FC07

Everolimus: Preliminary Data on Cancer and Skin Cancers

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Everolimus (Certican®) is an immunosuppressive and anti-proliferative macrolide derived from rapamycin (sirolimus). At intracellular level, everolimus and sirolimus are signal-transduction inhibitors, that bind to the FKBP-12, and the resulting complex binds and inhibits the FRAP protein (m-TOR). Its inactivation inhibits the phosphorylation of kinase p70-S6K, thus impeding the cell growth and proliferation and arresting the passage of the cells from the G1 to the S phase. In vitro studies have shown that everolimus can inhibit the proliferation of numerous tumor cell lines and that is associated with prolonged (96-120 hours) inactivation of p70-S6K in tumor cells, even after wash-out of everolimus from the culture medium. Exactly what molecular determinants predict responsiveness of tumor cells to rapamycin and its derivatives is still unclear. The mTOR kinase is postulated to be downstream of the PI-3 kinase-Akt pathway, a signalling module known to be heavily deregulated in many human cancers. Molecular analysis has revealed that relative sensitivity to everolimus in vitro correlates in many cases with the degree of activation of Akt/PI3K protein kinase pathway and in some cases with PTEN status. In vivo studies in animal models, have shown that everolimus, administered as a single oral dose, can inhibit p70 activity in tumors and skin. When the incidence of skin cancer was studied in transplant patients, the rapamycins significantly reduced the risk, even in the presence of cyclosporine. Clinical studies testing the potential antineoplastic effects of rapamycines in transplant recipients are in progress or are being initiated.

FC08

Increased Incidence of Melanoma in Renal Transplant Recipients

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Background: With the advent of effective immunosuppression, kidney transplantation has become an established and successful mode of treating end-stage renal disease. Immunosuppressed renal transplant recipients have an increased risk of diverse range of malignancies, of which non-melanoma skin cancers are the most frequent, in particular squamous cell carcinomas (SCC). Less extensively reviewed in the literature is the increased incidence of malignant melanoma. Objectives: To determine the incidence and characteristic of malignant melanoma in renal transplant recipients. Methods: We reviewed the case notes and pathology of all patients who developed melanoma within the Oxford Transplant Unit. The clinical details were recorded including date of transplant, immunosuppressive therapy, interval between melanoma and transplant, site of occurrence, type of clinical and histopathological diagnosis of melanomas and prognostic factors. Results: 15 patients developed 18 melanomas from a population of 1874 transplanted patients. The total number of transplant years was 11942.2. The incidence of melanoma in our population was 18/11942.2 transplant years, which is approximately 8 times greater than the standardised rate for this region. We found that the average interval between transplant and melanoma was ~11 years (median 8.5 years). Melanomas occurred on the trunk in the majority of cases (58%), followed by the upper limb (25%). All patients apart from 1 are alive with no recurrence of their melanoma. The median follow-up period post melanoma was 3.7 years. In all patients apart from the patient that died, the melanomas were less than 1 mm Breslow thickness. That patient’s melanoma was 4.5 mm thick. In the cases in vertical growth phase (VGP) the tumour infiltrating lymphocyte (TIL) response was absent in 4 cases and non brisk in 1 patient. Conclusion: In the Oxford transplant population studied melanomas occurred at approximately 8 times the rate of the general population. This is the largest increase in rate described in the literature. The patients had better outcome than would have been expected from series previously published. We feel that this was due to the fact that they were mostly detected at a relatively early stage. Renal transplant patients have dedicated dermatology clinics in Oxford, which may have contributed to the early diagnosis and good outcome. There is a necessity to set up regular Clinics for organ transplant recipients (OTR) in Poland.

FC09

Skin Cancers in Patients with HIV Disease in Romagna, Italy

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Background: During the last decade antiretroviral therapies have greatly changed the course of HIV disease, improving the life expectation of HIV+ subjects. However, the dark sides of this success are the complications of a lifelong immunosuppression and an increased risk of cancer. Objective: The current study was conducted in order to elucidate the spectrum of skin cancers in a population of HIV positive patients over a period of 10 years. Patients and methods: a retrospective chart review was performed on 2,012 subjects with HIV disease living in Romagna, in the North-East of Italy, who had been diagnosed with primitive skin cancers, excluding Kaposi’s sarcoma, between January 1994 and June 2004. The data collected included the patient’s age when the skin tumour was diagnosed, gender, location of the neoplasms, its pathologic findings, clinical outcome, length of immunosuppression, stage of HIV disease, viremia and CD4+ cell counts at the moment of skin cancer diagnosis, predisposing risk factors for AIDS. Results: data from 24 patients (with a total of 29 skin cancers) were included. Nine Basal Cell Carcinoma (BCC) were diagnosed in 7 patients; 8 Squamous Cell Carcinoma (SCC) in 6; Cutaneous Malignant Melanoma (CMW) in 7; Bowen’s Disease (BD) in 2; and Erythroplasia of Queyrat (EQ) was detected in a subject. The BCC/ SCC (both in situ and invasive) ratio in our patients was 0.18. Conclusions: in our population HIV+ subjects seem to be more prone of developing SCC, HIV+ homosexuals appeared to be higher risk patients for CMM in comparison with people that become HIV+ through heterosexual or drug addiction behaviours. The clinical outcome for skin cancer in our patients did not appear worse than that observed in HIV-immunocompetent population.

FC10

Skin Neoplasms in Ethiopia

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Skin cancer in dark-skinned African people is believed to be infrequent, but there are very little data available concerning the actual prevalence and incidence of skin cancer and melanoma in this population. Some authors reported an incidence of skin cancer in 1-2% of people of African descent (i.e. dark-skinned people) worldwide (1). Unlike among people of European descent, for whom basal cell carcinoma (BCC) is most common, squamous cell carcinoma (SCC) is the most frequent type of skin cancer among dark-skinned people, making up 60% of all cases of skin neoplasm (2). Melanoma is considered very rare amongst dark-skinned people; the most common type is acral lentiginous. Despite its rarity in the aforementioned population, however, it is still possible to witness the malignant evolution of a pre-existent nevus. This occurs in about one out of every two thousand cases. In our opinion, the aforementioned figures are underestimated; much of this population, particularly those living in Africa, does not have access to dermatological specialists, which may result in the under-diagnosis of melanoma and other skin cancers. On January 2005 a dermatological hospital named Italian Dermatological Hospital (IDH) has been opened in Quihii, a village near Mekele, the capital city of Tigray Region in Ethiopia. San Gallicano Institute and IISMAS (International Institute of Medical, Anthropological and Social Sciences) in collaboration with Tigray Regional Health Bureau and Mekele Civil Hospital have started the medical activity. We present the cases of skin cancer and melanoma that were observed at the Italian Dermatological Hospital, from January 2005 to December 2005.
ABSTRACTS

FC11
Is Skin Cancer Screening Worthwhile in a Working Population?

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Background: Over the last decades the incidence of skin cancer continuously increased in the Caucasian population. Early diagnosis and adequate therapy can lead to complete cure. Therefore skin cancer screening programmes seem to be reasonable.

Methods: Employees of an insurance company where asked to complete a self-assessment questionnaire regarding their sun behaviours (tanning ability, sunburns in childhood and adolescence, regular holidays in sunny climates, usage of sun beds), number and size (> 3 cm) of melanocytic nevi, former immunosuppression or chemotherapy and history of skin cancer. Afterwards a total body nevus count, an evaluation of the skin type as well as an assessment of pigmented and UV-induced features were performed by trained dermatologists.

A risk-dependant follow up schedule (casual self-assessment, regular self-assessment, and constant assessment by a specialist) according to the total number of nevi, existence and number of atypical nevi, skin type, and history of skin cancer was recommended for each employee individually. Results: 722 employees (male 49%, female 51%, age: 40 ± 21.06 y) were evaluated. Most employees underestimated their total number of nevi (0-10 n.: 35.5% self. vs. 11.4% expert; 11-30 n.: 31.8% self. vs. 35.1% expert; 31-50 n.: 26.5% self. vs. 24% expert; 51-100 n.: 19.7% self. vs. 15.9% expert; 100 + n.: 6.6% self. vs. 16.5% expert). 62.2% were judged as low-risk, 26.6% as intermediate risk and 11.2% as high risk patients. 27 employees (3.7%) with suspicious lesions were transferred to the clinics for further evaluation.

Conclusion: Skin cancer screening in a working population seems to be reasonable. Approximately every 10th employee was judged as high risk patient and encouraged to participate in a regular follow-up scheme.

FC12
Knowledge of Melanoma and Attitude Towards Moles in Italian Melanoma Patients

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Strategies aimed at improving early detection of melanoma are mainly based on the education of the population about criteria for recognizing suspicious skin lesions, on the rapid referral to dermatology centres and on regular dermatological visits in high risk patients. Our intent to assess the habits, knowledge of risk factors and attitude towards melanoma and correlate it with clinical features in melanoma patients from a population, such the Italian, that could acknowledged as a population not formally informed about melanoma. All the patients attending the departments of dermatology in Chieti, L’Aquila and Rome with the diagnosis of melanoma in the years 2004 and 2005 were given a questionnaire concerning their knowledge of melanoma risk factors, early detection melanoma rules (ABCD), on who prompted their referral to the excision of the melanoma and on the most important media sources of information on melanoma. Two hundred and ten questionnaire were given but only 160 patients returned it. Subtle changes in the colour, but not other features of the ABCD rule, was more frequently associated with thin melanomas (p < 0.008). Instead people who were referred only for gross changes of moles such as bleeding were associated with thicker lesions (p = 0.002). Self detection of melanoma did not help in the early diagnosis (p = 0.388). From our data it seems that applications of the ABCD rule is one of the most important features that can help in the early diagnosis of melanoma; moreover all the other information gathered may be useful to define educational strategies in the future.

FC13
Cellular Retinol Binding Protein-1 Expression in Normal Skin and Cutaneous Tumors

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Retinoids have important roles in growth and differentiation of epidermal cells. Cellular retinol binding protein 1 (CRBP-1) is a 15,000 Da cytosolic chaperone-like molecule regulating the pre-nuclear phase of retinoid signaling. CRBP-1 expression also influences the uptake and subsequent esterification of retinol and its intracellular bioavailability. We analyzed the expression of CRBP-1 in normal and abnormal epidermal differentiation, actinic keratosis and squamous and basal cell carcinomas by immunohistochemistry using a rabbit polyclonal antibody. CRBP-1 immunodetection was low in the basal layer of normal epidermis, with increased expression in granular layer keratinocytes; CRBP-1 was completely absent in the corneum. CRBP-1 expression was strong in normal adnexa. In psoriatic lesions, a hyperproliferative condition of the skin, an increased epidermal expression of CRBP-1 was also observed. In basal cell carcinomas, CRBP-1 expression was low or almost absent in classical nodular or superficial lesions, except in the keratotic variant of the tumor. Increased expression of CRBP-1 was present in actinic keratosis and well-differentiated squamous cell carcinomas, whereas it was reduced in less differentiated tumors. Investigation of mechanisms CRBP-1 expression in epidermal cells may help to understand the physiopathological changes, which occur in keratinocytes during hyperproliferative and oncogenic processes and better address possible adjuvant retinoid therapy. CRBP-1 immunodetection can also be applied as an adjuvant marker of keratinocyte differentiation.

FC14
Pegylated Interferon Alfa-2b and Temozolomide for Advanced Metastatic Melanoma (Stage IV AJCC). A Multicenter Phase II Trial of the Dermatologic Cooperative Oncology Group (DeCOG)

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Modifying the pharmacokinetic profile of IFN alfa-2b (PegIFN) may improve its activity and tolerability. The DeCOG evaluated the combination of temozolomide (TMZ) with pegylated interferon alfa-2b (PegIFN) in stage IV metastatic melanoma in an open-label, phase II trial at 10 study sites. Eligible patients with histologically confirmed metastatic melanoma were between 18 and 75 years, had a Karnofsky score of > 60%, no brain metastases and no prior chemotherapy. The regimen (28 d cycles) consisted of TMZ (200 mg/m2 d 1-5) in combination with PegIFN (100 µg s.c. of 1, 8, 15 and 21). OR and OS were primary and TTP and toxicity were secondary endpoints. 124 patients were accrued, 116 individuals were treated per protocol. At the time of data analysis, 81.0% had died from melanoma and median follow up time was 9.4 months. OR was 18.1% (2 CR, 1.7%; 16 PR, 16.4%); 25.0% of patients presented with SD and 54.3% progressed (2.6% not evaluable). Median TTP was 2.8 months, median > OS 9.0 months (95% CI 7.4,10.6). Grade (g) 3/4 leucopenia occurred in 22.8% and g 3/4 thrombocytopenia in 20.3%. Severe (gr 3/4) nausea was rare (1.7%). Liver enzyme elevation occurred in 30.5 % (26.3% gr 1/2; 4.2% gr 3). Combination therapy with TMZ and pegylated interferon alfa-2b constitutes a manageable treatment option in the outpatient setting for advanced metastatic melanoma. Its primary advantage is an increased patient convenience as a result of oral intake of TMZ and once weekly application of PegIFN.
Melanoma-Associated Chondroitin Sulfate Proteoglycan (MCSP): A Promising Target Antigen for Cancer Immunotherapy?

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The identification of tumour antigens recognized by T cells on human tumour cells has opened new avenues in cancer immunotherapy. Unfortunately, clinical responses in most studies have been observed only in the minority of vaccinated patients. There are several possible reasons for these disappointing results. First, tumour cells can downregulate antigen expression as most antigens identified so far do not play an essential functional role for their malignant phenotype. Second, tumour cells can downregulate or lose the expression of HLA molecules and thus escape recognition by T cells. Third, tolerance avoids the induction of potent and high-affinity T cell responses as most antigens used in tumour immunotherapy represent self antigens. An ideal target antigen, therefore, would be tumour-specific and functional relevant for the tumour. MCSP represents a transmembrane glycoprotein-proteoglycan complex, consisting of a N-linked glycoprotein of about 250 kDa and a > 450 kDa proteoglycan component and is expressed in > 90% of human melanoma tissues. MCSP was found to be involved in signal cascades concerning adhesion and extravasation of tumor cells and therefore thought to play an important role in determining the invasive and metastatic potential of melanoma cells. However, MCSP has been shown to be expressed in some normal tissues and thus tolerance or autoimmunity (when breaking tolerance) could be a major drawback also with this antigen. Surprisingly, we could rapidly generate MCSP-specific T cell clones from healthy blood donors by the use of antigen-loaded dendritic cells and identify several T cell epitopes within the core protein of MCSP. The isolated T cells directly recognized MCSP-expressing melanoma cells. Furthermore, we could demonstrate by ELISPOT analysis a strong MCSP-specific T cell immunity in the peripheral blood of the majority of healthy donors tested and these donors showed no clinical signs of autoimmunity. Melanoma patients also showed MCSP-specific T cell reactivity but clearly to a lesser extent than normal donors. This T cell reactivity seemed to decrease upon tumour progression. Our findings are interesting as they not only provide us with new potential target antigens for tumour immunotherapy but in addition they give new challenging insights in the concept of self tolerance and autoimmunity.