Protocol

Risk of cutaneous squamous cell carcinoma after four different treatments for actinic keratosis: long-term results of a randomized controlled trial

1. INTRODUCTION AND RATIONALE

Actinic keratosis (AK) is the most frequent premalignant skin disease in the Caucasian population. As stated in the Dutch guideline, AK is a major health problem, with approximately 1 million patients suffering from AK and 160.000 new patients diagnosed yearly in the Netherlands. Up to 25% of all persons older than 40 years will develop AK.[1,2] Hence, it represents the second most frequent reason for patients to visit a dermatologist. Malignant transformation into a squamous cell carcinoma (SCC) occurs in approximately 0.25-25% of all cases.[1,3,5] In the Netherlands, 15.000 patients develop a SCC of the skin each year with an estimated number of 750 metastases.[3-5]

The presentation of AK ranges from solitary to multiple lesions, characterised as erythema with irregular rough keratinisation. There is a number of treatment modalities with variation in treatment effect, costs and side effects. 5-FU (Efudix) cream is a topical chemotherapeutical agent, that should be applied by the patient at home during 4 weeks twice daily. Imiquimod (IMQ) cream is a topical immune modulator that should be applied by the patient at home three times per week for one or two courses of 4 weeks, separated by a 4 week treatment-free period. Because of the discomfort of the long term application and the assumed poor compliance, many physicians prefer an in-hospital treatment. This is why in many hospitals PDT is now first choice treatment.[6,7,8] However, PDT is more expensive and patients may experience it as very painful, because of the burning sensation it causes.

On the other hand, patients experience less local side effects.

Ingenol Mebutate (IM) gel is a novel topical product, approved by the Medicines Evaluation Board (MEB) and reimbursed by the Dutch healthcare insurances (as well as the other products): [9,10] The main advantage is a shorter duration of treatment of only 2-3 consecutive days (depending on the location of AK) and a shorter downtime, compared to 5-FU and IMQ. Since this new self-applicable treatment offers advantages in terms of treatment duration (and thus compliance), it is important to compare IM with the other common treatments for AK.

In the current Dutch guideline for AK there are no clear recommendations for treatment modality. Hence, which treatment the patient will receive, currently does not rely on evidence-based medicine but mainly on the preference of the physician and the patient.

So far, we do not know what is the most (cost) effective treatment for AK. No randomized trials with direct comparisons between the four treatments have been performed. A Cochrane systematic review performed by Gupta *et al.* in 2012, concluded that trials with direct comparisons are necessary.[11] Furthermore, the follow-up duration of most trials is short. Because AK is a chronic skin condition, effective treatments with long-term effect will also be cost-saving because less follow-up treatments are necessary.

With a better understanding of the (cost-)effectiveness of the treatments mentioned above, we expect to accomplish more uniformity in treatment choices and possibly a shift from an in-hospital treatment

(PDT) to a home-based treatment. Furthermore, by defining the most effective treatment, recurrences are prevented and less additional treatments are necessary. Moreover, this treatment will probably result in less AK's progressing into SCCs, with associated morbidity, mortality and costs.
These are all potential benefits for the patients.

This is the first study with a direct comparison between the most commonly used treatments. With all the data obtained in this trial, the information available to patients will be improved and there will be adjustment of the current national and international guidelines. Depending on the results, a potential reduction of healthcare costs could be achieved.

References

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2. OBJECTIVES

Primary Objective:

Previous work shows that the proportion of patients with complete clearance of AK is low. Therefore it is clinically meaningful to define treatment success at 12 months post final treatment, defined as

proportion of patients with ≥75% lesion reduction in the number of AK lesions counted at baseline in the treatment area (≥ 75% patient clearance at 12 months).

Secondary Objectives:

- Treatment failure: proportion of participants with <75% reduction in number of AK lesions after 3 and 12 months post final treatment compared to baseline (<75% patient clearance at 3 and 12 months).
- Treatment success at 3 months post-treatment: proportion of participants with ≥75% reduction in number of AK lesions at 3 months post final treatment (≥ 75% patient clearance at 3 months).
- Decrease in number AK from baseline per patient, at 3 and 12 months post final treatment.
- Complete lesion clearance: proportion of lesions with 100% clearance in all treated patients at 3 and 12 months post final treatment.
- Investigator Global Improvement Indices (IGII) at 3 and 12 months post final treatment.
- Number of new lesions at 3 and 12 months post final treatment.
- Healthcare/treatment costs
- Side effects
- Patient satisfaction
- Cosmetic outcome
- Treatment compliance, defined as the number of applied treatments as percentage of the number of prescribed treatments.
- Proportion of patients who develop a SCC in the treatment area during study follow-up, and long-term follow-up.

3. STUDY DESIGN

A multi-centre randomized controlled trial (RCT). Patients who are considered to be eligible for the study, will be randomly assigned to one of four treatment groups: 1) PDT, 2) 0.015% IM (Picato®) gel 3) 5% IMQ (Aldara®) cream or 4) 5% 5-FU (Efudix®) cream.
Randomization occurs according to computer-generated minimization in order to ensure concealment of allocation, with overall balance of prognostic factors. Stratifying factors were treatment center and severity of AK grade.

Relevant baseline characteristics will be recorded at time of inclusion. Data regarding primary and secondary outcome measures will be recorded during a follow-up period of one year commencing after final treatment.

Relevant baseline characteristics will be registered at baseline visit (e.g. prior history of skin cancer, age, smoking yes/no, history of sun exposure, use of immunosuppressant medication in history, prior treatments for AK and non-melanoma skin cancer, number of lesions in the treatment area (with a minimum of 5 lesions per treatment area), size of treatment area, localization of treatment area, severity of AK lesions in the treatment area). Lesion count will be performed using transparent sheets, by drawing all lesions on the sheet at their exact location. The overall severity of each lesion will be assessed using the Olsen scale, based on the overall thickness of AK: 1 = mild (slightly palpable, more easily felt than seen); 2 = moderate (moderately thick, easy to see and feel); 3 = severe (very thick and/or obvious AK).
An observer blinded to treatment allocation, will assess all outcome measures at 3 months and 12 months post-treatment. All results will be registered in the electronic patients case report form (eCRF). Digital photographs will be taken at baseline and at regular follow-up visits at 3 and 12 months. Photographs will be taken both with and without the transparent sheet visible.
All additional visits to the outpatient departments and additional costs in case of local skin infection or side effects post-treatment will be registered as well. Patient satisfaction will be measured by using patient diaries, in which patients' self-assessment of pain will be registered. Pain will be recorded using a visual analogue scale (VAS), with scores from 0 till 10, with 0 indicating no pain and 10 indicating unbearable pain. Cosmetic outcome will be evaluated using a 4 point scale (1=excellent, 2=good, 3= moderate and 4=poor), and scoring of the amount of erythema and pigmentation by the observer during follow-up visits. Treatment compliance is determined by self-reported applied treatments in patient diaries. Side effects can be expressed by the patient on a specific record form in the patient diary.
In case of treatment failure at 3 months follow-up post first treatment (<75% reduction in the number of AK lesions counted at baseline in the treatment area), the same treatment will be repeated (with a maximum of 2 courses per treatment).

See Annex F4.1 for a flow chart that gives an overview of the inclusion and procedures that subjects undergo. Procedures are also described in chapter 5.

4. STUDY POPULATION

4.1 Population base

Eligible are patients who visit the outpatient department of Dermatology of the Maastricht University

Medical Centre (MUMC), VieCuri medical centre (VIE), Zuyderland Medical Centre Heerlen or Catharina hospital Eindhoven (CZE), because of actinic keratosis. Diagnosis will be confirmed clinically by a dermatologist.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Patients older than 18 years
- Female in child bearing potential should be using contraceptive measures, during and till 3 months post-treatment
- Fitzpatrick skintype I-IV
- Clinically confirmed diagnosis of AK
- One joint area of minimal 25 cm^2 and maximal 100 cm^2 of AK - AK Olsen grade I-III
- Location: head/neck area (Forehead, cheeks, temples, scalp, neckline (>50% of treatment area has to be the upper part of the neckline, because of the SPC of IM).
- A minimum of 5 AK lesions in the treatment area

4.3 Exclusion criteria

- Received any kind of treatment for AK in the past 3 months, except for cryosurgery outside the treatment area.
- (N)MSC in target area
- Immuno-compromised status
- Use of systemic retinoid in the past 3 months
- Use of immunosuppressant drugs in the past 3 months and / or at time of treatment (such as oral glucocorticoids, cytostatic, antibodies, drug acting on immunophilins, interferon, opioids, TNF binding proteins, MMF, biologic agents). inhalation corticosteroids / nasal corticosteroids are permitted.
- Porphyria
- Not able to give informed consent
- Allergy to study drugs or peanut/nut/soy products
- Pregnant and breastfeeding women
- Genetic skin cancer disorders
- Not understanding Dutch language

4.4 Sample size calculation

The sample size will be based on the primary endpoint defined as the proportion of participants with a ≥ 75% reduction in the number of AK lesions counted at baseline in the treatment area, 12 months post final treatment. Only for Imiquimod this primary endpoint has been documented well yet; the proportion of patients with ≥ 75% reduction in the number of AK lesions compared with baseline was reported to be 65%. Based on this estimate a number of 156 patients per group is needed to detect a minimally clinically relevant difference between treatment groups of 15% with a power of 80% (alpha=5%). To account for a potential loss-to follow-up of 10%, a total of 624 (4x156) patients need to be included.

It is expected that in the outpatient departments of the four participating hospitals, an average of 810 patients with AK are treated per hospital per week. This means that there will be approximately 30 eligible patients per hospital per month.

MUMC and CZE, which are our own departments (the department of dermatology CZE is part of MUMC), will both be able to include 200 patients The remaining amount of patients will be divided by VC (n= 112) and Zuyderland (n= 112).

5. TREATMENT OF SUBJECTS

Prior to all treatments (PDT, 5-FU, IM, IMQ) superficial curettage of keratotic lesions as pretreatment will be executed to diminish hyperkeratosis. This is done by investigator blinded to treatment allocation.

5.1 Investigational product/treatment

Methylaminolevulinc acid – photodynamic therapy (Metvix®, Galderma), (MAL-PDT)

PDT involves the application of 5-aminolevulinic acid (5-ALA) or methyl aminolevulinate (MAL) to the affected skin (by means of a cream), which is converted within the cells into the photosensitizer protoporphyrin IX. Surface illumination with 585-720 nm is then used to trigger the photodynamic reaction causing destruction of tumour cells by both apoptosis and necrosis. MAL-PDT (Metvix®, Galderma) has been registered for treatment of AK in Europe. A side-effect of the treatment is a burning pain during illumination and slight erythema afterwards lasting a few days.

The MAL cream is applied to the treatment area and covered by an occlusive dressing (Tegaderm®, a gauze and tinfoil), in order to prevent contact with (UV) light. After 3 hours the area is illuminated with Omnilux or Aktilite (632 nm, 37 J/cm2).

During the MAL-PDT treatment cooling of the surrounding skin is allowed (with a coldpack located centimeters from the treatment area). After PDT, the treatment area will be immediately cooled with a coldpack during the first 10-15 minutes post treatment. After cooling, unguentum leniens (“koelzalf”)

will be applied on the treatment area and the treatment site is covered again with the above mentioned occlusive dressings, to prevent exposure to daylight during 48 hours. Treatment is performed by an authorized nurse. Patients are instructed to prevent exposure to sun during 2 days post-treatment. After treatment local skin reactions can appear, such as erythema, crusts and a burning sensation. Rarely local skin inflammation that needs antibiotic treatment, occurs. The side effects mentioned usually disappear within 1-2 weeks.

5% Imiquimod (Aldara)

Imiquimod is based on an immunomodulating mechanism which enhances the production of cytokines and natural killer cells, the proliferation of B cells and the activation of Langerhans cells, thereby stimulating the immune response. This treatment causes inflammation due to stimulation of the immune response at the tumour site resulting in erythema, oedema, scaling and erosions. Imiquimod cream is applied in a thin layer to the treatment area once daily. The patient is advised to apply the cream at least one hour before going to bed and after 8 hours the cream has to be washed off. This is repeated for 3 days per week (Monday, Wednesday, Friday) during 4 consecutive weeks. After a 4-week treatment-free period, clearance of AKs should be assessed by a physician. If > 25% of baseline lesions persist, treatment should be repeated for another four weeks (conform SPC). During treatment erythema and crust will appear. In some cases patients can experience flu-like symptoms when using Imiquimod. In those cases patients are advised to contact their treating physician. Post-treatment, erythema, crusts and tenderness will persist for approximately 1-2 weeks.
Rarely local skin inflammation that needs antibiotic treatment occurs.

5% 5-Fluorouracil (Efudix) (5-FU)

5-FU cream is a topically applied chemical ablative agent that inhibits DNA synthesis, prevents cell proliferation, and causes tumour necrosis. Similar side-effects as mentioned with Imiquimod occur during treatment with 5-FU.
5-FU is applied on the treatment area by the patient in a thin layer twice daily during 4 weeks. During treatment local skin reactions, such as erythema and crusts, will appear in most patients. Rarely local skin inflammation that needs antibiotic treatment occurs.
Post-treatment erythema, crusts and tenderness will persist for approximately 1-2 weeks.

Ingenol mebutate (Picato, Leopharma)(IM)

IM gel is a novel topical product, which is approved by Medicines Evaluation Board (MEB) and reimbursed by the Dutch healthcare insurances (as well as the other products) by health care insurances since October 2013. IM is a pleotropic effector inducing cell death and activates the immune response. The main advantage of treatment with IM is a shorter duration of treatment (3

consecutive days in head/ upper neck area, once daily) and consequently a shorter downtime (e.g. compared to 5-FU). IM 0.015% gel is applied by the patients themselves in a thin layer on the treatment area once daily on three consecutive days. The patient is advised to apply the gel at least two hours before going to bed. The first 6 hours after application the patient is not allowed to touch the area or wash the gel off. A maximum treatment area of $100cm^2$ will be applied at a time. The amount of prescribed IM will be proportional multiplied when the treatment area is > 25 cm2 (25 cm2 = 3*0.47g IM; 25-50 cm2 = 6*0.47g IM; 50-75 = 9*0.47g IM; 75-100cm2 =12*0.47g). Adverse events reported are equivalent to the use of Imiquimod or 5-FU cream and will disappear within approximately 2 weeks after application. Rarely local skin inflammation that needs antibiotic treatment occurs.

In case of clearance <75% at 3 months follow-up after final treatment, patients will not receive additional treatment, unless it is medically necessary (severe lesions with clinical complaints or suspected SCC). This will be recorded carefully, with respect to the cost-effectiveness analysis. Lesions that do need additional treatment (e.g. cryosurgery, biopsy) are evaluated as nonresponders. Cryosurgery is allowed in case of symptomatic non-responding lesions, in order to ensure good patient care.

Use of co-intervention (if applicable)

It is allowed to use co-medication, accept for any kind of immunosuppressive agents or any kind of intervention for AK other than cryosurgery. Pregnant or breastfeeding women cannot participate in the study.
Patients are allowed to use two oral Paracetamol 500 mg tablets, with a maximum of 8 tablets per day to reduce pain during treatment. During the MAL-PDT treatment cooling of the surrounding skin is allowed (with a coldpack located centimeters from the treatment area). After PDT, the treatment area will be immediately cooled with a coldpack during the first 10-15 minutes post treatment. After cooling, unguentum leniens (“koelzalf”) will be applied on the treatment area and the treatment site is covered again with an occlusive dressing, to prevent exposure to daylight during 48 hours. To prevent infection post treatment, all patients will be prescribed chlorhexidin cream twice daily until skin has recovered. In case there is clinical evidence for a bacterial infection, local or oral antibiotic treatment will be given.

5.2 Escape medication (if applicable)

Not applicable.

STATISTICAL ANALYSIS

Time-to-event analysis was used to estimate the cumulative probability of SCC. Follow-up started at the end of treatment. In patients who developed a SCC, follow-up ended at the date of diagnosis of SCC. Observations of patients who did not develop a SCC were censored at the date of the last follow-up visit. Both intention-to-treat and per protocol analyses were performed.

Univariate and multivariate Cox regression models were used to calculate hazard ratios (HR) with 95% confidence intervals (95% CI) and P-values for each a priori defined potential predictor. Retreatment occurring later during follow-up was entered as a time-dependent covariate. 5-FU was used as the reference group, because it was the treatment with the highest effectiveness in terms of AK lesion reduction.

Categorical variables are presented as numbers and percentages and continuous variables as mean with standard deviation or median with range.

A P-value of 0.05 or lower was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY, USA), and Stata software, version 14.0 (StataCorp).