006). A study has been performed comparing 5-fluorouracil (5-FU) to a single treatment of ALA-PDT, with comparable results (Kurwa et al 1999).

Cure rates for PDT with 16% MAL (3 hours' application), red light (75 J/cm^2), and two treatments were reported to be 89%–91% at 3-month follow-up (Pariser et al 2003; Freeman et al 2003). When treating thin actinic keratosis, it seems that one treatment is sufficient using MAL-PDT, although two treatments are recommended for more hyperkeratotic lesions (Tarstedt et al 2005). Studies comparing the outcome by two consecutive topical MAL-PDTs versus cryotherapy have been performed for AKs (Szeimies et al 2002; Morton et al 2006). The cure rates were found similar although the cosmetic results were superior using PDT. In addition, the patients were found to prefer PDT over cryotherapy.

Clinical studies with PDT of BCC

Superficial BCC

Several studies have been performed investigating PDT for superficial BCCs. For example, Wennberg et al (1996) report a 91% clearance of superficial BCCs treated with single sessions of 20% ALA-gel (4 hours' application) and red light (125–166 mW/cm^2, 75–100 J/cm^2). Soler et al (2000) found no differences in cure rates, ie, 82%–86%, comparing laser (630 nm, 120–150 mW/cm^2, 100–150 J/cm^2) and a broad band light source (100–180 mW/cm^2, 150–200 J/cm^2) when treating superficial BCCs with ALA-PDT. Horn et al (2003) demonstrated clearance rates at 92% when using two consecutive treatments of MAL-PDT (16% MAL, red light). The cosmetic results are usually excellent and relatively large areas can be treated.

Nodular basal carcinoma

There is some evidence for using topical PDT in nBCCs (Horn et al 2003; Vinciullo et al 2005). However, a careful curettage was carried out before application of the MAL-cream. Rhodes et al (2004) demonstrated potential problems with long-term recurrence rates when treating nodular BCC with MAL-PDT. In order to improve cure rates for PDT of nodular BCCs, intralesional treatment protocol has been suggested (Cappugi et al 2004). Again, the cosmetic outcomes with PDT are generally impressive. Thus, topical-PDT can be a preferable treatment choice for nodular BCCs in 'difficult-to-treat' areas, although special pre-operative handling is necessary.

Morpheic basal cell carcinomas

Morpheic BCCs shall not be treated with PDT. Instead, a Mohs' micrographic surgery is the golden standard (Wennberg et al 1999).

PDT in organ transplanted recipients

Recently, topical PDT has become an interesting treatment modality for dealing with NMSC among OTRs, who exhibit an increased risk of contracting NMSC due to their immune

suppression. Both ALA-PDT and MAL-PDT seem to be able to deal with AK and other epidermal dysplasia among OTRs (Dragieva et al 2004; Wulf et al 2006; Wennberg et al 2005). It appears that the therapeutic results from PDT are superior to that from 5-FU (Perrett et al 2007). Topical PDT in OTRs has been suggested to have a prevention potential prohibiting the development of new lesions (Wulf et al 2006), although contradicting results exist (de Graaf et al 2006).

Side effects of PDT

Acute

PDT is generally well tolerated. Immediately after treatment an erythema and a slight oedema is often seen. Crusts and superficial erosions are typically seen after a few days. Severe ulceration is rare. The most bothersome acute side effect is pain (Kennedy and Pottier 1992; Fijan et al 1995). Most patients experience a burning sensation, also described as 'stinging' or 'prickling', in the ALA-treated area during light exposure. The mechanism for this reaction is not clear. A possible explanation is hyperthermia of the tissue; however, Orenstein et al (1995) obtained performed IR imaging and could not relate the pain sensation with a temperature increase. This implies that the pain sensation is a consequence of the photochemical reaction in the tissue, and related to the presence of reactive singlet oxygen. This is consistent with the clinical experience that the peak pain is obtained after a few minutes of irradiation when the photodynamic activity is high, and then gradually decreased towards the background level (Kennedy and Pottier 1992; Ericson et al 2004).

It has been reported that the site of the lesion is of importance for the pain sensation (Grapengiesser et al 2002; Kapur et al 2003). Treatment of facial lesions, and lesions on the scalp result in more pain. Also, the amount of pain seems to be related to the size of the treated area and type of lesion, since patients with AKs have been reported to experience more pain than patients with BCCs (Grapengiesser et al 2002). There are reports that lower pain scores are obtained with MAL-PDT in comparison with ALA-PDT performed on tape-stripped normal skin (Wiegell et al 2003) and AKs (Kasche et al 2006). But even still, 4 out of the 28 AK patients included in the study by Kasche et al (2006) were not able to complete the treatment due to unbearable pain. Pain management most commonly involves local anesthetics, premedication, fan-cooling or spraying the treated area with water. However, the pain-relieving effects are diverging. Cold air analgesia has shown some effect (Pagliaro et al 2004), while tetracaine gel (Holmes et al 2004), capsaicin cream (Sandberg et al 2006), and morphine-gel (Skiveren et al 2006) seem to have no effect. Currently, no standard protocol for pain relief during PDT exists and further studies on the matter are desired.

Chronic side effects

Chronic side effects of topical PDT are rare. Only three case reports on contact allergy exist. One case report concerns contact allergy to ALA and the other two on MAL (Wulf and Philipsen 2004; Harries et al 2007). Thus, topical PDT can be considered to be a safe treatment.

Conclusion

Topical PDT, both with ALA and MAL, seems to offer a good therapeutic alternative to standard therapies in treating superficial NMSC, especially if widespread areas or field cancerization are involved. Treatment results are generally very good and the cosmetic results are excellent. Large areas of AK can easily be treated by topical-PDT, especially in the head and neck area, such as the scalp of old men. However, pain in these locations can sometimes be cumbersome to deal with and new pain-relieving strategies are required.

For BCCs, topical-PDT has proven especially suited for the superficial form, particularly for treatment of thin and multiple superficial BCCs. Also in this case, both clinical and cosmetic outcomes are excellent. Nodular BCCs are normally excised if possible. Surgery can easily be performed on the cheek, the forehead and the lips, but for lesions located on the nose, eyelids and external ear, simple excision is complicated. For these locations topical-PDT has shown some potiential, although thorough pre-treatment before application of ALA or MAL is necessary, and there is a risk for recurrences. In these instances, also cryotherapy may be good alternative to surgery (Lindgren and Larko 1997).

The OTRs constitute a patient group which suffer from widespread NMSC, and field cancerization constitute a major problem. For these patients, topical-PDT has shown several advantages. In addition, compliance is less of a problem using topical-PDT as the physician has total control over the treatment as opposed to topical treatments, eg, 5-FU, which should be used for a prolonged period (several weeks) and often lead to compliance problems.

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