Evidence for treatment of epidermal keratinocyte neoplasms

CHAPTER 5

General discussion and valorization

GENERAL DISCUSSION AND VALORIZATION

In this chapter, the main conclusions of my research will be summarised and discussed. Moreover, the interpretation of the results, the relevance for clinicians and patients, and implications for future research will be outlined.

RELEVANCE OF THE RESEARCH

There is an enormous increase in the incidence of skin malignancies and their precursors.[1-4] The incidence of basal cell carcinoma (BCC) is 1:5-6 in Dutch people and actinic keratosis (AK) is even more frequent, with a prevalence of 28% in female and 49% in male patients aged 45 years and older.[3,5] This increasing incidence is probably the result of more sun exposure during leisure time, but also due to our aging population. Once a patient develops a first keratinocyte carcinoma or melanoma, they have a higher risk of developing a subsequent skin cancer in the future.[6-9]

The high prevalence of patients with epidermal keratinocyte neoplasms will cause a higher burden on the dermatologic practice and therefore evaluation of current diagnostic and treatment strategies is required. More and more treatment options are available for treatment of epidermal keratinocyte neoplasms but head-to-head comparison studies are sparse. Comparison of effectiveness, but also other factors such as cosmetic outcome, patient satisfaction and costs are important items that need to be evaluated.

This thesis describes the outcome of several clinical studies conducted on treatments of AK, Bowen's disease and superficial BCC (sBCC).

TREATMENT OF ACTINIC KERATOSIS

Which treatment for AK is preferred?

For treatment of multiple lesions of AK within one distinct area field-directed therapies are suggested.[10-13] Till date, head-to-head trials which compared different field-directed treatments were lacking. In a multicentre randomized controlled trial (RCT) we included 624 patients with multiple lesions of AK in the head and neck region. In this study, we showed that of four of the most frequently prescribed field-directed treatments, 5-fluorouracil (Efudix®) is the most effective treatment with a cumulative probability of treatment success of 74.7%. For 5% imiquimod (Aldara®), 0.015% ingenol mebutate (IM) (Picato®), and methylaminolevulinate photodynamic therapy (MAL-PDT) this was 53.9%, 28.9%, and 37.7%, respectively (***chapter 2.1***).

Not only was 5-fluorouracil the most effective treatment. A cost-effectiveness analysis after one year of follow-up, showed that 5-fluorouracil was also a dominant cost-effective treatment (***chapter 2.2***). The cost-effectiveness analysis included the costs of the medication, adverse events, second treatment in case of insufficient initial treatment response after one treatment cycle etcetera. The total mean costs after 12 months follow-up were €421, €710, €748, and €1601, for treatment with 5-fluorouracil, imiquimod, IM, and MAL-PDT, respectively. These differences in costs are mainly attributable to differences in treatment costs. One tube of 40 grams of 5-fluorouracil covered a treatment area up to 100 cm^2. One sachet/tube of imiquimod, IM or MAL-PDT covered a treatment area of only 25 cm^2. Besides the higher costs per unit, also the amount of prescribed units was higher for treatment with imiquimod, IM, and MAL-PDT.

Recently, three studies investigated the effectiveness and costs of 5-fluorouracil in AK patients compared to placebo.[14-16] Pomerantz and colleagues performed a double-blinded, placebo-controlled, randomized trial in which 932 veterans, with at least 2 keratinocyte carcinomas within the past 5 years, were randomized to either 5-fluorouracil cream or vehicle control cream. They showed that a single course of 5-fluorouracil significantly reduced AK count (3.0 vs 8.1, $p<0.001$) and had higher complete clearance rates (38% vs 17%, $p<0.01$), 6 months post-randomization. They followed these patients up to a maximum of 4 years after enrolment. The median follow-up duration was 2.6 years in both groups. They found that there was less use of lesion directed treatments of AK in the 5-fluorouracil group every 6-months intervals ($p<0.01$).[14] They also found that the single course of 5-fluorouracil reduced the risk of SCC after one year.[17] Alongside the primary study, performed by Pomerantz et al., information was obtained on costs and utilization for AK and keratinocyte cancer care, up to 3 years after randomization. They concluded that after 3 years of follow-up, costs in the 5-fluorouracil group were $771 less per patient.[15] The same group of investigators, tracked the individual AK lesions of 319 of the patients described in the trial of Pomerantz et al.. In this study, lesions were photographed and mapped to study the effect of 5-fluorouracil on prevention of new lesions.[16] This prospective study showed that one course of 5-fluorouracil also significantly reduced the amount of new lesions of AK up to 36 months after treatment. The relative risk of mean number of new AK lesions per persons in 5-fluorouracil group compared to placebo was 0.65 (95% CI 0.51-0.83), 36 months post-treatment.[16]

As clinicians, we think that patients regard the most effective treatment as best therapy. However, other treatment factors, as cosmetic results, side effects, impact on quality of life, and patient satisfaction are important characteristics. Ideally, the most (cost)effective treatment includes the best results in these other factors as well.

In our study, the cosmetic outcome was assessed by the physician blinded to treatment allocation on a 4 point scale (1=excellent, 2=good, 3=moderate and 4=poor). Changes in erythema and pigmentation were taken into account. Good to excellent cosmetic result was found in 90.3%

of patients treated with 5-fluorouracil, in 89.7%, 96.6%, and 95.1% of the patients treated with imiquimod, PDT and IM, respectively. We found that the cosmetic result 12 months after treatment was slightly better for MAL-PDT and IM compared to 5-fluorouracil and imiquimod. A possible explanation for a better cosmetic outcome following PDT and IM could be the fact that these treatments led to a less intense tissue response but perhaps therefore also less effective. It seems reasonable to assume that the intensity of tissue response might result in post-treatment changes, such as change in erythema and/or hypo-, hyperpigmentation, that influenced the cosmetic appearance.

To obtain information on side effects, we asked patients to complete a diary during and two weeks post-treatment. All reported side effects, such as various irritations of the skin, were well known treatment related side effects that have been described in literature. Overall, treatment with 5-fluorouracil was not associated with a higher frequency of side effects when compared with the other treatments. Patients treated with MAL-PDT reported more often pain and burning sensation in comparison with the self-applied creams/gels. Pain can be an important reason for a patient to refuse further treatment or to influence patient satisfaction.

In our study, all patients filled out the Skindex-29 at their study visits (before start, 3, and 12 months post-treatment) to assess the impact of their AK on their quality of life. Twelve months post-treatment, patients treated with 5-fluorouracil and imiquimod reported the largest decrease in scores on the Skindex-29.

Patient satisfaction also plays an important role in the decision around treatment options. As AK has a high recurrence rate, it is likely that patients will need a subsequent AK treatment in their life. In our study, a second treatment cycle was offered in all patients with treatment failure after one cycle. Refusal to undergo this second treatment was seen more frequently in the imiquimod, MAL-PDT, and IM group than in the 5-fluorouracil group. When asking patients 12 months post-treatment about their satisfaction, a larger proportion of patients treated with 5-fluorouracil would recommend the received therapy to other people and would be willing to undergo the treatment again.

We conclude that improvement of quality of life and patient satisfaction were highest in the 5-fluorouracil group. This may partly be explained by the fact that 5-fluorouracil is the most effective treatment. But the high proportion of patients willing to undergo retreatment after initial treatment failure also suggests that patients treated with 5-fluorouracil may experience less inconveniences than patients treated with imiquimod, MAL-PDT, or IM, where proportions refusing retreatment were higher. The proportion of patients who would undergo PDT treatment again and would recommend it to others was lower than for the other treatments. Moreover, pain and burning sensation was more frequently reported by patients treated with

PDT. This might indicate that pain may have influenced patient satisfaction with PDT. In our study, conventional PDT (c-PDT) was used. Nowadays, daylight-PDT (d-PDT) is available for treatment of AK, which is a less painful treatment.[18,19] A recent meta-analysis compromising 8 studies on d-PDT and c-PDT, found that there was a similar efficacy between d-PDT and c-PDT.[20] Therefore, we think that d-PDT would also have a lower effectiveness compared to 5-fluorouracil.

Should we treat AK?
There is discussion among clinicians on whether to treat AK or not. There are different reasons to treat AK.

A reason to treat AK, is because AK is thought to be a precursor of squamous cell carcinoma (SCC). So, treatment of AK may potentially reduce the risk on SCC development.[10] A different reason to treat multiple AK (field change), is that its presence can mask the signs of a subtle keratinocyte carcinoma. Especially patients with AK are more at risk to develop a SCC or BCC compared to the general population, because all these tumours are mainly caused by UV exposure.[21] After treatment of AK, non-responding lesions such as other cutaneous malignancies may become more visible for the clinician. Moreover, whether or not to treat also depends on the request of patients. Some complaints of itching, pain, bleeding or cosmetic impairment might be relieved with treatment of AK. From a cost perspective, treatment of AK might be attractive for society. Recent research showed that a single course of treatment with 5-fluorouracil cream led to cost savings related to treatment of AK and keratinocyte cancer after one and three years of follow-up.[15]

One could also decide to renounce treatment of AK because the potential of AK to transform into a cutaneous SCC is not evident. The recent Dutch guidelines regard AK as 'potentially premalignant'.[22] Furthermore, a systematic review of Werner et al. found progression rates of 0% to 0.075% per lesion-year, but concluded that there was insufficient reliable data to estimate the risk of progression.[23] A different study, which was not included in the systematic review, found risk of progression ranging between 0.025% and 16%, per year.[24] A Cochrane review on interventions of AK did not find evidence at all for possible reduction in SCC after treatment of AK.[10] So, the relationship between AK and progression into a SCC is still a matter of controversy.

In my opinion, in the decision on whether to treat AK or not, patients should be informed about the controversy in literature on the potential of AK to become invasive and the possible side effects of treatment. If left untreated, patients should be warned that in case of symptoms as pain, bleeding, and fast growth, they should contact their physician. Moreover, patients should be warned that AK can be regarded as a biomarker and that they should be aware of the risk to develop keratinocyte cancer.

What are the implications for physicians and society?
In our study, described in ***chapter 2.1***, specific lesion follow-up was performed. For all patients transparent sheets with the exact localisation of the AK lesions were drawn to monitor the lesions over time. In this study we focused on effectiveness of AK treatments, but it is of future interest to evaluate the patients after 5 years of follow-up and analyse the number of SCC developed in the treatment area. A different interesting topic for future research would be comparison of field-directed treatment with watchful waiting in patients with mild to moderate AK to study whether there are differences in risk of progression into a SCC and patient satisfaction.

Recent guidelines state no clear recommendations on the treatment of choice for AK. Based on our results, 5-fluorouracil should be considered first choice therapy as field directed treatment for AK. Our results can lead to more uniformity in treatment advise of physicians and might change recommendations in guidelines. However, there is always need for more studies from different investigators demonstrating the same results.

We included patients with all grades of AK, whereas other studies excluded patients with grade III AK. Therefore, our study population is more representative for patients seen in daily practice of the dermatologist. All follow-up visits were in accordance to the Dutch Guidelines for AK.[22] By doing so, we tried to simulate daily practice as much as possible in our trial.

As AK is a very frequently seen problem, it causes a significant burden on our health-care resources, which is even likely to increase over the coming years.[25] Treatment of AK with the most cost-effective treatment will induce cost savings for society.

Conclusion
Based on the study in this thesis and recent literature there is no doubt: when deciding to treat AK, 5-fluorouracil cream is the first choice treatment option. It has proven to be (cost)effective, has a high patient reported satisfaction and improves of quality of life compared to imiquimod, PDT and IM. Only in patients for whom treatment with 5-fluorouracil is not possible, such as patients who are not able to apply the cream themselves, other topical treatment options might be discussed with patients.

TREATMENT OF BOWEN'S DISEASE

The incidence of most keratinocyte carcinomas is well-studied and these studies concluded that the incidence is increasing.[1-4] However, less is known about the incidence of Bowen's disease. Our study (***chapter 3.1***) showed that in our centre there was a trend towards an increase in the annual age-standardized incidence rates in Bowen's disease.

There are only limited studies comparing different treatment options for the treatment of Bowen's disease. To date, guidelines state no clear recommendations on which therapy is preferred.[26-28] A Cochrane review concluded that there was a lack of high quality studies on surgical excision and cream therapies for Bowen's disease. Only for the use of PDT in Bowen's disease, there was sufficient evidence. Therefore, clear recommendations could not be made.[29]

With the study described in ***chapter 3.2***, we add information on non-invasive therapies in the treatment of Bowen's disease. We showed that treatment with surgical excision had the lowest chance on recurrence, with a probability of treatment failure of 4.9% up to five years post-treatment. Patients treated with 5-fluorouracil cream and PDT were more than twice as likely to receive treatment failure compared to patients treated with conventional surgical excision five years after treatment. No significant difference was found between 5-fluorouracil cream and PDT.

The study we performed was a retrospective study and therefore has potential pitfalls. Because of the non-randomized design of this study, bias due to confounding by indication could not be ruled out. An attempt was made to minimize this bias by adjustment for differences in baseline characteristics between treatment groups.

It would be of future interest to compare the most frequently prescribed therapies for Bowen's disease in a head-to-head RCT. I would suggest that at least treatment with surgical excision, 5-fluorouracil and PDT would be compared.

In our study, 7.5% of the patients were excluded because the initial biopsy showed Bowen's disease, but the excision specimen showed invasive SCC. This phenomenon is also found in literature. Moioli and colleagues described rates of 3% to 16% after conventional excision or Mohs surgery, respectively.[30] Moreover, they found an odds ratio of 7.1 (p<0.05) for having a history of keratinocyte carcinoma in patients with this sampling error.[30] A different study showed that location on ears, nose, lips, and eyelids and a tumour diameter of >10 mm could be predictors of this so-called 'upstaging'.[31] As a biopsy only represents a small part of the tumour, clinicians should be aware of this sampling error.

Besides the risk of sampling error, there is also the risk of a recurrent lesion that transforms into a SCC over time, as Bowen's disease is regarded a precursor of SCC. Studies show diverging rates of 2.3-12.6% after treatment with excision, cryotherapy or PDT.[32,33] In our study, 8 recurrent lesions (<1%) progressed into an invasive SCC, after treatment with 5-fluorouracil or PDT. Transformation of recurrent tumours into SCC following surgical excision was not observed. An explanation for not finding any transformation of a recurrent tumour into SCC in the surgical excision group, might be that the treating physicians might have had a higher clinical suspicion of a SCC and therefore choose a surgical treatment instead of a non-invasive treatment.

What are the implications for physicians and patients?
Overall, surgical excision remains a first choice treatment option in terms of effectiveness. However, in my opinion, non-invasive treatment modalities might be a good alternative. Especially, as there is little substantial evidence in literature on the progression rates of Bowen's disease into an invasive cutaneous SCC. Non-invasive therapies are well established for the treatment of other epidermal neoplasms, such as AK and sBCC.

Cosmetic results and patient preferences are also important to take into account when choosing a therapy besides considering the effectiveness of treatments. Patients should be informed about all options.

Nevertheless, when considering a non-invasive therapy clinicians should be aware of the possibility that a biopsy may be prone to sampling error. Factors as tumour size, tumour localisation, clinical suspicion on a SCC, and history of skin cancer should also be considered in deciding on treatment.

TREATMENT OF SUPERFICIAL BASAL CELL CARCINOMA

Surgical excision is generally accepted as most effective therapy for the treatment of sBCC. However, in situations where surgical excision is regarded as contraindicated, impractical, or disfavoured by the patient himself, other therapy options can be discussed. Nowadays, there is the tendency to use non-invasive therapies more frequently.

For the treatment of sBCC a variety of therapies is available. These treatments and their associated advantages, side effects, and costs pose a challenge for physicians to adequately educate patients about their treatment options. A recent qualitative study underlined the preference of BCC patients to receive all relevant information about their treatment options.[34]

To assess what patients value about therapies, a discrete choice experiment (DCE) can be performed. A recent review of several DCEs for the treatment of BCC, showed that most patients valued low risk of recurrence and cosmetic result the most.[35] These factors play an important role in shared decision making. Head-to-head studies with long-term follow-up regarding recurrence rates and cosmetic results are pivotal. Only a few studies describe long-term follow-up results of non-invasive therapies for treatment of sBCC.[36-39]

With this background, a RCT composing 601 patients with a primary sBCC treated with MAL-PDT, 5-fluorouracil, or imiquimod with 5 years of follow-up was performed (***chapter 4.1***). The

one and three year follow-up results showed that 5-fluorouracil was non-inferior and imiquimod was superior compared to MAL-PDT, but no conclusions could be drawn between 5-fluorouracil and imiquimod.[40,41] We assessed the efficacy five years post-treatment. We found that after five years of follow-up the differences in recurrence rates between the three therapies became larger and that imiquimod cream was superior compared to both 5-fluorouracil and MAL-PDT. The probability of tumour-free survival 5-years after treatment was 80.5% for imiquimod, 70.0% for 5-fluorouracil and 62.7% for MAL-PDT. So, in terms of efficacy, 5% imiquimod cream should be considered first choice non-invasive treatment option in most primary sBCC.

As written in the DCE, patients also valued cosmetic outcome as an important factor. Next to the efficacy, we assessed the cosmetic outcome five years post-treatment, in the same study as described above (***chapter 4.2***). The cosmetic outcome was judged by a physician blinded to treatment allocation at a 4-point scale (poor, fair, good and excellent) five-years after initial treatment. Here we found that MAL-PDT had a better cosmetic result compared to imiquimod and 5-fluorouracil in treatment of sBCC at five-years post-treatment when remaining recurrence-free. Retreatment of a recurrence with surgical excision or an alternative treatment showed a worse cosmetic outcome. So, patients are facing a trade-off. Only considering the risk of recurrence, imiquimod would be first choice treatment. In terms of cosmetic result, patients who respond well to treatment with MAL-PDT and 5-fluorouracil can expect better cosmetic outcome compared with imiquimod. However, taking into account that treatment of the recurrence with surgical excision has a lower chance on a good cosmetic result, the net effect was that there were no significant differences in cosmetic results, as treatment with MAL-PDT and 5-fluoroucil recurrences occur more frequently.

What are the implications for physicians and patients?
In terms of effectiveness, surgical excision is a first choice treatment option. However, I think patients should also carefully be informed on alternative treatment options as non-invasive treatments, and the advantages and disadvantages of all options should be explained to allow patients to make a well informed decision. When considering a non-invasive therapy for treatment of sBCC, I would primarily advise 5% imiquimod cream, based on its efficacy up to five years post-treatment. The fact that it is a home-based treatment were patients should apply the cream themselves could be an advantage for some patients, where it is a disadvantage for patients not able to do so.

The studies presented in this thesis, add evidence on different aspects of treatment options for sBCC. It would be of future interest to develop a decision aid on different treatment options and explanation of the different aspects. This would be very useful for both patients and physicians.

PREVENTION

The main risk factor for the development of AK, Bowen's disease and sBCC is extensive sun exposure. The studies presented in thesis focussed on the improvement of various treatments for epidermal keratinocyte neoplasms. Of course, one should not forget that preventing the occurrence of skin cancer is just as important or even more important. Therefore, extensive education of patients is essential. This education should not only include raising awareness on the risks of the sun and consequently the risk on skin cancer, but should also encompass promotion of sun-protective behaviour. Sun protection measures as primary prevention is proven to be effective.[42]

To conclude, I would like to cite a song of 1999 from Baz Luhrmann (Everybody's free (to wear sunscreen)): 'Ladies and Gentlemen of the class of '99. Wear sunscreen. If I could offer you only one tip for the future, sunscreen would be it. The long term benefits of sunscreen have been proved by scientists whereas the rest of my advice has no basis more reliable than my own meandering experience. … Be careful whose advice you buy, but, be patient with those who supply it. Advice is a form of nostalgia, dispensing it is a way of fishing the past from the disposal, wiping it off, painting over the ugly parts and recycling it for more than it's worth. But trust me on the sunscreen.'

CONCLUSIONS

In conclusion, the research presented in this thesis showed that for the treatment of AK, 5-fluorouracil is not only the most effective, but also the most cost-effective therapy. Moreover, it is a treatment that is well accepted and regarded by patients.

For treatment of Bowen's disease, surgery remains gold standard. However, more direct comparisons between non-invasive therapies are needed to determine the best therapeutic approach and the most patient-preferred treatment.

For non-invasive treatment of sBCC, we showed that 5% imiquimod cream is statistically significant more effective compared to two other non-invasive therapies. When considering the effectiveness and hereby the risk of retreatment with surgical excision in case of treatment failure, there were no significant differences in cosmetic results. Therefore, 5% imiquimod cream is considered as the first choice non-invasive therapy for sBCC.

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