6th World Congress on Melanoma

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The beautiful city of Vancouver (Canada, B.C.) hosted this year's World Congress on Melanoma. As a person responsible for the cancer clinic at my department I couldn't miss this important event. I attended the meeting and was not disappointed. The congress brought together dermatologists, medical and surgical oncologists, plastic surgeons and basic researchers whose common denominator is research and care of patients with this deadly disease. The spectrum of lectures covered all aspects of melanoma etiology, diagnosis and treatment. In this brief review I will concentrate mostly on features relevant for the dermatologists.

The diagnosis

In Europe dermoscopy became standard of care. I was therefore quite surprised to learn that only approximately 20% of American dermatologists use dermoscopy. Our colleagues in USA were however warned, that the prime cause of lawsuit in dermatology is due to the failure of early melanoma diagnosis and virtually all doctors that did not use dermoscopy were found guilty of malpractice. Dermoscopy issues were covered in two, very well attended sessions where the leading experts (*Alfred Kopf, Giuseppe Argenziano, Wilhelm Stolz, Scott Menzies*) reviewed the principles of practice. There are no really new developments, but the dermoscopic knowledge gets better consolidated. Retrospective review of the high-risk patients seen in the pigmented lesion clinic at NYU (Dr. Kopf) has not revealed a single death of melanoma, clearly indicating that the diagnosis is made early and the treatment is curative. This contrasts the disturbing tendencies in the melanoma diagnosis in general population; *Rona MacKie* (Glasgow, UK) reported that approximately 1/3 of the newly diagnosed melanoma cases in Scotland were made at the stage of II or higher and that mortality of melanoma has not decreased over the last years. The possible diagnostic pitfalls in dermoscopic diagnosis were reviewed. Metastatic tumours in the skin can show pigmentation and tend to be misdiagnosed as dermatofibromas. Kaposi's sarcoma can resemble blue naevus and and accessory mammary nipples can present with atypical pseudopigment network resembling melanoma. There is little agreement as to how the high-risk patients with dysplastic naevus syndrome should be followed. *Scott Menzies* presented the Australian experience where all atypical naevi are photographed and those showing any change during a short (3–4 months) follow-up are removed. In about 20% of these early melanoma, otherwise featureless in dermoscopy, is found. However, this may not be universally applicable and *Claus Garbe* (Tubingen, Germany) pointed out that in his experience the naevi are quite stable and change only rarely during this short follow-up. I have the same feeling with my patients in Denmark and it may well be that in European patients the naevi are more static due to less sun exposure than in Australia.

Etiology and pathogenesis

Slow, but significant progress has been made in the understanding of the cause of melanoma. Not one, but at least two different pathways play a role. There is overwhelming epidemiologic and molecular evidence that melanomas arising on the chronically sun exposed skin (face, ears) are different from the tumours occurring on the relatively protected sites on the trunk and buttocks. The prognosis of the tumours on the chronically exposed skin is much better; they arise most often in the more advanced age in individuals with few melanocytic naevi. The mutations in *BRAF*, the most commonly mutated gene in melanoma, are rare. In contrast, in younger individuals the melanomas often arise from the preexisting naevi, are more malignant and frequently contain mutated *B-RAF*. Very recent gene array analysis has shown a clear separation in gene expression profiles between these two types of tumours (B. Bastian; N Engl J Med 2005; 353: 2135). However, *B-RAF* mutations lack the UV signature so it is still unclear which role this oncogene plays in tumour development.

Tanning beds, sun exposure and sun blockers – confusion solved

Many of us were excited and puzzled by the data published several years

ago suggesting, in contrast to what can be expected, that the incidence of melanoma is positively correlated with the use of UV blockers. This has now been completely refuted. Although the prospective, randomized study on melanoma and sun blockers is lacking, very solid prospective data show a beneficial effect of sun blockers in actinic keratoses, basal cell carcinoma and spinous cell carcinoma. Use of sun blockers in children is also negatively correlated with the number of naevi. Moreover, several studies testify that the use of sun blocking creams does not increase sun exposure. There is no reason to believe that sun blockers have any deleterious effect and all experts agreed that they are an important aspect of photoprotection. On the other hand, there were bad news for the enthusiasts of tanning beds. A new Canadian study and the re-analysis of the Scandinavian study show concordantly a ×1.5–×2 increased risk for melanoma in persons using solaria. The risk has been positively correlated to the number of tanning sessions and the age of onset. All experts felt that tanning beds should be forbidden before the age of 18.

How to break the immunological tolerance in malignant melanoma

Melanoma is one of the most immunogenic tumours and specific T-cell clones directed against membrane antigens are often detectable in the patients. However, the cells are functionally defective and are not able to trigger a substantial anti-tumour response. One of the explanations is the emergence of the so-called T regulatory (Treg) cells. These are the CD4+CD25+ cells induced by interleukin 10 and transforming growth factor beta. Studies in mice showed that inhibition of Tregs breaks the tolerance to melanoma and triggers an effective immune response leading to the eradication of metastases. Several strategies, mainly based on monoclonal antibodies, were proposed to target Tregs in humans. Another cause of immunosuppression in melanoma is the lymphocyte surface molecule CTLA4 which blocks T-cell function. A novel anti-CTLA4 antibody has shown promise in phase I clinical trials and in several patients a complete regression of metastases has been documented. Most oncologists feel that this antibody has a great future in oncology. Finally, it has been realized that tumour vaccination can be augmented by a moderate lymphocyte depletion (e.g. by total body irradiation or fludarabine) enhances immunization by melanoma vaccines. The successful immunotherapy of melanoma might be a matter of few years and is likely to rely on the combination of anti-Treg, anti-CTLA4 and tumour vaccination.

What can we do today for the patients with metastatic disease?

Although the dermatologists in Nordic countries are seldom involved in the care for patients with disseminated melanoma it is nevertheless important to be aware of the current treatment methods. The message is to never give up, since various treatments in combination can produce significant clinical effect. Distant metastases should be surgically excised, except for the metastases in brain where better results are produced by stereotactic radiotherapy. If tumour mass is localized in an extremity, limb perfusion with melphalan or tumour necrosis factor alpha with melphalan can produce excellent effect in over 80% of patients (*A. Eggermont*, Amsterdam, Holland). High dose interferon alpha produces response in a very low proportion of patients but can be tried in motivated individuals (by the way, do not combine interferon with dacarbazine since the effect is abolished).

Finally, all patients with metastatic disease should have a possibility to join clinical studies. Several new drugs are on the way, including sorafenib (BAY 43-9006 BRAF blocker), CCI 779 (mTOR inhibitor), farnesyltransferase inhibitors or the already mentioned anti-CTLA4 antibody.

Congenital naevi – can we assess the risk of melanoma?

Let us go back to the issues relevant for clinical dermatologists. We often see children with congenital naevi and follow them because of the putatively increased risk of melanoma. In fact we do not know the risk of melanoma in these patients. The very large prospective study on several hundreds of patients with congenital naevi has not yielded a single melanoma after a 7-year observation period. Retrospective studies suggest a moderately

(×2) increased risk of melanoma in the childhood in patients with large naevi and in adulthood in patients with small naevi. Radical surgery or curettage probably reduce the risk, albeit not completely. It is important to remember that children with large congenital naevi are prone to develop rhabdomyosarcoma of the skin and in case of naevi with many satellites the potentially fatal neurocutaneous melanosis. Many centers (including my own department) choose to offer an early cerebral magnetic resonance scan at the age of approximately 6 months to all high-risk children, i.e. those with large naevi, localized to the head or over the spinal column, and composed of many satellite nodules.

How has this meeting changed my practice?

The information delivered and the meeting and discussions with the experienced colleagues made me much more confident about the following:

1. Teach all dermatologists dermoscopy. Again and again the data show that dermatologists trained in dermoscopy are vastly more accurate in the diagnosis of melanoma than those who do not master this technique. I got convinced that all dermatologists should know dermoscopy and use it in everyday practice. Dermoscopy should play a more prominent role in the education of young dermatologists and should be made available to all.

2. Patients with atypical mole syndrome should be followed closely. Most leading pigmented lesion clinics choose to follow the patients with atypical moles indefinitely. Patients with more than 5 atypical moles have x6 increased risk of malignant melanoma (adjusted for other risk factors) and the risk is further increased in case of the familial atypical naevus syndrome. All these patients should be followed by a dermatologist with experience in dermoscopy. None of these patients should die of malignant melanoma!

3. Reassure the patient with metastatic disease. Although prognosis is not good, there are treatments to be tried, and spectacular effects are seen in a small proportion of patients. Metastases should be cut out, radiation and systemic therapies can be considered. Refer the patient to an oncology center with the interest in this disease; they will be able to guide the patient and enrol in clinical trials.

Sunrise at WMC Vancouver.