

Non-invasive treatment of epidermal keratinocyte neoplasms

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Summary

Over the past years there has been a rise in the incidence of skin cancer. The work presented in this thesis focused on non-invasive treatment modalities for both actinic keratosis (AK) and superficial basal cell carcinoma (sBCC): several retrospective data studies and prospective randomized trials were performed.

Chapter 1 gives a general introduction to both AK and sBCC. *Chapter 2* discusses treatment options for AK. In *chapter 2.1* an overview of the available literature is presented, in which the most frequently used therapies are summarized. Photodynamic therapy (PDT), for example, is a well-established treatment for several keratinocyte carcinoma (KC) and its precursors. It is known that AK patients experience pain during PDT illumination. This frequently leads to discontinuation of treatment or refusal of future follow-up treatments. In a split face study (*chapter 2.2*), we investigated whether the use of a pulsed dye laser (PDL) device as illumination source during PDT, was associated with lower pain scores compared to conventional LED-PDT. We found that patients reported lower pain scores and side effects after PDL illumination. The PDL device is however expensive and not available in all clinics, which makes it only an alternative treatment option in case in-clinic treatment is desired and pain is a limiting factor.

In the literature review of chapter 2.1, we found that studies were methodologically heterogeneous and there was a need for more head-to-head trials comparing the most frequently used treatments. It was not possible to draw a solid conclusion on what treatment is the most effective for a continuous area with multiple AKs (so called field-AK). This initiated a large randomized controlled study in *chapter 2.3*, that compared the effectiveness of topical 5-fluorouracil, imiquimod, ingenol mebutate and methylaminolevulinate photodynamic therapy (MAL-PDT) with one another. A total of 624 patients in 4 different hospitals participated. Three months follow-up data show that 5-fluorouracil cream is superior to the other mentioned treatments for field AK: 90.2% of patients treated with 5-fluorouracil had $\geq 75\%$ reduction in AK lesions, compared to baseline. Results for imiquimod, PDT and ingenol mebutate were respectively 76.4%, 76.0% and 67.3%. In this study patients could only receive one re-treatment in case of $< 75\%$ lesion reduction. Only 14.8% of the patients treated with 5-fluorouracil needed a second treatment cycle due to initial insufficient effectiveness, before the 3 months assessment was done. For imiquimod, MAL-PDT and ingenol mebutate these percentages were 35.9%, 43.6% and 47.8%, respectively.

Various treatments are available for BCC, with surgical treatment as gold standard. As invasive treatment is not always the preferred treatment, especially in the case of the superficial BCC, many topical non-invasive treatments are used. Nowadays, cancer medi-

cine increasingly aims to focus on molecular medicine and targeted therapies in order to block tumour growth more specifically. The majority of BCC contains patched 1 (PTCH1) mutations, which lead to an inhibition of the Hedgehog (HH) pathway. There is some evidence that there might be a role for the Wntless (WNT) pathway in BCC. Dysregulation of the WNT pathway leads to the stacking of nuclear β -catenin enhancing tumour cell proliferation. We aimed to investigate whether topical sinecatechin ointment (which consists among others of epigallocatechin-3-gallate), could lead to tumour proliferation arrest or tumour clearance. In a randomized placebo controlled study we could not find a statistically significant clinical, histological or immunochemical effect of the topical sinecatechin ointment on BCC (*chapter 3*).

Previous studies showed that when comparing PDT with topical 5-fluorouracil and imiquimod in the treatment of sBCC, PDT was less effective both at one and three and five-year follow-up in sBCC. It might however still be a desired treatment for a certain subcategory of patients. One can think of the elderly, patients who are unable to complete a self-applicable treatment etcetera). Previous studies showed a high efficacy using a fractionated ALA PDT scheme. We performed a retrospective study (*chapter 4.1*) assessing 323 primary sBCC treated with this fractionated 2-fold aminolevulinic acid 20% (ALA) PDT. With this scheme, two light fractions of 20 and 80 J/cm² are delivered, 4 and 6 hours after 5-ALA application, respectively. Our results showed a cumulative probability of recurrence free survival of 88.8% after 12 months, 81.8% after 24 months and 77.1% after 48 months follow-up. In order to further assess the effectiveness in a more controlled setting and in order to compare it to the conventional MAL-PDT scheme, we performed a multi-centre randomized controlled trial in which 162 patients with primary sBCC participated (*chapter 4.2*). Although the difference was not statistically significant, the 2-fold ALA-PDT scheme did lead to fewer recurrences at 12 months follow-up compared to MAL-PDT: 6 versus 13. Another advantage of this scheme above the conventional MAL scheme is that the one day treatment is more efficient than two illuminations one week apart, as is the case with the conventional MAL scheme.

In *chapter 4.3* we retrospectively assessed the effectiveness of an ambulatory PDT (aPDT) device to treat sBCC. Results show that aPDT is an effective treatment for primary sBCC with a clearance rate of 89.9% at 12 months follow-up. Limitations of the device are its costs and the inability of treating tumours on every location and tumours larger than 2 centimetres. In *chapter 5* results and implication for clinical practise are described and discussed in further detail.