Karolinska Dermatology Symposium 2013 "Melanoma – Today and Tomorrow, an Update on Pathogenesis, Current and Future Treatments"

Åsa Ingvar, MD, PhD Resident, and Mona Ståhle, MD, PhD
Dermatology Unit, Karolinska University Hospital, Stockholm, Sweden
E-mail: asa.ingvar@karolinska.se

For the 25th time, the Karolinska Dermatology Symposium was launched on October 25th 2013. Karolinska Dermatology Symposium is a forum for continuing medical education at an advanced international level. This year the symposium was made possible by a successful cooperation between the Dermatology Unit at Karolinska University Hospital and Roche AB. This year's theme was malignant melanoma and the aim was to elucidate pathomechanisms, epidemiology, clinical aspects and treatments. The day offered many interesting lectures that are presented in a condensed version below.

The first lecturer, *James M Grichnik*, Professor at the Department of Dermatology, University of Miami, USA, wanted to get the audience to question well-recognized models of melanoma pathogenesis. One such model is the initiation of melanoma that traditionally has been depicted to start with neoplastic cells within the epidermis that proliferate and invade into dermis and eventually enter the body through the lymphatic system. The lecturer argued that this model is deficient, for example it is incoherent with the natural presence of benign naevus cells in the dermis and the modest effect of sentinel node biopsy on melanoma-specific survival. He proposed alternative models, such as "perhaps the melanomas are not initiated in the epidermis but are drawn there because the early tumour cells need the epidermal environment for survival and progression"? Professor Grichnik continued to discuss the one-way direction model of differentiation from a melanoma stem cell to a melanocyte. He demonstrated that the melanoma stem cells give rise to a population of transient amplifying cells that can differentiate into melanocytes but can also give rise to new stem cells, i.e. the differentiation path is probably bidirectional. Lastly, he questioned the widely accepted sequence of acquired mutations in melanoma development, with early occurrence of BRAF/NRAS mutations. This is illogical according to Dr Grichnik since such mutations would have set the tumour in senescence in the absence of prior mutations.

Leonard Girnita from the Department of Oncology-Pathology at Karolinska Institutet, Stockholm, Sweden, continued with "Cell signalling in melanoma – a clue to future therapies". He outlined the complexity of cell signalling in malignant melanomas that can be modified at several levels: at receptor, adaptor protein, and at transcription factor level. Despite the abundance of genetic and epigenetic modifications, it is likely that a specific tumour is driven by one or a few selected mutations. Since these mutations usually result in a continued activity of certain oncogenes this phenomenon is called "oncogene addiction". This explains why the BRAF-inhibitors have such a substantial effect on $BRAF^{V600E}$ mutated tumours even though they only inhibit one specific mutation in an oncogene in the RAS-RAF signal pathway. From the BRAF-inhibitors we have also learned that melanomas often develop resistance against targeted therapies. This can be mediated by several mechanisms, for example through bypass of a signal pathway, i.e. activation of another signal pathway to circumvent the inhibited pathway. For future therapies it is essential to identify the keys that control this switch in signalling.

Marie Andersson, Chair of "Melanomföreningen" (Melanoma Patient Organization), reported on their work with support for melanoma patients and prevention. She presented selected parts of their homepage, www.melanomforeningen.se, where you can find updated and valid information about the disease, risk factors and treatments.

After lunch, *Susan M Swetter*, Professor of Dermatology at Stanford University Medical Center and Cancer Institute, Stanford, USA, gave a lecture on prevention and screening of melanomas. Prevention can be divided into primary and secondary prevention. Primary prevention refers to the reduction of harmful UV-light exposure which about 65% of the melanomas in the light-skinned population can be attributed to. Secondary prevention is achieved by the early detection of a melanoma, either by the patient (self- or kindred monitoring) or by health care professionals. On patient level the secondary prevention is dependent on gender and socioeconomic status (SES). In studies it has been observed that men >60 years of age is the patient group that benefit the most (in terms of tumour thickness at diagnosis) from a physician skin examination the year prior to melanoma diagnosis. SES

impacts both the incidence and the tumour thickness with a higher incidence rate overall and a more rapid increase of thin melanomas in middle-high SES individuals. The rate of thick melanomas, however, grows faster in low SES patients. This seems to be due in part to insufficient perception and knowledge of melanoma risk in these patients, but it has also been shown that physicians are less inclined to give low SES individuals adequate information on preventive measures. Professor Swetter also presented evidence that malignant melanomas discovered by a physician were significantly thinner compared to melanomas found by the patient and that melanoma patients that previously had been screened by a doctor had a decreased mortality. Furthermore, melanoma screening has been instated in Schleswig-Holstein in Germany as a result of a prospective melanoma screening study where a decreased melanoma-specific mortality could be demonstrated. In the light of these results she argued for the advantages of melanoma screening in the population or in high-risk patients. At the end of the lecture the possibility for chemoprevention of malignant melanoma was discussed and more specifically the decreased risk of melanoma in individuals that have used ASA/NSAID. Based on these findings a phase IIa study is conducted that investigates the effect of NSAID (Sulindac) treatment on the risk of melanoma in patients with dysplastic naevi.

A patient previously diagnosed with a malignant melanoma has an increased risk of developing a second primary melanoma (5–10%). This risk of multiple primary melanomas is most pronounced at the first physician skin examination and during two years following the first melanoma diagnosis, but it remains elevated lifelong. Patients with several benign and dysplastic naevi have a particularly high-risk of multiple melanomas, as do patients with heritability for malignant melanoma. *Jan Lapins*, Chief dermatologist at Karolinska University Hospital, reported on the behaviour and appearance of this subset of melanomas in his lecture "Multiple primary cutaneous malignant melanomas". He emphasized the importance of performing a full body skin examination of patients that have a suspected or confirmed malignant melanoma. Furthermore he demonstrated the potential of discovering early melanomas with the assistance of a dermoscope by presenting several instructive clinical cases.

Mari-Anne Hedblad, Dermatopathologist that recently retired from the Dermatology Unit, Karolinska University Hospital, Stockholm, Sweden, continued with a lecture on "Grenz ray treatment of lentigo maligna". Lentigo maligna (LM) and lentigo maligna melanoma (LMM) frequently arise on cosmetically sensitive areas and they are often large and diffusely demarcated. Furthermore, the tumour has an unpredictable behaviour and up to 50% relapse after excision with 5 mm margin. Thus, there is a need for an alternative to surgical treatment. Already in 1954, Miescher discovered that LM is sensitive to radiation, including radiation with Grenz rays, a superficial kind of X-rays. The advantages of Grenz ray therapy of LM/LMM are that is it simple and easily accessible for dermatologists, the cosmetic results are excellent, it is possible to treat large areas (with adequate margins) and it can be combined with surgery. At Karolinska University Hospital 834 patients were treated for LM/LMM with Grenz rays from 1990 to 2012 with excellent results. 88% of the patients achieved complete clearance and only one patient developed metastasis. The causes for incomplete effect of the treatment were: the radiated area was too narrow, the administered dose was too low, the skin was not stretched (the rays do not reach the bottom of the skin folds), or the tumour had deeper adnexal extension than indicated by the pathology report (adnexal punctuate recurrences). As a result of these findings (Hedblad, Mallbris. J Am Acad Dermatol 2012), Grenz ray treatment of LM/LMM has been included in the Swedish national guidelines for malignant melanoma.

"Targeted melanoma therapy" was the title of *Johan Hansson's* lecture. Johan Hansson is a Chief oncologist and Associate Professor at the Department of Oncology-Pathology at Karolinska Institutet, Stockholm, Sweden. He began to narrate the incredible paradigm shift that has occurred in the therapy of metastatic melanoma following the introduction of personalized treatments. The BRAF-inhibitor vemurafenib was the first targeted drug studied and the results showed significantly increased "progression free survival" and "overall survival" compared to dacarbazine. Unfortunately resistance develops in the majority of the patients. Studies have therefore been designed to try to counteract or delay the emergence of BRAF-inhibitor resistance and there has been some success with combined BRAF and MEK inhibition. MEK 1/2 is a small protein downstream of BRAF in the RAS/RAF pathway and a MEK-inhibitor (trametinib) is now approved for the treatment of metastatic malignant melanoma in USA but it has not yet reached Europe. Of dermatological (and patient) interest, this combination also reduces BRAF-inhibitor induced skin toxicity. Immunotherapy is another type of treatment for metastatic melanoma. Ipilimumab blocks the CTLA-4 receptor on the T cells which prevents the tumour from shutting down the activation of T lymphocytes. This treatment has also shown a superior effect on survival with a slower onset but a better "drug-survival" (>20% of the patients alive after 3 years) compared to BRAF-inhibitors. Unfortunately, sometimes ipilimumab therapy cause serious delayed autoimmune events such as autoimmune colitis and hypophysitis. In addition to the BRAF and MEK inhibitors, a third kind of

targeted therapy for spread melanoma is coming – the anti-PD-1 antibody (nivolumab, PD = programmed death). PD-1 is expressed on the lymphocytes that infiltrate the tumour tissue and when a specific ligand binds to this receptor the lymphocyte dies. When PD-1 is blocked the lymphocyte survives and can continue to attack the tumour which has been shown to have a good therapeutic effect. The next step in melanoma treatment is to try to combine existing drugs to get an even better treatment for metastatic melanoma and there are several "combination-studies" coming.

The last lecture of the day was presented by *Ada Girnita*, Chief Dermatologist and Head of the Tumour Department at the Dermatology Unit, Karolinska University Hospital, Stockholm, Sweden, and the topic was cutaneous side effects from new cancer treatments. Ipilimumab treatment often causes skin reactions but they are seldom severe. Maculopapular rashes and prurigo are most common but other skin reactions such as photosensitivity, acne, pyoderma gangrenosum, melanoma-associated hypopigmentation has been reported. Side effects from the targeted therapies (sorafenib, sunitinib, imatinib, vermurafenib, dabrafenib, trametinib) are similar for the most part and include acneiform eruptions/folliculitis, prurigo, skin tumours, photosensitivity, and hand/foot skin reactions. The adverse effects can be solitary or combined, they are often dose-dependent and can occur at any time during treatment but has a tendency to fade towards the end of the treatment. Management is directed at the clinical appearance, viz acneiform eruptions are treated as acne. In the occurrence of severe reactions, lowering the dose or interrupting the treatment should be considered. The various targeted therapies also have specific cutaneous side effects, e.g. sunitinib can cause reversible hair depigmentation and sorafenib alopecia and eruptive naevi/cysts/keratoacanthomas.