Diagnosis and Treatment of Premalignant Changes of Photodamaged Skin: Novel Hyperspectral Imaging and New Therapeutical Aspects

Noora Neittaanmäki-Perttu, MD, PhD
Department of Dermatology, Allergology and Venereology, Helsinki University Hospital and Päijät-Häme Central Hospital. Doctoral Programme in Clinical Research, University of Helsinki. FIN-00029 Helsinki Finland. E-mail: noora.neittaanmaki-perttu@hus.fi

Noora Neittaanmäki-Perttu defended her thesis on 29th May 2015, Skin and Allergy Hospital, Helsinki University Central Hospital. Supervisors: Professor Erna Snellman, MD, PhD, Department of Dermatology, Tampere University and Tampere University Hospital, Tampere, Finland and Professor Olli Saksela, MD, PhD, Allergology and Venereology, University of Helsinki and Helsinki University Central Hospital. Supervisory group: Professor Annamari Ranki, MD, PhD, Department of Dermatology, Allergology and Venereology, University of Helsinki and Helsinki University Central Hospital and MD Mari Grönroos, Department of Dermatology, Päijät-Häme Central Hospital. Opponent: Professor Olle Larkö, MD, PhD, Sahlgrenska Akademin, Göteborgs Universitet, Sweden.

As the skin cancer burden continues to increase, there is an urgent need for novel methods for the early detection of skin cancers, and for new cost-effective treatments. The hyperspectral imaging system (HIS) is a novel technique, which offers the dual advantages of allowing the imaging of large skin areas rapidly and non-invasively. Daylight photodynamic therapy (DL-PDT), with the advantages of excellent tolerability and convenience, is an attaractive therapy for actinic keratoses (AK) and field cancerization. This thesis aimed to enable early and effective treatment of common premalignancies of photo-damaged skin. The first purpose of this thesis was to evaluate the feasibility of HIS in the detection of field cancerized skin and in the detection of ill-defined borders of lentigo maligna (LM) and lentigo maligna melanoma (LMM). In addition, this thesis aimed to further develop the treatment of field cancerized skin with photodynamic therapy using a novel photosensitizer in combination with daylight (DL-PDT), and to evaluate the cost-effectiveness of DL-PDT.

Fig. 1. Noora Neittaanmäki-Perttu (*left*) defended her thesis on May 29, 2015. As custos acted Professor Annamari Ranki and as Opponent served Professor Olle Larkö.

Methods

This thesis included 4 non-sponsored prospective clinical studies. The novel prototype HIS, used in studies I–II, was developed for the study at the VTT Technical Research Centre of Finland. The technique enabled *in vivo* imaging of the skin prior to surgical procedures and produced abundance maps of the affected skin areas. The results were verified by histopathology. Study III was a randomized double-blinded intra-individual split-face trial comparing novel photosensitizer formulation, 5-aminolaevulinate nanoemulsion (BF-200 ALA) with methyl-5-aminolaevulinate (MAL) in DL-PDT of AKs. In addition to blinded clinical and histological treatment efficacy, tolerability of the treatment was assessed. Study IV evaluated the cost-effectiveness of MAL-DL-PDT compared to conventional MAL-LED-PDT.

Results

In studies I–II HIS showed its feasibility in both the detection of subclinical borders of ill-defined lentigo malignas (LM) and lentigo maligna melanomas (LMM), and in the detection of early subclinical actinic keratoses (AK). In study I HIS accurately detected 20 of 23 (87%) of the LM/LMM borders as confirmed by histology. HIS was useful, i.e. it detected the lesion borders more accurately than a clinician using Wood's light in 11 of 23 (47.8%) cases. Six re-excisions could have been avoided with

HIS. In 3/23 cases (13%) HIS was not in concordance with the histopathology, while in two cases HIS showed lesion extensions which were not verified histologically (wrong positive) and in one case HIS missed the subclinical extension (wrong negative). In study II with 12 patients and 52 clinical AKs, HIS accurately detected all the clinical lesions in addition to numerous areas of subclinical damage. HIS findings matched the histopathological findings in all 33 biopsied areas (AK, $n=28$, photo-damaged skin, $n=5$), revealing 16 subclinical lesions of which 10 were not detected by fluorescence diagnosis.

In study III (13 patients, 177 lesions) in a per patient (half-face) analysis BF-200 ALA cleared thin AKs more effectively than did MAL ($p=0.027$). In per lesion analysis the complete clearance rates were 84.5% for BF-200 ALA, and 74.2% for MAL ($p=$ns). The area response rates, including also the new appeared lesions (i.e.preventive effect), were 79.8% for BF-200 ALA and 65.6% for MAL, $p=0.044$. Histologically, DL-PDT effectively cleared all the signs of dysplasia in 61.5% lesions treated with BF-200 ALA and in 38.5% with MAL ($p=$ns). The mean decrease in p53 expression was 54.4% with BF-200 ALA, 34% with MAL ($p=$ns). DL treatment was nearly painless with both photosensitizers. BF-200 ALA and MAL DL treatments were similarly tolerated as regards to adverse reactions.

In study IV 70 patients (210 target lesions) randomized to receive DL-PDT or LED-PDT with MAL, at 6 months the patient complete response rates were 15 of 35 (42.9%) and 24 of 35 (68.6%), ($p=0.030$) and lesion clearance rates were 72.4% and 89.2%, respectively ($p=0.0025$). DL-PDT required significantly less time at the clinic ($p<0.0001$) and could be used with lower total costs (132 EUR) compared to conventional LED-PDT (170 EUR), $p=0.022$. However, in terms of cost-effectiveness MAL-DL-PDT was found to give less value for money compared to MAL-LED-PDT. The incremental cost-effectiveness ratio (ICER) showed a monetary gain of 147 EUR per unit of effectiveness lost. Thus, the use of DL-PDT instead of LED-PDT would decrease the healing probability but only low incremental cost savings would be achieved. The costs per complete responder were 308 EUR for MAL DL-PDT and 248 EUR for MAL LED-PDT, $p=0.004$.

Conclusions

The more accurate pre-surgical assessment of the subclinical borders of LM and LMM with HIS could lead to fewer re-excixions, which furthermore could reduce the burden to both patients and clinics. In addition, the early non-invasive detection of skin field cancerization could enhance the treatment process by revealing the as yet subclinical areas in need of treatment, and could possibly aid the monitoring of treatment efficacy. Even though HIS was found to be useful in these two indications, more studies are warranted to qualify the optimal mathematical algorithms for diagnostic use. The use of a novel photosensitizer formulation, BF-200 ALA, in DL-PDT could lead to lower costs and increase the efficacy. Interestingly, the efficacy of DL-PDT with BF-200 ALA was approaching the efficacy achieved with conventional LED-PDT. As field cancerized skin should be treated as a chronic disease requiring repeated treatments, DL-PDT offers a painless and convenient option for this purpose. However, DL-PDT with MAL provided less value for money compared to conventional MAL-PDT. The cost-effectiveness of BF-200 ALA in DL-PDT for AKs needs further studies.

List of original publications

I. Neittaanmäki-Perttu N, Grönroos M, Jeskanen L, Pölönen I, Ranki A, Saksela O, Snellman E. Delineating margins of lentigo maligna using a hyperspectral imaging system. Acta Derm Venereol 2015; 95: 549–552.

II. Neittaanmäki-Perttu N, Grönroos M, Tani T, Pölönen I, Ranki A, Saksela O, Snellman E. Detecting field cancerization using a hyperspectral imaging system. Lasers Surg Med 2013; 45: 410–417.

III. Neittaanmäki-Perttu N, Karppinen TT, Grönroos M, Tani T, Snellman E. Daylight photodynamic therapy for actinic keratoses: A randomized double-blinded non-sponsored prospective study comparing aminolevulinic acid nanoemulsion (BF-200) with methyl-5-aminolaevulinate. Br J Dermatol 2014; 171: 1172–1180.

IV. Neittaanmäki-Perttu N, Grönroos M, Karppinen TT, Snellman E, Rissanen P. Photodynamic therapy of actinic keratoses: a randomized prospective non-sponsored study on cost-effectiveness comparing conventional LED and daylight-mediated treatment. Acta Derm Venereol 2015, in press. http://ethesis.helsinki.fi. ISBN 978-951-51-1216-3 (pdf).