42 Survival Increase with Autologous, Hapten-Modified Melanoma Vaccine (M-Vax)

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We have devised a novel approach to the immunotherapy of cancer based on the modification of autologous tumor cells with the hapten, dinitrophenyl (DNP). This technology is being developed by AVAX Technologies as a treatment for melanoma under the brand name, M-Vax. The treatment program consists of multiple intradermal injections of DNP-modified autologous tumor cells mixed with BCG (bacille Calmette Guérin) as an immunological adjuvant. Administration of DNP-vaccine to patients with metastatic melanoma induces a unique reaction—the development of inflammation in metastatic masses. Following DNP-vaccine treatment, almost all patients develop delayed-type hypersensitivity (DTH) to autologous, DNP-modified melanoma cells; about half also exhibit DTH to autologous, unmodified tumor cells. The toxicity of the vaccine is mild, consisting mainly of papules or pustules at the injection sites. Clinical trials have been conducted in two populations of melanoma patients: stage IV with measurable metastases, and clinical stage III patients rendered tumor-free by lymphadenectomy. In 83 patients with measurable metastases, there were 11 anti-tumor responses: 2 complete, 4 partial, and 5 mixed. In 214 stage III patients the 5-year overall survival rate was 44%, which compares favorably to the reported surgical rate of 20-25%. In both populations, the induction of DTH to unmodified autologous tumor cells was associated with significantly longer survival. This is a platform technology that is adaptable to other human cancers, including non-small cell lung cancer, ovarian and renal cell carcinomas.

43 Interferon and Melanoma: A Wedding with Ups and Downs

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High dose alpha-2 recombinant interferon (aIFN) - according to the so-called Kirkwood regimen — is to date the only adjuvant treatment which demonstrated a clear-cut benefit in disease-free survival (DFS) of stage IIIB and III melanoma patients, even though results in stage IIIB patients are biased by the lacking availability of sentinel node biopsy data in part of the patients. Ongoing clinical trials with pulsed i.v. high dose aIFN treatment have been designed in order to maximize the anti-proliferative efficacy on residual tumor while minimizing the side effects and impact on the quality of life. Notwithstanding the lack of evidence-based data about the benefit of low dose aIFN adjuvant treatment, there is an increasing attention to the possible crucial interference of aIFN with a genetically modulated, specific immune response and the angiogenic properties of tumor cells. In this case, the length and schedule of treatment could be of much higher importance as compared to the dose. This latter consideration also affects the use and possible benefit of aIFN in stage IV melanoma patients.

44 Genetic Testing and Imaging Technique

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Nearly 10% of cutaneous melanoma (CM) occurs in a familial setting. Two main genes involved in melanoma susceptibility have been described. The first, CDKN2A, located on chromosome 9p21, encodes two distinct proteins: p16INK4A and p14ARF both involved in inhibition of cell cycle. The second melanoma susceptibility gene, cyclin-dependent kinase 4 (CDK4), is mutated in less than 1% of families. Germline CDKN2A mutations have been described in 10-50% of families from several countries. But CDKN2A germline mutations have also been described in patients with more than one primary CM (MPM) (8.3-15% of MPM patients). The risk to identify a CDKN2A mutation increased with the number of primary melanomas, the early age of onset and the presence of familial history of melanoma and/or pancreatic cancer. Dysplastic nevi (DN) are also observed in many of familial cases or MPMs. This is probably more frequent repuent than we documented. Digital dermoscopy is helpful not only in the diagnostic procedures, compared precisely, the presence or absence of even minor changes can be assessed. The dermoscopy was the first milestone introduced in the diagnostic procedure of malignant melanoma. In the last decade a growing interest has developed in automated analysis of digitized images obtained by digital dermoscopy technique to assist clinicians in differentiating early melanoma from benign skin lesions. The computer-aided assessment of melanocytic skin lesions offers the dermatologist considerable assistance in evaluating suspicious pigmented skin lesions. The computer digital analysis can be successfully applied when the lesions are flat, with dimensions included within 5-12 mm in diameter, just as the feature of malignant melanoma is in early stages of development. The digital standardized dermoscopic point score must always be correlated with the patient’s history, the clinical nature of the lesion and the conventional dermoscopic assessment. Digital dermoscopy systems make it easy for clinician to send the dermatopathologist standardized images of pigmented skin lesions, improving the reliability of dermatopathological diagnosis. The use of digital dermoscopic systems has a very powerful impact on the follow-up examinations of patients with multiple atypical moles. During the monitoring period current and past images can be compared precisely, the presence or absence of even minor changes can be documented. Digital dermoscopy is helpful not only in the diagnostic procedures, but also in gradual dermatological education, in self training and teledermatology.
Metallothioneins as a Prognostic Marker in Primary Melanoma

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Metallothioneins (MT) are ubiquitous, cystein-rich intracellular small proteins with high affinity for heavy metal ions such as zinc, copper or cadmium. In the last decades it could be shown, that MT-overexpression in a variety of cancers is associated with resistance to anticancer drugs and is combined with poor prognosis. In a prospective study we examined the role of MT overexpression in melanoma patients as a prognostic factor for progression and survival. Between 1993 and 2004, 3386 patients with primary cutaneous melanoma were investigated by using a monoclonal antibody against MT on routinely fixed, paraffin-embedded tissues. 1270 patients with invasive tumors could be followed up for further statistical analysis (Fisher’s exact test, Mantel-Haenszel’s test, Kaplan-Meier curves). The MT data of disease-free interval and overall-survival were compared univariately and multivariately in Cox regression analysis. Immunohistochemical overexpression of MT in the tumor cells of patients with primary melanoma (310/1270; 24.4%) was associated with a higher risk for progression (117/167; 70.1%) and reduced survival (80/110; 72.7%) of the disease (both p < 0.0001). Similarly, Kaplan-Meier curves gave highly significant disadvantages for the MT-positive group. Univariate analysis (relative risk 7.4; CI 95% 5.2–10.2; p < 0.0001 for disease-free survival and relative risk 7.1; CI 95% 4.7–10.9; p < 0.0001 for overall survival), as well as multivariate analysis with other prognostic markers, turned MT-overexpression out as a highly significant and independent factor for estimating the prognosis in primary melanoma patients, even in patients with low risk melanomas.

Out-door Work as Potential Risk for Melanoma?

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Melanoma prevention programmes have become increasingly important. However, at this point, these initiatives are exclusively designed for the public and no systematic approach exists for those who undergo occupational sun exposure. To clarify the necessity of such a programme for the industry, we analysed 1,442 employees of the Austrian Mineral Oil Association working either outdoor, indoor, or both. By using a questionnaire and examinations by a dermatologists, we defined and correlated work place/life style and skin related melanoma risk factors. The general melanoma risk of the whole study cohort (Clark nevi in 4.4%, workers with nevi fulfilling at least one of the ABCD criteria in 20.3%) corresponded to the situation of the general public. By comparing the different out-door and in-door study cohorts, significant differences in the work/life style related, but no substantial differences in the skin related melanoma risk factors were detected. With the general amount of UV-exposure as the leading cause for a high melanoma risk, the outdoor group seemed to generate their level of risk by occupational sun exposure, frequent leisure time outdoor activities and the general lack of any sun protection measures, while the office workers showed a high frequency of sun bed visits and holidays in the south/mountains. Taken together, we showed for the first time that discontinuous as well as (occupation associated) continuous UV-exposure is mainly and equally important for the development of skin related melanoma risk factors. Consequently, we propose the need of additional melanoma prevention programmes specifically designed for the affected industries.