Melanoma Literature

Mark H Smith

Queens, New York 11418, USA
mark20082009@gmail.com

Abstract: Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, the cancer can cause serious illness and death. Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researches on the cancer and the.

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Keywords: cancer; biology; life; disease; research; literature

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person’s life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures


BACKGROUND: The local and systemic effects of bacillus Calmette-Guerin (BCG) have been known for decades. To investigate the adjuvant effect of BCG on resected American Joint Committee on Cancer (AJCC) Stage I-III melanoma, the Eastern Cooperative Oncology Group conducted a large trial to study the use of BCG alone or a combination of BCG and dacarbazine between 1974 and 1978. METHODS: A total of 734 patients were randomized to 4 clinical groups consolidated into 2 cohorts. Cohort I compared BCG with observation and Cohort II compared BCG with a combination of BCG and dacarbazine. The primary end points were survival time and time to disease progression. RESULTS: Within Cohort I, no statistically significant difference in disease-free survival (DFS) (P = 0.84) or overall survival (OS) (5-year survival 67% vs. 62%; P = 0.40) was observed between BCG treatment and observation. Within Cohort II, the addition of dacarbazine to BCG did not improve DFS (P = 0.74) or OS (P = 0.81) compared with BCG alone. Toxicity was mild to moderate in both cohorts. Although toxicity with this agent is mild, the use of BCG is associated with the development of punctate abscesses in greater than two-thirds of patients treated. CONCLUSIONS: In what to our knowledge is the largest ever trial to test the role of BCG as adjuvant therapy for melanoma, no benefit for BCG was observed for patients with AJCC Stage I-III disease. The mature results of the current trial projected to 30 years confirmed the negative results of previous smaller studies utilizing this agent.


There is a resurgence of interest in lymphoscintigraphy because of attention to the sentinel node concept and the availability of the surgical gamma probe that can be used in the operating room to localize radiolabeled sentinel nodes. Conventional surgical management of melanoma has been altered for intermediate thickness tumors such that lymph node dissection is performed for a lymph node bed only if the sentinel node is tumor positive on histological exam after gamma probe-guided excision. This approach is cost effective, saving about 80% of these patients (sentinel node tumor negative) the cost and morbidity of unnecessary "elective lymph node dissection." In addition, a biopsy can be performed on all lymph node beds that receive lymphatic drainage from the tumor site thereby improving staging and perhaps survival by providing the most appropriate therapy. Substantial work has been done to develop optimum imaging techniques and the best radiopharmaceutical preparation to achieve accurate, reproducible lymphatic drainage images. Our
methodology includes the following intradermal injections of a technetium 99m sulfur colloid (modified preparation) are followed by dynamic imaging (10 seconds per frame); static imaging up to 30 minutes and late imaging at 1 to 2 hours. Images show lymphatic channels that lead to sentinel nodes in 1, 2, 3, or more anatomic locations. Surgical management is altered to include sampling sentinel nodes of nodal beds, many of which would not have been sampled by previous conventional surgical estimates of lymphatic drainage. While clinical success of lymphoscintigraphy and intraoperative probe localization of the sentinel node in melanoma is evident, use of lymphoscintigraphy and the sentinel node concept in breast cancer is investigational, but promising. The radiopharmaceutical is injected around the tumor in the breast followed by imaging to delineate lymphatic drainage to the sentinel node(s). Optimum methodologies for radiopharmaceutical, volume and/or activity of injectate, and imaging have yet to be determined. Breast lymphatic drainage can be to axilla, internal mammary, and/or supraclavicular nodes in any combination.


Primary skin melanoma and skin cancers have been more prevalent in the previous decades and therefore have become a very significant public health problem. Dermatologists of the Skin and Venereal Diseases Clinic of the University of Sarajevo Clinics Centre initiated the first public preventive action called "Days of Fighting Melanoma" in May 2008. The objective of the campaign was to provide free dermatological examinations to all volunteers and to inform, through the media, wider population on early signs and recognition of skin cancer and the importance of sun protection. The total of 325 citizens were examined clinically and with dermatoscope in the period between 5 and 31 May 2008. The examination also included histological diagnoses: 7 patients with confirmed melanoma, 30 with basal cell carcinoma and 2 with spinocellular carcinoma. The results suggested a need for the expansion of the campaign to other towns in our country in order to demonstrate the importance of early detection of the disease and treatment options.


BACKGROUND: Previous studies suggest that chemokines and chemokine receptors have a role in the metastatic process. A correlation exists between the specific expression of these chemoattractive, pro-inflammatory cytokines and the ability of cancer to disseminate. Prior studies have shown that in metastatic melanoma and squamous cell carcinoma of the head and neck upregulation of CXC (alpha) chemokine receptor (CXCR)4 and CC (beta) chemokine receptor (CCR)7 expression is accompanied by downregulation of the chemokine receptor CCR6. However, the expression patterns of CCR6, CCR7 and CXCR4 in non-melanoma skin cancer have yet to be elucidated. METHODS: The expression patterns of CCR6, CCR7 and CXCR4 were determined using an immunohistochemical approach on formalin-fixed, paraffin-embedded normal, pre-cancerous actinic (solar) keratosis, squamous cell carcinoma and basal cell carcinoma tissues. RESULTS: Analysis of chemokine receptor expression showed downregulation of CCR6 and upregulation of CCR7 and CXCR4 in potentially metastatic non-melanoma skin cancer, invasive squamous cell carcinoma, but this pattern did not exist in non-melanoma skin cancer with no metastatic potential, basal cell carcinoma; or actinic keratosis, when compared with normal skin. CONCLUSIONS: Chemokine receptor expression may influence the biological behavior of non-melanoma skin cancer. The exact mechanism by which this occurs requires further study.


BACKGROUND: Recombinant human Interleukin-2 (IL-2) has been effective at inducing measurable antitumor responses in adults with renal cell carcinoma and melanoma. It also is being tested as adjuvant therapy for patients with acute myeloid leukemia after autologous bone marrow transplantation. METHODS: The authors tested IL-2 in a pediatric Phase II trial using a regimen that has antitumor effects in adults and was proven to be tolerated acceptably in a prior Phase I pediatric trial. Thirty-eight patients were entered into this study of whom 36 received IL-2 and were evaluable (20 with sarcoma, 9 with neuroblastoma, 5 with renal cell carcinoma, and 1 each with melanoma and lymphoma). RESULTS: Interleukin-2 dose modifications were based on tolerance and toxicity, such that 46% of these patients received a 50% increase in IL-2 dose during the second week, and 81% of those receiving the elevated dose continued receiving this dose level during the third week of treatment. A single patient with renal cell carcinoma
had a complete response that was maintained; the remaining 35 patients did not show objective evidence of tumor response sufficient to qualify as either a complete response or a partial response.

CONCLUSIONS: Absolute lymphocyte counts were indicative of the immunostimulatory effect of this IL-2 regimen as observed for adults, with a median 7.2-fold increase. Nevertheless, despite immune activation, a sufficient number of patients were evaluated, indicating that IL-2 does not have measurable antitumor effects in children with large refractory sarcomas or neuroblastomas, whereas one of five children with renal cell carcinoma had a complete response, consistent with the 10-20% response rate observed in adults.


Although there has been initial success with some types of immunotherapy, such as adoptive cellular therapy and monoclonal antibody therapy for cancer, the experience with therapeutic cancer vaccines has been much less encouraging. Almost all randomized phase III trials testing therapeutic cancer vaccines have failed to meet their end points. There are several potential explanations for this, ranging from factors related to the clinical trial design and the vaccine itself. Perhaps the most important are host-related factors. Specifically, progression and metastases of many cancers are associated with induction of multiple cancer-specific immunoinhibitory pathways. These inhibitory pathways include induction of T-cell anergy through dendritic cell dysfunction, release of immunosuppressive cytokines, T-cell exhaustion through inhibitory T-cell signaling and T regulatory cell-mediated tumor-specific immune suppression. All of these pathways have been shown to be operational in patients with melanoma. To enhance the activity of therapeutic cancer vaccines, these immunosuppressive pathways need to be addressed and reversed. A number of new immunomodulatory reagents that are able to interfere with some of these pathways are now being assessed in the clinic. Sanofi Pasteur designed a clinical trial in patients with advanced or metastatic melanoma that is intended to both induce tumor-specific T-cell responses and modulate or reverse some of the immune suppression pathways that the melanoma has induced. To accomplish this, the recently optimized ALVAC melanoma multi-antigen vaccine is administered with high doses of IFN-alpha. Clinical trial parameters have also been optimized to enhance the likelihood of inducing and documenting antitumor activity. Success with other therapeutic cancer vaccine approaches will likely require similar approaches in which promising immunogenic vaccines are integrated with biologically and clinically active immunomodulatory reagents.


Human MAGE and GAGE genes encode tumor-specific antigens presented by HLA I molecules recognized on tumor cells by cytolytic T lymphocytes. To determine if pancreatic cancer patients would be suitable for MAGE- or GAGE-based immunotherapy, the expression frequency of MAGE-A1, -A2, -A3, -A4, -A6 and GAGE1-8 genes was assessed in 15 pancreatic tumor cell lines and 23 pancreatic tumor specimens using reverse transcription-polymerase chain reaction (RT-PCR). In 67% of the cell lines at least one of the MAGE-A genes was detected, 53% revealed concomitant expression of two or more genes. GAGE1-8 expression was detected in 47% of the cell lines. In the primary pancreatic tumors, MAGE-A analysis revealed exclusive MAGE-A1 and MAGE-A2 gene expression in 26 and 30% of the specimens, respectively, independent from clinicopathologic factors. Treatment of MAGE-A expression-negative pancreatic tumor cells with the demethylating agent 5-aza-2'-deoxycytidine could activate MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4 and GAGE transcription suggesting silencing due to promoter methylation. Interestingly, a metastatic lesion to the liver revealed concomitant expression of MAGE-A1, -A2, -A3 and -A6 consistent with a more pronounced genome-wide hypomethylation in metastases. Therefore, a subset of pancreatic cancer patients could be eligible for active, specific immunotherapy directed against MAGE-A antigens and demethylating agents could increase the number of candidate patients.


In toto, there is strong circumstantial evidence from both experimental and clinical studies to support a role for omega-3 FA in the prevention of non-melanoma skin cancer (NMSC). In experimental animal studies there is direct evidence that dietary omega-3 FA inhibits ultraviolet radiation (UVR) carcinogenic expression, with regard to both increased tumor latent period and reduced tumor multiplicity. Equivalent levels of omega-6 FA increase UVR carcinogenic expression. Dietary omega-3 FA dramatically reduces the plasma and cutaneous pro-
inflammatory and immunosuppressive PGE(2) levels in mice. Dietary omega-6 FA increases prostaglandin E synthase type 2 (PGE(2)) level. Dietary omega-3 FA significantly reduces the inflammatory response and sustains, or enhances, the delayed type hypersensitivity immune response in mice when compared to an equivalent dietary level of omega-6 FA. Supplementary omega-3 FA significantly increases the UVR-mediated erythema threshold in humans. Supplementary omega-3 FA significantly reduces the level of pro-inflammatory and immunosuppressive PGE(2) levels in Ultraviolet B-irradiated human skin.


The effect of a low-fat diet on occurrence of non-melanoma skin cancer was examined in a 2-year dietary intervention trial. A total of 101 skin-cancer patients were randomized either to a control group that consumed, on average, 38% of caloric intake as fat, and in which no changes in dietary habits were introduced, or to a low-fat dietary-intervention group, in which patients were instructed to limit their calories from fat to 20% of total caloric intake. Patients were examined at 4-month intervals by dermatologists blinded to their dietary assignments. Nutrient analyses, conducted at each of the 4-month follow-up visits, indicated that the % calories of fat consumed in the intervention group had been reduced to 21% at 4 months and remained below this level throughout the 2-year period. There were no significant differences in total calories consumed, or in mean body weights, between the control and the intervention groups. Nor were there significant group differences in P/S ratios until month 24. Numbers of new skin cancers treated at each examination were analyzed in 8-month periods of the 2-year study. Comparisons of skin-cancer occurrences revealed no significant changes in the control group from baseline values. However, cancer occurrence in the low-fat intervention group declined after the first 8-month period and reached statistical significance by the last 8-month period. Patients in this group had significantly fewer cancers in the last 8-month period than did patients in the control group. In addition, there was a significant reduction in the number of patients developing skin cancer in the last 8-month period, as compared with the first 8-month period, within the low-fat intervention group. There were no significant changes in the control group. These data indicate that a low-fat diet can significantly reduce occurrence of a highly prevalent form of cancer.


BRAF encodes a RAS-regulated kinase that mediates cell growth and malignant transformation kinase pathway activation. Recently, we have identified activating BRAF mutations in 66% of melanomas and a smaller percentage of many other human cancers. To determine whether BRAF mutations account for the MAP kinase pathway activation common in non-small cell lung carcinomas (NSCLCs) and to extend the initial findings in melanoma, we screened DNA from 179 NSCLCs and 35 melanomas for BRAF mutations (exons 11 and 15). We identified BRAF mutations in 5 NSCLCs (3%; one V599 and four non-V599) and 22 melanomas (63%; 21 V599 and 1 non-V599). Three BRAF mutations identified in this study are novel, altering residues important in AKT-mediated BRAF phosphorylation and suggesting that disruption of AKT-induced BRAF inhibition can play a role in malignant transformation. To our knowledge, this is the first report of mutations documenting this interaction in human cancers. Although >90% of BRAF mutations in melanoma involve codon 599 (57 of 60), 8 of 9 BRAF mutations reported to date in NSCLC are non-V599 (89%; P < 10(-7)), strongly suggesting that BRAF mutations in NSCLC are qualitatively different from those in melanoma; thus, there may be therapeutic differences between lung cancer and melanoma in response to RAF inhibitors. Although uncommon, BRAF mutations in human lung cancers may identify a subset of tumors sensitive to targeted therapy.


OBJECTIVE: To identify risk factors of non-melanoma skin cancer (NMSC) in US veterans patients. BACKGROUND: There are an estimated one million new NMSC cases annually in the United States alone. While other studies with varying foci have evaluated risk factors in different subsets of the general populace, none have examined veterans as a group with potentially unique exposures and risks. METHODS: An investigation of risk factors for skin cancer through questionnaire and physical examination on 145 veteran patients with skin cancer and 59 veteran patients without a history of skin cancer was conducted. RESULTS: Parents' ethnicity, actinic keratosis on the face or other anatomic sites, solar elastosis of the neck, facial telangiectasias, age of first sunburn, and residency in Indiana were risk factors significantly associated with the development
of skin cancer. Other possible risk factors included smoking and radiation therapy. CONCLUSIONS: We documented several risk factors which significantly increased the chance of developing skin cancer among veterans. These included ethnic background and solar damage of the skin among others. A review of the literature confirms these risks in the general population, but also further study is warranted to address risk factors like smoking and radiation, particularly in veterans populations. Identification of pertinent risk factors will help to identify high risk individuals, allow detection of new skin cancer at its earliest stage, and develop a profile of favorable lifestyle characteristics that reduce NMSC risk.


Definition of immune variables that correlate with the antitumor activity of cancer vaccines is critical for monitoring immunotherapy protocols. To define surrogate end points predictive of the therapeutic efficacy of recombinant vaccines based on melanoma antigen tyrosinase-related protein (TRP)-2, we evaluated several properties of antigen-specific CD8(+) T lymphocytes in single mice undergoing either prophylactic or therapeutic immunization. Predictive markers for the efficacy of genetic vaccination were identified in the prophylactic model used. Interestingly, the number of tetramer(+) CD8(+) T lymphocytes expanded in vitro after a single cycle of stimulation with the immunodominant TRP-2 peptide was of the highest predictive value. In the therapeutic model, no variable examined at a single mouse level predicted the long-term therapeutic effect. Mice that survived did not show the highest expansion of antigen-specific lymphocytes or the more functionally active effectors, ex vivo or after in vitro culture with the peptide antigen. Successful therapy correlated strictly with the skewing of the T-cell receptor repertoire of tetramer-sorted, TRP-2-specific CD8(+) T lymphocytes, which showed a preferential alpha chain usage with a common CDR3 region.


The aim of this study was to evaluate the risk of occurrence of malignancies of different site of origin in patients with malignant melanoma (MM) of the skin and their first-degree relatives from families with cancer familial aggregations with unknown pathogenetic background (CFA). We analysed tumour spectrum and age at diagnosis of malignancies in 51 families with MM/CFA. In addition, we evaluated observed frequency (OF); expected frequency (EF); and relative risk (RR) of occurrence of malignancies in these families. In all cases peripheral blood examination of common Polish founder BRCA1 mutations was performed. In 25 families, we analysed loss of heterozygosity of BRCA1 and BRCA2 genes. We identified two subgroups of cases: 22 MM/CFA families with MM diagnosed before 55 years (< or =55 MM/CFA) and 29 MM/CFA families with MM diagnosed after 55 (>55 MM/CFA). In these families we observed increased proportion of breast cancers: 17.52% in the first subgroup (mean age of diagnosis 48.5) and 12.15% in the second subgroup. The odds ratio for breast tumours occurring before 50 in < or =55 MM/CFA families was 3.71. We also observed increased numbers of liver cancers, CSU and leukaemias. OF and EF analyses revealed increased risk of occurrence of cancers of breast (OF 10.4%, EF 4.5%) and liver (OF 1.9%, EF 0.8%) in women from MM/CFA families, RR for breast tumours was approximately 3.3 in < or =55 MM/CFA families. Molecular examination of MM/CFA families revealed no alterations within the BRCA2 gene and one germline mutation of the BRCA1 gene. In conclusion, it seems to be justified to consider systematic breast surveillance beginning at the age around 35-40 years as an option in women from < or =55 MM/CFA families.


BACKGROUND: Beside the primary goal of complete eradication, the cosmetic result is an important aspect of the treatment of non-melanoma skin tumors especially in the head and neck region. PATIENTS AND METHODS: From 1990 to 2000, we treated a total of 5,227 large basal cell carcinomas (BBC) and 1,189 squamous cell carcinomas (SCC) in the head and neck region by surgical excision in 4,239 inpatients at the Department of Dermatology, University of Tubingen. The procedure used in all patients was a conservative excision controlled by complete three dimensional histology of all margins (3D-histology) and specifically targeted follow-up surgery where required (histographic surgery). As part of the prospective tumor follow-up, we asked the treating outdoor physician one and four years later to evaluate the results of our surgical procedures. RESULTS: Of the 5,565 follow-up questionnaires sent back, 4,868 contained answers regarding the cosmetic result. The data from both answers were pooled. In 1,972 (40.5 %) patients the cosmetic result...
was evaluated as "excellent", in 1,992 (40.9%) as "good", in 662 (13.6%) as "satisfactory", in 191 (3.9%) as "mediocre" and in 51 (< 1.0%) as "poor". In 697 of the responses, the physician did not comment the cosmetic results or the patient was lost for follow up. CONCLUSION: With respect to both long term safety and cosmetic outcome, tumor surgery with 3D-histology of excisional margins has set very high quality standards in the treatment of non-melanoma skin cancer of the head and neck area.


The EORTC Melanoma Group (MG) was founded in 1969 by both clinicians and scientists from various disciplines and fields of research with a common interest in malignant melanoma. This collaborative approach has always been the foundation of the groups strength. With an interest in tumour biology and especially the immunological aspects of the disease, the group has always pursued a scientific approach to treatment development in malignant melanoma. Over the years, the group has performed many clinical trials, epidemiological studies, histopathological studies defining standards and guidelines, translational research regarding prognostic factors and various metastatic and immunological aspects of melanoma, and developed quality assurance programmes for immunological and molecular biological assays in laboratory networks. At present, the EORTC MG runs the worldwide largest clinical trial programme in stages II, III and IV melanoma involving some 140 cancer centres in and outside Europe. Each trial is associated with the appropriate translational research programmes.


To grow and metastasize, solid tumours must develop their own blood supply by neo-angiogenesis. Thalidomide inhibits the processing of mRNA encoding peptide molecules including tumour necrosis factor-alpha (TNF-alpha) and the angiogenic factor vascular endothelial growth factor (VEGF). This study investigated the use of continuous low dose Thalidomide in patients with a variety of advanced malignancies. Sixty-six patients (37 women and 29 men; median age, 48 years; range 33-62 years) with advanced measurable cancer (19 ovarian, 18 renal, 17 melanoma, 12 breast cancer) received Thalidomide 100 mg orally every night until disease progression or unacceptable toxicity was encountered. Three of 18 patients with renal cancer showed partial responses and a further three patients experienced stabilization of their disease for up to 6 months. Although no objective responses were seen in the other tumour types, there were significant improvements in patients' sleep (P < 0.05) and maintained appetite (P < 0.05). Serum and urine concentrations of basic fibroblast growth factor (bFGF), TNF-alpha and VEGF were measured during treatment and higher levels were associated with progressive disease. Thalidomide was well tolerated: Two patients developed WHO Grade 2 peripheral neuropathy and eight patients developed WHO grade 2 lethargy. No patients developed WHO grade 3 or 4 toxicity. Further studies evaluating the use of Thalidomide at higher doses as a single agent for advanced renal cancer and in combination with biochemotherapy regimens are warranted.


BACKGROUND: Malignant melanoma accounts for most of the growing mortality from skin cancer. However, survival rates are increasing for individual cases, probably because of earlier diagnoses. METHODS: Skin cancers collected by the SEER population-based data base between 1973 and 1987 are described in terms of their histologic classification and their distribution by sex, race, anatomical location, geographic locality, and time period of occurrence. RESULTS: There were 30,519 invasive skin cancers in the 15-year reporting period. Because the common basal cell and squamous cell cancers are not reportable to SEER, most of the cancers (28,206) were melanomas. In addition, 4386 in situ melanomas were reported. The rate of melanoma was 13-fold higher in whites than in blacks and 29% higher in white males than in white females. There was a 52% increase in the age-adjusted incidence rate for invasive melanoma and a 600% increase in the incidence rate of in situ melanoma over the 15-year period for whites and a 12% decrease in the incidence rate of invasive melanoma in blacks. The incidence of melanoma in the ear and trunk predominated in males, whereas melanoma of the lower limb predominated in females. Incidence rates and rate of increase of incidence of melanoma varied by anatomical subsite, sex, and geographic location within the United States. CONCLUSIONS: The variations among incidence rates of melanoma by sex, subsite, race, geographic location, and time period support prevailing theories of a solar cause for most but not all cases of this disease. Although melanoma rates are rising overall, the disproportionate rise in the
rate of diagnosis of in situ compared with invasive melanoma suggests that melanomas are being diagnosed earlier.


Scintigraphy with I123-N-(2-Diethyl aminoethyl) 4-Iodobenzamide (I123-IDAB), a radiolabeled benzamide, has recently been introduced to visualize sigma receptors in vivo. In this study we evaluated the potential clinical applicability of I123-IDAB scintigraphy in patients with melanoma and in patients with non-small cell lung carcinoma (NSCLC); tumors in which sigma receptors are expressed. Twenty-six patients with a history of malignant melanoma and 8 patients with proven NSCLC were studied. Whole body scintigraphy was performed 4-5 hours after the injection of 170 MBq of I123-IDAB. All patients with ocular lesions and those with NSCLC underwent SPECT imaging of the head or thorax, respectively. For other patients additional spot- and or SPECT scans of suspected regions were acquired if necessary. Three patients with a history of malignant melanoma were considered to be in complete remission. None presented abnormalities on the I123-IDAB scintigraphy. In 20 of the 23 patients (87%) with proven melanoma, lesions were identified on the I123-IDAB scintigraphy. On a lesion site basis the sensitivity averaged 64% (43/67) Lesions located in the liver and those originating from an amelanotic melanoma could not be detected, while a sensitivity of 89% was observed for ocular sites when SPECT was used. In patients with NSCLC all primary lesions showed an increased uptake of tracer, but only 4 out of 18 (22%) mediastinal lymph nodes that were suspected radiologically. I123-IDAB scintigraphy can be used to visualize melanoma and NSCLC lesions in vivo. In malignant melanoma this may be useful to confirm the melanoma nature of lesions that are not easily accessible to biopsy. Differences in sensitivity between the various sites however must be kept in mind when interpreting the I123-IDAB scintigraphy. In patients with NSCLC the value of I123-IDAB SPECT is at least questionable.


Caucasian renal transplant recipients from Queensland, Australia have the highest non-melanoma skin cancer (NMSC) risk worldwide. Although ultraviolet light (UVR) exposure is critical, genetic factors also appear important. We and others have shown that polymorphism in the glutathione S-transferases (GST) is associated with NMSC in UK recipients. However, the effect of high UVR exposure and differences in immunosuppressiv regimen on these associations is unknown. In this study, we examined allelism in GSTM1, GSTM3, GSTT1 and GSTP1 in 361 Queensland renal transplant recipients. Data on squamous (SCC) and basal cell carcinoma (BCC), UVR/tobacco exposure and genotype were obtained. Associations with both NMSC risk and numbers were examined using logistic and negative binomial regression, respectively. In the total group, GSTM1 AB [P = 0.049, rate ratio (RR) = 0.23] and GSTM3 AA (P = 0.015, RR = 0.50) were associated with fewer SCC. Recipients were then stratified by prednisolone dose (< or =7 versus >7 mg/day). In the low-dose group, GSTT1 null (P = 0.006, RR = 0.20) and GSTP1 Val/Val (P = 0.021, RR = 0.20) were associated with SCC numbers. In contrast, in the high-dose group GSTM1 AB (P = 0.009, RR = 0.05), GSTM3 AB (P = 0.042, RR = 2.29) and BB (P = 0.014, RR = 5.31) and GSTP1 Val/Val (P = 0.036, RR = 2.98) were associated with SCC numbers. GSTM1 AB (P = 0.016) and GSTP1 Val/Val (P = 0.046) were also associated with fewer BCC in this group. GSTP1 associations were strongest in recipients with lower UVR/tobacco exposure. The data confirm our UK findings, suggesting that protection against UVR-induced oxidative stress is important in NMSC development in recipients, but that this effect depends on the immunosuppressiv regimen.


OBJECTIVES: To describe the epidemiology of melanoma and nonmelanoma skin cancers. DATA SOURCES: Review and research articles, book chapters, and Surveillance, Epidemiology, and End Results (SEER) data. CONCLUSIONS: In 2002, an estimated 1.3 million Americans were diagnosed with skin cancer. Of these, 53,000 individuals were diagnosed with melanoma, the most common fatal form of skin cancer, and more than 7,000 Americans died of melanoma. Nonmelanoma skin cancer has the highest incidence of all cancers and the rise in the rate of cutaneous melanoma exceeds all other preventable cancers. IMPLICATIONS FOR NURSING PRACTICE: Nurses can act as case-finders and as advocates and educators for prevention of overexposure to ultraviolet radiation. Nurses should ascertain possible inherited risk and monitor patients for additional primary skin cancers.

Geller, A. C., K. Emmons, et al. (2003). "Skin cancer prevention and detection practices among siblings of

BACKGROUND: Family members of patients with melanoma have an increased risk of the disease, and families with multiple affected members account for about 10% of melanoma cases. These statistics suggest that first-degree relatives of patients with melanoma, who are at particularly high risk, warrant targeted public health action. OBJECTIVE: We sought to document rates for dermatologist examinations for cutaneous lesions, the practice of skin self-examination, and sunscreen use in this at-risk group. METHODS: Before participation in a randomized trial, 404 siblings of recently diagnosed patients with melanoma completed a survey on beliefs and practices regarding skin cancer prevention and detection. RESULTS: Sixty-two percent of participants had carefully examined their skin, 54% routinely used sunscreen, and 27% had received a skin cancer examination by a dermatologist during the past year; 47% had never received a dermatologist examination. Multivariate analysis found modifiable positive predictors for skin self-examination and dermatologist examinations, including having a clinician with whom to talk about melanoma and believing in the importance of regular skin examinations by a physician. Significant modifiable negative predictors included enjoyment of being tanned, not being sure what to look for when examining moles, and feeling uncomfortable having others look at their skin. CONCLUSIONS: Skin self-examination rates among these high-risk siblings are markedly higher than in population-based studies. However, many siblings were not screened for skin cancer by a dermatologist despite having strong risk profiles, being nearly fully insured, and being under care of primary care physicians. Improvements in communication between physicians and high-risk families and changes in office systems to assess family history of melanoma could increase screening rates for the estimated 1 million siblings of patients with melanoma.


BACKGROUND: Recently, the Institute of Medicine (2000) and the Third United States Preventive Services Task Force (2001) called for studies to help clinicians identify patients, especially elderly patients, who are at high risk for melanoma. In the current study, the authors sought to identify factors associated with a high yield in skin cancer screening and to explore strategies for improving mass screenings for melanoma. METHODS: The authors analyzed the data base of the 242,374 skin cancer screenings conducted on more than 206,000 Americans who attended the American Academy of Dermatology National Skin Cancer Screening Programs during the period 1992-1994. RESULTS: Ninety-six percent of 3476 screenees with a presumptive diagnosis of melanoma or possible melanoma were contacted, and follow-up records were obtained for 73% of screenees. Of these, 363 screenees had histologically proven melanoma. Middle-aged and older men (age >or= 50 years) comprised only 25% of screenees but comprised 44% of those with a confirmed diagnosis of melanoma. The overall yield of melanoma (the number of confirmed diagnoses per the number of screenees) was 1.5 per 1000 screenings (363 diagnoses of 242,374 screenees) compared with a yield of 2.6 per 1000 screenings among men age >or= 50 years. The yield was improved further for men age >or= 50 years who reported either a changing mole (4.6 per 1000 screenings) or skin types I and II (3.8 per 1000 screenings). The predictive value of a screening diagnosis of melanoma was more than twice as high for men age >or= 50 years with either a changing mole or skin types I and II compared with all other participants. CONCLUSIONS: The yield of mass screening for melanoma would be improved by outreach to middle-aged and older men, with particular focus on men with changing moles or with skin types I and II. Primary care physicians should be attuned to the risk factors among all of their patients but should be alerted in particular to the heightened risk of melanoma for men age >or= 50 years. Formal assessment of the impact of targeted screening on mortality warrants further study.


PURPOSE: The majority of invasive primary melanomas are thin (< or = 1.00 mm). Since the current staging system imperfectly predicts outcome in patients with such lesions, we sought to develop a more effective classification scheme to better identify both patients at high risk of metastasis who are candidates for further staging and therapy and those with little risk. PATIENTS AND METHODS: This prospective cohort study included 884 patients who had thin invasive melanomas. A tree-structured analysis of 10-year metastasis was used to develop a new classification scheme. RESULTS: The overall 10-year metastasis rate was 6.5% (95% CI, 4.8% to 8.1%). The prognostic tree defined four risk groups:
High-risk: men with vertical growth phase (VGP) lesions that had mitotic rates (MRs) greater than 0, and for whom the 10-year metastasis rate was 31% (22% to 42%; n = 90); moderate-risk: women with VGP lesions that had MRs greater than 0 and for whom the rate was 13% (9% to 18%; n = 136); low-risk: patients with VGP lesions that had MR of 0 for whom the rate was 4% (2% to 7%; n = 247); and minimal-risk: patients with invasive lesions without VGP for whom the rate was 0.5% (0% to 1.2%; n = 411). Survival curves differed significantly among the four groups (P < .001). CONCLUSION: Growth phase, mitotic rate, and sex are important prognostic factors for patients with thin melanomas, and they identify subgroups at substantial risk for metastasis. After validation in other populations, the proposed prognostic tree will be useful in the design of clinical trials and clinical management.


BACKGROUND: Since its inception in 1985, the American Academy of Dermatology (AAD) National Melanoma/Skin Cancer Screening Program has strived to enhance early detection of cutaneous malignant melanoma (MM) by providing nationwide skin cancer education campaigns in combination with free skin cancer screenings. OBJECTIVE: To analyze the AAD screening data from 2001 to 2005 in order to identify factors associated with MM detection, and thereby derive a model of increased likelihood for MM detection through visual skin examinations at screenings. MATERIALS AND METHODS: Patients completed a standardized AAD pre-screening form with historical and phenotypic information. Clinicians then recorded suspected clinical findings noted at visual skin examination. Statistical analyses were conducted using SPSS 14 (SPSS Inc., Chicago, Ill). RESULTS: Five factors, which can be remembered with the acronym HARM, independently increased the likelihood of suspected MM being found in the 362,804 persons screened: History of previous melanoma (odds ratio [OR] = 3.3; 95% confidence interval [CI], 2.9-3.8); Age over 50 (OR = 1.2; 95% CI, 1.1-1.3); Regular dermatologist absent (OR = 1.4; 95% CI, 1.3-1.5); Mole changing (OR = 2.0; 95% CI, 1.9-2.2); and Male gender (OR = 1.4; 95% CI, 1.3-1.5). Individuals at highest risk (4 or 5 factors) comprised only 5.8% of the total population, yet accounted for 13.6% of presumptive MM findings, and were 4.4 times (95% CI, 3.8-5.1) more likely to be diagnosed with suspected MM than individuals at lowest risk (0 or 1 factor). Receipt of a total skin examination at screening independently increased the likelihood for identifying suspected MM (OR = 1.4; 95% CI, 1.3-1.6). However, significantly fewer screenees in the highest risk group versus those in the lowest risk group underwent total skin examinations (53.7% vs 62.5%). LIMITATIONS: Risk factors studied limited to variables collected in screennee enrollment form. CONCLUSIONS: A higher-risk subgroup of the skin cancer screening population can be identified through assessment of MM risk factors using the HARM criteria. Refocusing efforts to provide a total skin examination to those individuals with multiple risk factors has the potential to both reduce costs and increase yields for suspected MM in future mass screening initiatives.


INTRODUCTION: Melanoma and Merkel cell carcinoma (MCC) are both aggressive skin malignancies associated with immunosuppression and possible UV exposure. Both tumors get similar surgical treatment; however, MCC is a relatively rare tumor in which less is known about prognosis and clinical behavior. METHODS: The California Cancer Registry (CCR), a population-based registry, was reviewed from the years 1988-2003. Merkel cell carcinoma and melanoma were compared with relation to gender, age, ethnicity, disease stage, site, and survival. RESULTS: A total of 113,187 cases of melanoma and 1,878 cases of MCC were identified in the CCR. Though both cancers are more common in men than in women, MCC had a higher incidence in men than melanoma (63% vs 57% p < 0.005). MCC occurs in the more elderly, with 73.6% of cases occurring in people over 70 years. In contrast, 69% of melanoma cases occurred in people younger than 70 years (p < 0.005). MCC shows a predilection for the head and neck compared to melanoma (47% vs 25.8%). Additionally, melanoma occurs more frequently on the trunk than MCC (47% vs 25.8%). Finally, the 10-year cumulative survival is lower for MCC than for melanoma (17.7% vs 61.3%, p < 0.005). CONCLUSION: Many clinicians assume MCC and melanoma behave similarly. However, MCC occurs in an older population, more frequently on the head and neck, in a higher percentage of men. Additionally, MCC has a higher rate of regional metastasis and thus may have more of a benefit from regional staging procedures. Overall, MCC has a worse prognosis.
Rhizoxin is a new anti-tumour agent isolated from the pathogenic fungus Rhizopus chinensis. It has shown broad activity against murine tumour models and is also active against vinca alkaloid-resistant cells. The purpose of our studies was to determine the clinical activity of this compound in patients with advanced breast cancer and melanoma. Based on the results of a phase I study, 2.0 mg m⁻² was administered as intravenous infusion over 5 min every 21 days. Nineteen patients were entered into the breast cancer phase II trial and received a total of 50 courses (median 2, range 1-6). Of these, dose reductions were performed in three courses because of leucopenia or stomatitis (1.5 mg m⁻², one course; 1.45 mg m⁻², two courses). Twenty-six patients were entered into the melanoma trial and received a total of 70 courses (median 2, range 1-12). No dose reductions were required. All patients were eligible for toxicity. Haematological toxicity included neutropenia CTC grade 3 (29/120 courses, 24.2%) and grade 4 (11/20 courses, 9.2%). Only drug-related CTC grade 1 thrombocytopenia was observed. Non-haematological toxicity included alopecia in all patients after two courses of treatment as well as CTC grade 3/4 stomatitis and asthenia. In the breast cancer study, one patient achieved a more than 50% tumour reduction after six cycles but was progressing after 6 weeks. Another patient showed a partial remission after the first course but was taken off the study because of CTC grade 3 skin toxicity. One patient was not evaluable for response (early death). No objective remissions were observed in 15 evaluable patients. In melanoma, no objective remissions were observed. We conclude that rhizoxin can be safely administered at 2.0 mg m⁻² every 3 weeks. However, it has little activity in patients with advanced breast cancer and melanoma.


BACKGROUND: The number needed to treat (NNT) is a key measure of the quality of melanoma diagnosis. There are few data on this measure from primary care skin cancer clinics in Australia. OBJECTIVE: We sought to report the NNT from a large pathology database and examine several patient characteristics. METHODS: We calculated NNT by doctor and clinic among 10,612 lesions, 6796 patients, 57 doctors, and 15 clinics from a pathology database. NNT was calculated with and without seborrheic keratoses. RESULTS: Overall NNT was 30 (with seborrheic keratoses) and 23 (without seborrheic keratoses). Excluding the 4 doctors with NNT greater than 60, total NNT decreased from 30 to 21 and from 23 to 15, respectively (with and without seborrheic keratoses). NNT was higher for female patients and younger patients (<30 years). NNT varied by doctor from 0 to 192 and 117, respectively (with and without seborrheic keratoses). LIMITATIONS: Given the retrospective design, we were unable to examine doctor characteristics such as age, sex, medical training, and patient pressure to excise. CONCLUSIONS: Substantial variability in individual doctor NNT produced an overall NNT similar to that reported from mainstream general practice, and higher than specialist practice.


This study aimed to identify risk markers for prevalent solar keratoses (SKs) and squamous cell carcinomata (SCC) combined, for incident SKs and for spontaneous remission of SKs and to evaluate primary preventative measures. It was a cross-sectional study, with follow-up, conducted in South Wales, and involved 1034 subjects aged 60 years and over. The main outcome measures were the presence of and changes in SKs, and presence of skin cancers, on sun-exposed skin, and risk factors for prevalent SKs/SCCs and for incidence and remission of SKs. We found that variables independently associated with prevalent SKs/SCCs were: age [80 + years vs 60-64 years, odds ratio (OR) 3.7]; sex (male vs female OR 2.2); cumulative sun exposure (top quintile vs bottom quintile OR 3.3) and skin type (skin type 1 vs 4 OR 12.4). Use of sunscreen or protective clothing was not protective after controlling for confounders. Males and those who sunbathed infrequently showed greater remission of SKs. Older subjects and those spending most time in the sun in the preceding 2 years were most likely to develop new SKs. We conclude that the risk factors identified are consistent with results from sunnier countries. The failure of sunscreen or clothing to emerge as protective raises doubts as to whether these measures are as effective in routine use in the general population as theoretical considerations and the limited trial evidence would predict. Recently reported sun exposure appears to influence the risk of developing new SKs.

Harvey, I., S. Frankel, et al. (1996). "Non-melanoma skin cancer and solar keratoses. I. Methods and
This study aimed to describe the prevalence and incidence of solar keratoses and skin cancers and the natural history of solar keratoses in a random population sample. It was a cross-sectional study, with follow-up, conducted in South Wales, and involved 1034 subjects aged 60 years and over drawn from the Family Health Services Authority register. The main outcome measures were detection of the presence of solar keratoses and skin cancers on sun-exposed skin and photographic validation of solar keratoses and biopsy confirmation of cancers wherever possible. We found that solar keratosis prevalence was 23% (95% confidence interval 19.5-26.5) and that of skin cancer (all types) 2% (95% confidence interval 1.0-3.5). The incidence rate of solar keratoses was 149 lesions per 1000 person-years and of non-melanoma skin cancer 9 per 1000 person-years. In all 21% (95% CI 16-26) of solar keratoses regressed spontaneously during follow-up. None underwent malignant change. We believe that the failure of individuals to seek medical advice and the variable under-registration of non-melanoma skin cancer makes population-based study important. The high prevalence and incidence of malignant and pre-malignant skin lesions in this random sample raise major public health concerns. The high rate of spontaneous regression of solar keratoses and the low rate of malignant change challenges conventional views about the need for routine treatment of these lesions.


Crassocephalum rabens (Asteraceae) is a popular anti-inflammatory folk medicine and food supplement. We investigated the cancer chemopreventive bioactivity of C. rabens phytocompounds in vitro and in vivo using cell- and gene-based bioassays and a mouse B16 melanoma model. The bioactive glyceroglycolipid 1,2-di-O-alpha-linolenoyl-3-O-beta-galactopyranosyl-sn-glycerol (dLGG) that was identified from C. rabens was found in vitro and in vivo to be a potent nitric oxide (NO) scavenger. dLGG treatment inhibited both mRNA and protein expression of inducible NO synthase and cyclooxygenase-2 (COX-2) in murine macrophages and inhibited COX-2 gene transcription in 12-O-tetradecanoylphorbol-13-acetate (TPA)-treated B16 cells. In immunohistochemical studies, dLGG inhibited TPA-induced expression of COX-2 and nitration of proteins in mouse skin. dLGG could also significantly inhibit lipopolysaccharide-induced prostaglandin E(2) production in murine macrophages. Furthermore, dLGG prevented nuclear translocation of cytoplasmic nuclear factor-kappaB (NF-kappaB) by suppressing IkappaBalpha phosphorylation and degradation. Structure-activity relationship study by electrophoretic mobility shift assay indicated that the dilinolenoylglycerol moiety in dLGG is the essential structural feature preventing NF-kappaB-DNA complex formation. A dLGG-enriched extract from C. rabens (10 mg/kg) markedly suppressed B16 melanoma growth in C57BL/6J mice following i.p. administration, an effect comparable with that of cisplatin, a cancer chemotherapeutic drug. This study shows the detailed molecular mechanism(s) underlying the anti-inflammatory and tumor-suppressive effects of a natural galactolipid.


The Tasmanian Cancer Registry carried out population-based surveillance of non-melanoma skin cancer (NMSC) from 1978 to 1987. A total of 8,651 NMSC were recorded in 7,160 individuals, representing an age-standardized rate of 161/100,000 per year. Ninety-four percent of cases were based on histological diagnosis. Incidence of basal-cell carcinoma (BCC) was higher than the incidence of squamous-cell carcinoma (SCC). The incidence of NMSC was twice as high in men as in women. Incidence increased substantially with age, more markedly for SCC than BCC. For most body sites, BCC was more frequent, but on highly exposed sites such as the backs of hands, lower limbs in women and ears in men, the incidence of SCC was higher. There was an overall increase of 7% per year in the age-standardized incidence rate of NMSC. The increase was more marked for BCC than for SCC, and was consistent across age groups and both sexes. A first NMSC during the study period was associated with a 12-fold increase among men and a 15-fold increase among women in the risk of development of a new NMSC within 5 years, when compared with the NMSC incidence recorded for the population as a whole.


PURPOSE AND METHODS: T cells play an important role in in vivo rejection of human melanoma. Human melanoma antigens recognized by autologous T cells were identified. These antigens are classified as tissue (melanocyte)-specific proteins, cancer-testis antigens (proteins expressed in normal testis and various cancers), tumor-specific peptides
developed from mutations in tumor cells, and others. RESULTS: A variety of mechanisms generating T cell epitopes on tumor cells were discovered. Various clinical observations, including tumor regression observed in adoptive transfer of gp100-reactive T cells suggest that these identified melanoma peptides may function as tumor rejection antigens. Immunodominant common epitopes that could expand melanoma-reactive cytotoxic T lymphocytes (CTLs) in vitro were found in the MART-1 and gp100 antigens. New immunization protocols--including immunization with peptides, recombinant viruses, plasmid DNAs, and dendritic cells pulsed with peptides as well as adoptive transfer of in vitro-generated CTLs by stimulation with antigenic peptides--were developed (phase I clinical trials have been performed in the Surgery Branch of the National Cancer Institute, Bethesda, MD, U.S.A.). Immunization with the gp100(209(210M)) peptide that was modified to have high HLA-A2 binding affinity, along with incomplete Freund's adjuvant and interleukin (IL)-2, resulted in a 42% response rate in patients with melanoma. CONCLUSION: These immunotherapies need further improvement due to the mechanisms of tumor escape from T cell responses.


PURPOSE: The combination of interferon alfa-2a (IFN alpha) and high-dose interleukin-2 (IL-2) is active in metastatic melanoma. The addition of cisplatin (CDDP) has resulted in response rates greater than 50%. This study was performed to determine whether the addition of CDDP to a cytokine treatment regimen with IFN alpha and high-dose IL-2 influences survival of patients with metastatic melanoma. PATIENTS AND METHODS: Patients with advanced metastatic melanoma were randomly assigned to receive treatment with IFN alpha 10 x 10(6) U/m2 subcutaneously on days 1 through 5 and a high-dose intravenous decrescendo regimen of IL-2 on days 3 through 8 (18 mIU/m2/6 hours, 18 mIU/m2/12 hours, 18 mIU/m2/24 hours, and 4.5 mIU/m2/24 hours x 3) without (arm A) or with (arm B) CDDP 100 mg/m2 on day 1. Treatment cycles were repeated every 28 days to a maximum of four cycles. RESULTS: One hundred thirty-eight patients with advanced metastatic melanoma, of whom 87% had visceral metastases, were accrued for the trial. Both regimens were feasible in a multicenter setting. The objective response rate was 18% without and 33% with CDDP (P = .04). The progression-free survival was 53 days without and 92 days with CDDP (P = .02, Wilcoxon; P = .09, log-rank). There was no statistically significant difference in survival between treatment arms, with a median overall survival duration for all patients of 9 months. CONCLUSION: The addition of CDDP to cytokine treatment with IFN alpha and IL-2 does not influence survival of patients with advanced metastatic melanoma, despite a significant increase in response rate and progression-free survival.

BACKGROUND: Based on phase II trial results, chemoimmunotherapy combinations have become the preferred treatment for patients with metastatic melanoma in many institutions. This study was performed to determine whether interleukin-2 (IL-2) as a component of chemoimmunotherapy influences survival of patients with metastatic melanoma. PATIENTS AND METHODS: Patients with advanced metastatic melanoma were randomly assigned to receive dacarbazine 250 mg/m2 and cisplatin 30 mg/m2 on days 1 to 3 combined with interferon-alpha-2b 10 x 10(6) U/m2 subcutaneously on days 1 through 5 without (arm A) or with (arm B) a high-dose intravenous decrescendo regimen of IL-2 on days 5 through 10 (18 x 10(6) U/m2/6 hours, 18 x 10(6) U/m2/12 hours, 18 x 10(6) U/m2/24 hours, and 4.5 x 10(6) U/m2 for 3 x 24 hours). Treatment cycles were repeated in the absence of disease progression every 28 days to a maximum of four cycles. RESULTS: Three hundred sixty-three patients with advanced metastatic melanoma were accrued. The median survival was 9 months in both arms, with a 2-year survival rate of 12.9% and 17.6% in arms A and B, respectively (P = .32; hazard ratio, 0.90; 95% CI, 0.72 to 1.11). There was also no statistically significant difference regarding progression-free survival (median, 3.0 v 3.9 months) and response rate (22.8% v 20.8%). CONCLUSION: Despite its activity in melanoma as a single agent or in combination with interferon-alpha-2b, the chosen schedule of IL-2 added to the chemoimmunotherapy combination had no clinically relevant activity.


PURPOSE: This article reviews the currently available data on phase II and III trials regarding the efficacy of recombinant interleukin-2 (rIL-2)-based regimens in the treatment of stage IV melanoma, and discusses the rationale and outcome of past and currently ongoing rIL-2-based chemo-immunotherapy phase III trials conducted by the European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. PATIENTS AND METHODS: In the first EORTC-MCG phase III trial, stage IV melanoma patients were stratified on the basis of serum lactate dehydrogenase levels and tumor burden and randomized to receive rIL-2 (decrescendo regimen) plus interferon-alpha (IFN-alpha) plus or minus cisplatin. In the second trial, which is still ongoing, patients are being randomized to receive dacarbazine plus cisplatin plus IFN-alpha plus or minus rIL-2. These studies are designed to address the relative impact of cisplatin and rIL-2, respectively, on response and survival. RESULTS: The addition of cisplatin to immunotherapy (rIL-2 plus IFN-alpha) doubled the response rate from 18% to 35%, but had no impact on survival. The second trial is still ongoing, and no data is available yet on the contribution of rIL-2 to response and survival. CONCLUSIONS: Review of the literature and the outcome of our first trial indicate that the addition of single-agent cisplatin or polychemotherapy regimens to immunotherapy with rIL-2 and/or IFN-alpha can dramatically improve response rates. However, what impact, if any, these regimens have on overall survival is not known at this time. We could not demonstrate a survival benefit in the cisplatin-containing arm in spite of the increased response rate. Chemotherapy may yield only short-term responses, whereas immunotherapy appears to yield durable complete responses in a subset of patients. Further randomized phase III studies are needed to identify the essential components in combination regimens and to determine whether the toxicity associated with these regimens is outweighed by potential cure or a significant survival benefit.


Nonmelanoma skin cancer is the most common form of cancer in the United States. The incidence of melanoma is increasing more rapidly than any other form of cancer (with the exception of lung cancer in women). Public education programs have the potential to prevent future skin cancers and promote early detection of skin cancer and melanoma. This article describes a statewide awareness campaign and outlines important nursing activities and educational resources. Among results of a pre- and postevaluation poll are an increase in the number of respondents correctly identifying melanoma as the most serious type of skin cancer and an increase in the number of respondents who stated that sunburn in children was very serious.


The interferon-inducible, double-stranded RNA (dsRNA)-activated protein kinase, PKR, plays key roles in regulation of cell growth and differentiation, and has been postulated as a tumor suppressor. Downstream effectors of PKR include the translation initiation factor, eIF2alpha, and the
transcription factor, NF-kappaB. We found elevated levels of PKR protein, dsRNA-dependent PKR autophosphorylation activity, and phosphorylated eIF2alpha in melanoma cells compared to nontransformed melanocytes in culture. Treatment with interferon-alpha2b further induced PKR expression and activity. Immunohistochemical analysis of primary melanomas demonstrated minimal PKR immunoreactivity, but melanoma lymph node metastases expressed a high level of PKR protein. Furthermore, analysis of colon cancer specimens revealed that transformation from normal mucosa to adenomas and carcinomas was coincident with an increase in PKR expression. These data do not support the concept of PKR as a classic tumor suppressor but instead suggest that PKR upregulation occurs at defined steps in cancer progression, probably as a cellular response to neoplasia.


Worldwide, non-melanoma skin cancers (NMSCs), which include squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most commonly diagnosed cancers among Caucasians. It is well established that ultraviolet radiation (UVR) plays a central role in the development of these cancers, and more recently, a role for specific genetic mutations in the pathogenesis of BCC has been identified. The possibility that certain types of HPV, either alone or in conjunction with UVR, may play a role in the pathogenesis of these cancers is suggested by several lines of evidence reviewed below.*9 @2depidemiology / non-melanoma skin cancer / papillomavirus


BACKGROUND: There has been an alarming recent increase in skin cancer incidence among fair-skinned populations. Information from Asian populations is less readily available. OBJECTIVES: This study examines time trends and ethnic differences of skin cancers among Asians in Singapore. METHODS: Data from 1968 to 1997 was obtained from the Singapore Cancer Registry, a population-based registry. Age-standardized incidence rates (ASRs) and age-adjusted average annual percentage change, using the Poisson regression model, were calculated. RESULTS: A total of 2650 basal cell carcinomas (BCCs), 1407 squamous cell carcinomas (SCCs) and 281 melanomas were reported. There was an overall increase of skin cancer from 6.0 per 100000 person years (1968-72) to 8.9 per 100000 person years (1993-97). BCC incidence increased 3% annually, melanoma remained constant, and SCC decreased 0.9% annually. BCC ASRs were highest among Chinese, then Malays and Indians. A similar pattern was noted for SCC and melanomas. CONCLUSIONS: The incidence rates of skin cancer increased in Singapore during the period 1968-97. Fairer-skinned Chinese had a higher incidence of skin cancer.


Although screening for melanoma/skin cancer is theoretically of value, few data are available to evaluate its effectiveness or the value of a visual exam by a dermatologist as a cancer screening tool. From the 2560 persons screened for melanoma/skin cancer in Massachusetts in 1986 and 1987, the authors followed the positive screenees to determine their final diagnosis. The authors obtained information on 85% of these persons, and found nine malignant melanomas, 91 non-melanoma skin cancers, 39 dysplastic nevi, and three congenital nevi. The sensitivity of the visual exam by a dermatologist was 89% to 97% and the predictive value positive was 35% to 75% for skin cancer. The authors conclude that the yield of screening is equivalent to that of other major cancer screening efforts and that the sensitivity and predictive value of the visual examination by the dermatologist is appropriate for a cancer screening tool.


Approximately one million Americans are diagnosed with skin cancer each year. Since melanoma and skin cancer are amenable to prevention, education, and early detection, efforts to reduce the incidence of and death from melanoma have developed in many countries. Programs promoting behavioral changes and the incorporation of skin cancer control into national health care agendas have begun in a number of countries. Additional programs for the at-risk and general populations require further development and evaluation.


We conducted a survey of persons who voluntarily attended melanoma/skin cancer screenings
in Massachusetts in 1987. Of 1219 persons asked to fill out a questionnaire, 1116 (92%) completed it. Our study demonstrates that persons attending the melanoma/skin cancer screening program were, for the most part, at risk for the disease and appropriately selected themselves to be screened. Most were women, well educated (with college or advanced degrees), and white. More than 86% had at least one risk factor for melanoma/skin cancer whereas 78% had at least two risk factors. Future studies are necessary to determine whether our experience can be verified. Additional efforts should try to attract those who are at risk but perhaps are less willing to attend screening programs--men and those of lower socioeconomic status. These efforts can help target screening to those at highest risk and maximize the yield of these public health efforts.


Although screening for melanoma and skin cancer is theoretically appealing, too few data exist to evaluate its effectiveness. The rising incidence and mortality rates of melanoma and the continued incurability of metastatic disease underscore the desperate need for effective screening. The extraordinary incidence of NMSC is a public health problem, but the value of screening for NMSC has not been established. The AAD screening program offers an opportunity to obtain critical data. Further research must make our screenings more effective and efficient. We need rigorous design and evaluation of all screening efforts. In the absence of a randomized controlled trial, other design measures, with careful tracking of incidence and mortality, are critical to assessing whether screening for melanoma and skin cancer can reduce morbidity and save lives.


There is increasing national interest concerning strategies for the early detection of melanoma/skin cancer. Screening has been implemented on a national scale in an effort to decrease morbidity and mortality from this disease; however, many crucial questions about the proper methods and ultimate value of screening remain unanswered. In this review we apply the scientific principles of cancer screening to dermatology, address the theoretic and practical challenges of cancer screening in terms of melanoma/skin cancer, analyze existing data on skin cancer screening, and identify issues that require future research.


We have previously demonstrated that the EP1 subtype of PGE2 receptor is expressed in the differentiated compartment of normal human epidermis and is coupled to intracellular calcium mobilization. We therefore hypothesized that the EP1 receptor is coupled to keratinocyte differentiation. In vitro studies, radioligand binding, RT-PCR, immunoblot and receptor agonist-induced second messenger studies demonstrate that the EP1 receptor is up-regulated by high cell density in human keratinocytes and this up-regulation precedes corneocyte formation. Moreover, two different EP1 receptor antagonists, SC51322 and AH6809, both inhibited corneocyte formation. SC51322 also inhibited the induction of differentiation-specific proteins, cytokeratin K10 and epidermal transglutaminase. We next examined the immunolocalization of the EP1 receptor in non-melanoma skin cancer in humans. Well-differentiated SCCs exhibited significantly greater membrane staining, while spindle cell carcinomas and BCCs had significantly decreased membrane staining compared with normal epidermis. This data supports a role for the EP1 receptor in regulating keratinocyte differentiation.


In the USA malignant neoplasms of the skin are the most common cancers of man. Annually, over 500,000 new cutaneous cancers are diagnosed. Of particular concern is the inexorable increase in the incidence and mortality rate of malignant melanoma (in 1978: 25,000 new cases; 5800 deaths). There are substantial data that (1) implicate sunlight as the probable cause of many cancers of the skin, and that, (2) indicate early diagnosis and prompt treatment results in cure in most instances. The time has come to create, implement, and evaluate a National Program on Education of the Medical Profession and the Public on Cancers of the Skin with emphasis on cutaneous malignant melanoma.

The purpose of this study was to evaluate the efficacy and safety of a continuous-infusion interleukin 2 (IL-2) regimen for patients with metastatic melanoma and renal cell cancer. To investigate the contribution of adoptively transferred lymphokine-activated killer cells, patients were randomized to receive either IL-2 alone or IL-2 plus lymphokine-activated killer cells. Twenty-three patients with renal cell carcinoma and 20 with melanoma were entered into the protocol. There were no objective responses noted in the 38 assessable patients (20 with renal cell carcinoma, 18 with melanoma). Most patients demonstrated progressive disease following one 31-day cycle of weekly continuous-infusion IL-2. Grade I and II toxic reactions, including fever, rash, anorexia, and weight gain, were common and treated symptomatically. Significant in vivo stimulation of lymphokine-activated killer and natural killer cell activity was noted in most patients. This continuous-infusion IL-2 regimen with or without lymphokine-activated killer cells was ineffective in the treatment of melanoma and renal cell carcinoma.


High-risk non-melanoma skin cancer (NMSC) of the head and neck is difficult to manage, given its propensity for regional metastasis, perineural invasion, direct parotid invasion, and bony destruction. Management of these tumors demands awareness of the characteristics contributing to their recurrence. Recent studies emphasize the importance of treatment of the parotid gland and cervical lymph nodes to improve locoregional control. A multidisciplinary approach to the assessment and treatment of high-risk NMSC is required to provide comprehensive care. This review also covers recent advances in the understanding of NMSC biology and new approaches in chemoprevention.


PURPOSE: This study examines the demographics, presentation, and outcomes of children and teenagers with melanoma using a US hospital-based oncology database. PATIENTS AND METHODS: Data from the National Cancer Data Base from 1985 through 2003 were examined for demographics, presentation, and survival of patients aged 1 to 19 years, as well as a comparison group of patients aged 20 to 24 years. Two-sided linear and Pearson chi2 tests were calculated to examine associations. Proportions were compared using two-sided z tests. Five-year overall observed survival was evaluated using the Kaplan-Meier method and the log-rank test. Cox proportional hazards regression was used to estimate risk of mortality. RESULTS: Of 3,158 patients aged 1 to 19 years, 96.3% had cutaneous melanoma, 3.0% had ocular melanoma, and 0.7% had an unknown primary tumor. Cutaneous melanoma in patients aged 1 to 19 years was more common in girls (55.5%) and patients older than 10 years (90.5%). The demographics and presentation of cutaneous melanoma were age related; younger children were significantly more likely to be nonwhite and male and more likely to present with a head and neck primary tumors and with regional or distant metastases (linear chi2, P < .001 for sex, race, and extent of disease). Poorer survival was associated with higher stage and younger age. In contrast to patients aged 20 to 24 years, survival was not related to thickness in patients aged 1 to 19 years with localized invasive melanoma. CONCLUSION: Melanoma in children and teenagers differs from melanoma in young adults in demographics, presentation, and survival. Further investigation is warranted to elucidate possible biologic correlates of the unique aspects of melanoma in children and teenagers.


Using the unique Utah Population Database, which links Utah genealogical data with Utah cancer data, we examined risks for other cancers among relatives of 4,079 melanoma cases. Age- and sex-specific rates for 35 different cancer sites were calculated, and used to estimate relative risks among relatives. In addition to the well-recognized risk for melanoma among first-degree relatives, we found significantly increased risks for prostate, breast, and colon cancers, non-Hodgkin's lymphoma, and multiple myeloma, ranging from 32 to 72% increased risk. Among second-degree relatives, in addition to increased risk for melanoma, we identified significantly increased risks for prostate cancer and multiple myeloma (27 and 53% increase, respectively). Among first-degree relatives of melanoma cases diagnosed before the age of 40 years, we found significantly elevated risks for cutaneous melanoma (380% increase) and prostate cancer (83% increase). Significantly increased risks for prostate cancer and multiple myeloma in both first-and second-degree relatives of melanoma cases are suggestive of heritable cancer syndromes. The increased risks for five additional cancer types in first-degree relatives of melanoma cases suggest that
individuals with a family history of melanoma should strictly adhere to recommended screenings for all cancers.


The development of monoclonal antibodies for use as in vivo carriers of radioactivity for diagnosis and therapy of malignant neoplasms is proceeding rapidly within academic and commercial sectors. The author and his colleagues studied antitumor antibodies formed against tumors of both somatic and hematopoietic origins. Several general principles have been established with the work with somatic tumors, including the following: Improved tumor-to-normal-tissue ratios can be achieved with Fab fragments as opposed to whole IgG; each antitumor antibody has a characteristic biodistribution in humans that cannot be readily predicted from tissue or small animal studies; and for many antibodies, there is a strong dependency of tumor uptake on total mass amount of antibody administered (greater uptake with greater mass dose). Initial work with iodine-131 labeled Fab fragments of the antimalanoma antibodies, 96.5 and 48-7, documented that tumor uptake was broadly proportional to antigen content of the tumors and that under optimal conditions, some tumors were sufficiently loaded with radiolabeled antibody to serve as radiation therapy. In one patient, an objective response was seen that lasted for 4 months; of five other patients, one had long-term stabilization of a previously rapidly growing tumor; two other patients had no response at doses of radioactivity that had caused significant bone marrow suppression but no treatment-related symptoms or morbidity. The antitumor antibody B-72.3, as IgG, has been particularly promising when administered intraperitoneally. In ten patients who were administered I-131 B-72.3 via a Tenkhoff catheter, the sensitivity and specificity of tumor location were excellent for peritoneal implants, and in three of these patients, surgically confirmed tumor was seen with the radiolabeled antibody technique when abdominal computed tomography and magnetic resonance studies were negative. In a separate series of 20 patients with mycoses fungoides, the anti-lymphoma antibody T-101 (recognizes the pan T-cell antigen, T-65), when labeled with indium-111, demonstrated lymph node involvement with greater sensitivity than conventional diagnostic methods and with excellent specificity. Radiolabeled antitumor B-72.3 and T-101 both show promise in antitumor therapy. Although much remains to be done on technical and biologic research levels before these radiopharmaceuticals can be routinely applied to all forms of cancer, these clinical research examples suggest that under proper conditions of use, radiolabeled monoclonal antibodies will have a major impact on the future practice of nuclear medicine.


Non-melanoma skin cancer is historically known to be associated with certain professions. Reporting is mandatory in Denmark when occupational exposure is suspected. In a retrospective register-based study of all cases of suspected occupational non-melanoma skin cancer reported to the Directorate of National Labour Inspection and the National Board of Industrial Injuries in Denmark in the period January 1, 1984 to December 31, 1994, we assessed the extent to which occupational exposures today are of importance in the occurrence of non-melanoma skin cancer. A total of 74 individuals (11 women and 63 men) aged 32-82 years (median 58 years) had been reported. Of these, 15 cases (20%) were approved as being occupational, 37 (50%) were rejected and 22 (30%) were either shelved or could not be further clarified. Most commonly approved were exposures such as asphalt, tar, and the like, and ionizing radiation, and localization on the arms or multiple tumours. Unexpected occupational exposure could not be identified but continued reporting is recommended in order to follow this in the future.


S100 calcium-binding proteins such as S100B are elevated in primary malignant melanoma and are used as markers for this and numerous other cancers. Wild-type p53 protein levels are relatively low in these cancer cells (i.e. when compared with cells without S100B) but are elevated when RNA antisense to S100B is introduced. This result implicates S100B in the down-regulation of p53 and is consistent with the large decreases in p53 protein levels observed previously in transient co-transfections of p53 and S100B (Lin, J., Blake, M., Tang, C., Zimmer, D., Rustandi, R. R., Weber, D. J., and Carrier, F. (2001) J. Biol. Chem. 276, 35037-35041). Down-regulation of p53 in primary malignant melanoma cells is likely the result of a direct interaction with S100B, which was observed by co-immunoprecipitation experiments. Furthermore, p53 binds regions of the S100B promoter, one of which matches the 20-nucleotide p53-binding consensus DNA sequence perfectly. Therefore, when p53 levels increase, it contributes to its own demise by up-
Lymphoma (n=35). Other, less common tumors were carcinoma (n=533), melanoma (n=46) and cutaneous material (n=2002), followed by squamous cell was most commonly identified in the histopathology record forms. Basal cell carcinoma skin cancers were recorded study period. All newly diagnosed invasive and in situ melanoma, leading to growth arrest, differentiation, senescence, or self destruction. Translating the promise inherent in tumor cell plasticity to the clinical arena remains a major challenge, but it is likely that a variety of epigenetic methods will play an increasingly important and effective role in the future control of malignant melanoma and other cancers.


Current treatments of many advanced malignancies, including melanoma, have failed to significantly reduce mortality rates, necessitating newer approaches. There is now abundant evidence that cancer cells, given the appropriate environmental and molecular context, are capable of remarkable plasticity, including complete reversal of the malignant phenotype. Such reprogramming involves both extrinsic and intrinsic factors and can occur via three routes: perturbations of extracellular matrix-cell receptor interactions, modulation of intracellular signaling pathways, and exploitation of epigenetic inheritance. Studies demonstrate the potential for producing dramatic changes in structural, biochemical, immunological, and functional properties of a broad spectrum of tumor cell types, including melanoma, leading to growth arrest, differentiation, senescence, or self destruction. Translating the promise inherent in tumor cell plasticity to the clinical arena remains a major challenge, but it is likely that a variety of epigenetic methods will play an increasingly important and effective role in the future control of malignant melanoma and other cancers.


The purpose of this retrospective and hospital-based study was to evaluate the epidemiology of nonmelanoma and melanoma skin cancer at University Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine during the 2003-2006 period. The study yielded population based results on 2911 cases of skin tumors in 2402 patients out of 16938 biopsies performed at Laboratory of Dermatologic Histopathology, University Department of Dermatology and Venereology, Zagreb University Hospital Center nd School of Medicine during the study period. All newly diagnosed invasive and in situ skin cancers were recorded by use of the histopathology record forms. Basal cell carcinoma was most commonly identified in the histopathology material (n=2002), followed by squamous cell carcinoma (n=533), melanoma (n=46) and cutaneous lymphoma (n=35). Other, less common tumors were noted. The number of tumors, and differences in age, sex and localization were analyzed. During the study period, there was no increase in the total number of cases recorded: 4305, 4202, 4116 and 4315, respectively. Study results showed skin tumors to be mostly diagnosed in elderly population (median age, 71 years). There were no significant sex differences, with the exception of the adult age group in 2006. As expected, skin tumors were mostly found in sun-exposed areas with some specific localization of individual tumor types. Study results were consistent with recent literature data.


The role of host factors in the etiology of pancreatic cancer has received a paucity of systematic investigation. Anecdotal reports and one population-based study have supported the concept that familial clustering of this disease exists. We have studied a kindred with a cancer-associated genodermatosis known as familial atypical multiple mole melanoma (FAMMM) syndrome (hereditary dysplastic nervous syndrome). Three key relatives have manifested pancreatic carcinoma. Since FAMMM may account for as much as 10% of the total malignant melanoma burden, its association with pancreatic cancer harbors important public health implications. Given the fact that the etiology of pancreatic cancer remains enigmatic, it is important to investigate all possible clues to its causality, including the potential role of host factors.


The high molecular weight melanoma-associated antigen (HMW-MAA), also known as melanoma chondroitin sulfate proteoglycan, has been used as a target for the immunotherapy of melanoma. This antigen is expressed on the cell surface and has a restricted distribution in normal tissues. Besides its expression in a broad range of transformed cells, this antigen is also found in pericytes, which are important for tumor angiogenesis. We generated a recombinant Listeria monocytogenes (Lm-LLO-HMW-MAA-C) that expresses and secretes a fragment of HMW-MAA (residues 2,160-2,258) fused to the first 441 residues of the listeriolysin O (LLO) protein. Immunization with Lm-LLO-HMW-MAA-C was able to impede the tumor growth of early established B16F10-HMW-MAA tumors in mice and both CD4(+) and CD8(+) T
cells were required for therapeutic efficacy. Immune responses to a known HLA-A2 epitope present in the HMW-MAA(2160-2258) fragment was detected in the HLA-A2/K(b) transgenic mice immunized with Lm-LLO-HMW-MAA-C. Surprisingly, this vaccine also significantly impaired the in vivo growth of other tumorigenic cell lines, such as melanoma, renal carcinoma, and breast tumors, which were not engineered to express HMW-MAA. One hypothesis is that the vaccine could be targeting pericytes, which are important for tumor angiogenesis. In a breast tumor model, immunization with Lm-LLO-HMW-MAA-C caused CD8(+) T-cell infiltration in the tumor stroma and a significant decrease in the number of pericytes in the tumor blood vessels. In conclusion, a Lm-based vaccine against HMW-MAA can trigger cell-mediated immune responses to this antigen that can target not only tumor cells but also pericytes in the tumor vasculature.


Non-melanoma skin cancer (NMSC) comprised of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common cancers in humans in many countries. Sunlight plays a major part in the development of these tumours which appear predominantly on areas of the most frequently exposed skin. The site distribution for BCC and SCC is not the same, with SCC being most common on the sites of very heavy exposure and BCC becoming more common on areas of only moderate exposure, e.g. upper trunk in men and women and lower leg in women. Incidence rates of NMSC, where they are being recorded, show rises over time. Mortality rates, on the other hand, have been dropping most of this century until they have been levelling out recently. The case fatality rate due to SCC appears to be between 1-2%. The malignant transformation rate of actinic keratoses to SCC appears to be very low. Studies on similar populations at different latitudes allow estimates to be made of increases which might occur with increasing exposure to ultraviolet radiation (UVR) over a life time. These have been used to estimate the possible increases in NMSC due to stratospheric ozone depletion. Finally, recent studies on the reduction of existing actinic keratoses and prevention of new ones with regular use of sunscreen augurs well for prevention of NMSC in the future.


Non-melanoma skin cancers (NMSC) are the commonest cancers in Australia. Their incidence rate is more than three times the rate of all other cancers combined. The incidence rate continues to rise to a stage where they now affect at least 1% of the population annually, necessitating treatment of more than 150,000 people per year. Exposure to sunlight in susceptible people appears to be the major environmental carcinogen in causation of these tumours. The exact nature of sunlight exposure necessary to induce them is still not entirely clear. Childhood exposure to sunlight stands out as being the major contributor to the development of all the common skin cancers. Solar keratoses are risk factors for NMSC and are precursors of squamous cell carcinoma. They appear to be more sensitive measures of carcinogenic sunlight exposure than frank invasive tumours. They are labile, and fluctuate in appearance clinically over time. Regular use of sunscreen can prevent new solar keratoses and increase clinical remission in existing ones. This is early evidence of the value of regular and adequate photoprotection in the long-term reduction of NMSC in Australia.


In the United States, the incidence of skin cancer is greater than that of all other cancers combined, and early diagnosis can be lifesaving. A substantial public health concern, skin cancer is increasingly being diagnosed and managed by primary care physicians. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (known collectively as nonmelanoma skin cancer) and malignant melanoma are the most common cutaneous malignancies. Shave biopsy is usually performed if BCC is suspected; punch biopsy is preferred if SCC is thought to be present. The choice of biopsy techniques depends on the presumed depth of the lesion. Treatment has 3 goals: complete eradication of the cancer and preservation or restoration of normal function and cosmesis. Risk of recurrence or metastasis determines whether the tumor is high risk or low risk. Based on the level of risk, treatment options are considered, including whether the patient can be treated by a primary care physician or should be referred to a dermatologist. Choice of treatment approach depends on the tumor's location, size, borders, and growth rate. The standard treatment approaches are superficial ablative techniques (electro-desiccation and curettage and cryotherapy) used primarily for low-risk tumors and full-thickness techniques (Mohs micrographic surgery, excisional surgery, and radiotherapy) used to treat high-risk
tumors. Removal of the entire tumor is essential to limit and prevent tumor recurrence.


The development of resistance to cisplatin (DDP) occurs rapidly both in vitro and in vivo, and constitutes a major obstacle to effective therapy. We have previously demonstrated that there is a highly synergistic interaction between tamoxifen (TAM) and DDP against cell lines representative of three different human cancers: melanoma, ovarian carcinoma and small-cell lung cancer. The purpose of these studies was to determine if TAM interferes with the development of resistance to DDP. T-289 melanoma cells and 2008 ovarian cancer cells were cultured with increasing concentrations of DDP +/- TAM in an attempt to induce resistance to DDP. At various time points the cells were removed from culture and the degree of resistance to DDP was quantitated. Concurrent exposure to TAM and DDP decreased both the rate and the absolute magnitude of resistance to DDP in both melanoma and ovarian cancer cell lines. In the T-289 cell line the rate was decreased by a factor of 3.4 +/- 1.4 (P < 0.05), while in the 2008 cell line the rate was decreased by a factor of 2.4 (P < 0.01). TAM decreases the rate as well as the absolute magnitude of in vitro resistance to DDP in both melanoma and ovarian cancer cell lines. These data suggest that the concurrent administration of TAM and DDP may result in a delay in the development of resistance to DDP which may have important clinical implications in the design of DDP-containing regimens.


Activation-induced cell death (AICD) as well as programmed cell death (PCD) serve to control the expansion of activated T cells to limit untoward side effects of continued effector responses by T cells and to maintain homeostasis. AICD of T cells in tumor immunotherapy can be counterproductive particularly if the activated T cells undergo apoptotic death after the very first secondary encounter of the specific epitope. We examined the extent to which tumor epitope-specific CTLs that are activated and expanded in an in vitro-matured dendritic cell-based primary stimulation protocol undergo AICD following their first secondary encounter of the cognate epitope. Using the MART-1(27-35) epitope as a prototype vaccine epitope, we also examined whether these CTLs could be rescued from AICD. Our results demonstrate that a substantial fraction of MART-1(27-35) epitope-specific primary CTLs undergo AICD upon the very first secondary encounter of the cognate epitope. The AICD in these CTLs is neither caspase dependent nor is it triggered by the extrinsic death signaling pathways (Fas, TNFR, etc.). These CTLs, interestingly, could be rescued from AICD by the JNK inhibitor, SP600125. We also found that SP600125 interferes with their IFN-gamma response but does not block their cytolytic function. The rescued CTLs, however, regain their capacity to synthesize IFN-gamma if continued in culture without the inhibitor. These observations have implications in tumor immunotherapy and in further studies for regulation of AICD in CTLs.


A clinical trial of N-[4-hydroxyphenyl]retinamide (4-HPR) has been in progress for the past 4 years to evaluate its role in chemoprevention of breast cancer. However, it is currently not known whether the effect of 4-HPR in breast cells is mediated by 4-HPR directly or through one of its metabolites. In this report, we investigated in vivo and in vitro effects of 4-HPR on three different breast carcinoma cells and two different melanoma cell lines. In vitro, the growth of all three breast carcinoma cell lines was inhibited by 4-HPR. Only one of two melanoma cell lines (UISO-Mel-1) showed growth inhibition to 4-HPR. The cell lines sensitive to 4-HPR in vitro also showed inhibition to 4-HPR in a xenograft model. Dietary 4-HPR (0.5 mmol/kg diet) reduced the growth of UISO-BCA-1 xenografts in female athymic mice, but had no effect on UISO-Mel-6 xenografts. Metabolism investigations of the 4-HPR-sensitive and insensitive cell lines indicated that N-[4-methoxyphenyl]retinamide (4-MPR), the major metabolite of 4-HPR, was detected only in cells sensitive to 4-HPR. Further in vitro studies with 4-MPR suggested that it is not an active metabolite of 4-HPR as it failed to inhibit growth of 4-HPR-resistant UISO-Mel-6 cells, and showed no dose-dependent inhibition of 4-HPR-sensitive breast carcinoma and melanoma cell lines. Our results in the present study indicate that, although 4-MPR is not an active metabolite of 4-HPR, detection of this metabolite in the malignant cells may serve as an indirect biomarker to predict response of cells to 4-HPR.

Most cancers contain morphologically heterogeneous populations of cells. While this observation may partly be explained by the coexistence of multiple genetic sub-clones arising through independent somatic mutations and/or as a result of differentiation processes in the tumor microenvironment, it also implies that the tumor may be formed from undifferentiated "stem cell-like" cells called "cancer stem cells" or "cancer-initiating cells". These cells are thought to constitute one or several rare subpopulations in a given tumor and would be strongly responsible for initiation of tumor development and growth as well as for metastasis and recurrence after cytoeducative therapy. However, while the concept of cancer stem cells has been first established for human myeloid leukemia in the 1960s, it has only much later been extended to other solid tumors such as breast or brain cancers and most recently to melanoma. Thus, it is presently unclear which role a sufficiently characterized population of melanoma stem cells plays in cancer promotion and progression. Here, we review the emerging melanoma stem cell model and discuss the biological and therapeutic implications of the model.


The authors have studied the natural history of 377 patients with Stage I cutaneous malignant melanoma followed at the Arizona Cancer Center, Tucson. Two hundred eight patients, or 55%, remained free of metastatic disease after a median follow-up of 30 months. The survival at 5, 8, and 10 years was 69, 65, and 63%, respectively. Natural breakpoints in Breslow thickness for survival occurred at 0.85, 1.95, and 4.00 mm. These are not significantly different from those found by other investigators. A step-down multivariate analysis using the Cox regression model yielded four factors as highly significant in predicting survival: Breslow thickness (P less than 0.001), an age/sex interaction (P = 0.0012), clinical ulceration (P = 0.0039), and a prophylactic node dissection (P = 0.019). No predictive value for a BANS or non-BANS location was detected. These results are discussed in reference to other large series which describe the natural history of cutaneous melanoma.


Retinoids, the natural and synthetic analogs of vitamin A, are growth-inhibiting and differentiation-inducing agents and show clinical promise as chemopreventive and antineoplastic agents. Fenretinide, a new synthetic retinoid, has antitumor activity in certain in vitro and in vivo model systems and was relatively nontoxic in phase I trials. Based on these data, we designed a phase II study of Fenretinide involving 31 patients with advanced breast cancer [15] and melanoma [16], two cancers shown to be responsive to this agent in preclinical models. Fenretinide was inactive in patients with advanced disease. Toxicity was mild, and reversible. Mucocutaneous side effects occurred in 16 (52%) patients. Nyctalopia developed in three patients one of whom developed decreased B-wave amplitude of the scotopic electroretinogram. The minimal toxicity and significant activity in preclinical studies make this an attractive agent for future breast cancer chemoprevention studies.


A retrospective study of 143 patients histologically diagnosed with non-melanoma skin cancer (NMSC) was carried out in order to evaluate the influence of ultraviolet (UV) radiation on the appearance of more than one NMSC in the same person. Descriptive statistical and logistic regression analyses were carried out for each variable and its possible interaction, in order to determine the potential appearance of multiple NMSC. The results obtained were in agreement with those of earlier studies. A significant relationship was observed between occupational UV exposure and individuals with more than one NMSC. Those patients tended to be blue-eyed and were chronically exposed to UV radiation as a result of occupational activities (although not always in leisure activities); most did not take protective measures such as the use of hats or creams.


A review of 1134 patients from the John Wayne Cancer Clinic with melanoma metastatic to regional lymph nodes was carried out to evaluate the
importance of various prognostic features after lymphadenectomy. Univariate analysis identified the prognostic significance of clinical stage for lesions with a depth of 0.76 to 4.0 mm (p = 0.0018); number of involved nodes (p = 0.0001); Breslow’s thickness (p = 0.0487); gender (p = 0.0103); location on an extremity (p = 0.0104); synchronous versus asynchronous detection of nodal metastases (p = 0.0107); age as a continuous variable (p = 0.0670); and unknown primary site (p = 0.088). Multifactorial analysis showed that number of involved nodes (p = 0.0001), extremity location of primary (p = 0.0059), and Breslow thickness (p = 0.0334) maintained their significance, whereas gender (p = 0.0627) and clinical stage (p = 0.0942) were almost significant. The long-term survival of the entire patient population at 5, 10, and 15 years of follow-up was estimated to be 46%, 41%, and 38%. When individual characteristics found to be significant by multivariate analysis were combined into different subsets, there was considerable heterogeneity, with 5-year survival varying from 79% to 14%. To quantify this heterogeneity better, a mathematical model was developed and found to approximate closely the observed survival rates in the heterogeneous subsets and in the group as a whole.


Prostate cancer, colorectal cancer, and melanoma are three malignancies that appear to have strong genetic components that can confer additional risk to family members. Screening tools, albeit controversial, are widely available to potentially aide in early diagnosis. Family members are now more attuned to the risks and benefits of cancer screening, thus, it is imperative that physicians understand the screening tools and how to interpret the information they provide. We reviewed the current literature regarding the cancer risks for individuals with a family history of prostate cancer, colon cancer, and melanoma, the current screening recommendations for family members, and actual screening practices of individuals with a family history of these malignancies. This review should serve as a guide for physicians and cancer control planners when advising their patients and the public regarding screening decisions.


Mutations of RAS, RAF, and PTEN, all important members of the RAS/MAPK and PI3K/AKT cascades, are reported in a variety of human tumors, including melanomas and endometrial cancer. In endometrial cancer, mutually exclusive mutations of PTEN and KRAS have been reported. On the other hand, mutation of BRAF is highly frequent, and mutually exclusive mutations of BRAF and NRAS have also been reported in melanomas. In this study, we elucidated the involvement of the up-regulation of RAS/MAPK and PI3K/AKT cascades in the pathogenesis of endometrial cancer and melanoma by analyzing the genes and molecules in these cascades. Twelve cell lines, six melanoma and six endometrial cancer, were analyzed; 4 (67%) of the 6 melanomas had gene mutations in the RAS/MAPK cascade, and a decrease or loss of PTEN expression was also observed. These results suggested that simultaneous up-regulations in these two cascades play important roles in carcinogenesis of melanocytes. However, no activation of AKT by phosphorylation was observed. On the other hand, 4 (67%) of the 6 endometrial cancer cell lines had mutually exclusive up-regulations in these cascades. However, two cell lines with up-regulation of the PI3K/AKT cascade also had up-regulation in the RAS/MAPK cascade induced by inactivation of DUSP6. These results suggest that simultaneous up-regulation of RAS/MAPK and PI3K/AKT cascades are crucial events in the pathogenesis of melanocytes, whereas up-regulation of either the RAS/MAPK or PI3K/AKT cascade is crucial for the majority of endometrial cancers.


The major histocompatibility complex (MHC) is known to have a role in the development of non-melanoma skin cancer (NMSC), although the genes and mechanisms involved have yet to be determined. To identify the susceptibility locus for NMSC within the MHC, we used a collection of well-defined polymorphic microsatellite markers from the Human leucocyte antigen (HLA) region for an association analysis of 150 cases with NMSC and 200 healthy controls selected from the Busselton population in Western Australia. High-resolution mapping was undertaken using a total of 40 highly polymorphic markers located at regular intervals across the HLA region (3.6Mb). Polymerase chain reaction (PCR) analysis was initially performed on

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pooled DNA markers to detect those markers that showed different allele profiles. Statistically significant differences in allelic frequencies (differentiating alleles) were found between cases and controls at three polymorphic microsatellite loci within a 470-kb genomic susceptibility region ranging between 6 kb centromeric of the HLA-B gene and intron 5 of the DDR gene. Interestingly, this genome region corresponded completely with the psoriasis-susceptibility locus. The three differentiating alleles and another four markers outside the susceptibility region were then PCR tested by individual genotyping of cases and controls. The newly identified susceptibility locus for NMSC within the MHC was found to be significantly different between the cases and controls by comparisons of allele frequencies at the three differentiating loci estimated from DNA pools and then confirmed by individual genotyping. This is the first study using high density microsatellite markers to localize a NMSC susceptibility region within the human genome.


BACKGROUND: Cutaneous malignant melanoma (CMM) is a recognized feature of the Lynch type II cancer-family syndrome and the Li-Fraumeni's syndrome. A significant contribution of these syndromes to the total burden of CMM would be reflected in an increased risk of nonmelanoma cancers in first degree relatives. METHODS: Pedigrees were taken from 85 patients with CMM using a family history questionnaire. The relative risk of death from all cancers and individual cancers in first degree relatives was calculated. RESULTS: Of the 85 questionnaires, those of 79 patients were completed and of adequate quality for analysis. The first degree relatives of CMM patients showed no increased risk of cancer death, the relative risk of cancer death being 1.0. Six patients (7.6%) had first degree relatives with CMM. One patient had a family history compatible with the dominant transmission of a predisposition to cancer. CONCLUSIONS: It is important to establish whether an increased cancer risk is present in relatives of patients with malignancies so that screening programs may be offered. This study provides little evidence to support seeing relatives for noncutaneous malignancies in the absence of a dominant family history of predisposition to cancers. The increased frequency of CMM in relatives suggests that relatives of CMM patients should be counseled on protection from the sun and examination of the skin for melanoma.


Tumor-targeted delivery of immune stimulatory genes, such as pro-inflammatory cytokines and suicide genes, has shown to cure mouse models of cancer. Total tumor eradication was also found to occur despite suboptimal tumor engineering; a phenomenon coined the "bystander effect". The bystander effect in immune competent animals arises mostly from recruitment of a cancer lytic cell-mediated immune response to local and distant tumor cells which escaped gene modification. We have previously described a Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) and Interleukin 2 (IL2) fusokine (aka GIFT2) which serves as a potent anticancer cytokine and it here served as a means to understand the mechanistic underpinnings to the immune bystander effect in an immune competent model of B16 melanoma. As expected, we observed that GIFT2 secreted by genetically engineered B16 tumor cells induces a bystander effect on non-modified B16 cells, when admixed in a 1:1 ratio. However, despite keeping the 1:1 ratio constant, the immune bystander effect was completely lost as the total B16 cell number was increased from 10(4) to 10(6) which correlated with a sharp reduction in the number of tumor-infiltrating NK cells. We found that B16 secretes biologically active TGFbeta which in turn
inhibited GIFT2 dependent immune cell proliferation in vitro and downregulated IL-2R beta expression and IFN gamma secretion by NK cells. In vivo blockade of B16 originating TGFbeta significantly improved the immune bystander effect arising from GIFT2. We propose that cancer gene immunotherapy of pre-established tumors will be enhanced by blockade of tumor-derived TGFbeta.


Ultraviolet B (UVB) radiation exposure increases the risk of skin cancer in whites. Motivated by indications that United States geographic variation of relative skin cancer risk in blacks approaches that in whites, we used Poisson regression to estimate the risk of skin cancer in blacks as a function of average annual surface-levels of UVB radiation, measured by Robertson-Berger meters. United States data were used on deaths in 506 state economic areas, 1970-1994, and on incident cases in the nine areas of the Surveillance, Epidemiology, and End Results Program, 1973-1994. For black males, the age-adjusted relative risk of mortality for a 50% increase in UVB radiation was significantly above one for malignant melanoma, 1970-1994 (1.16; 95% confidence interval, 1.02-1.32) and nearly so for nonmelanoma skin cancer, 1970-1981 (1.18; 95% confidence interval, 1.00-1.39), for which the time period was chosen to avoid AIDS-related deaths from Kaposi's sarcoma. However, for black females, the relative risk of mortality was not significantly elevated for either skin cancer, and, for both black males and females, the relative risk of incidence was not significantly elevated for melanoma in the period 1973-1994. Incidence data on nonmelanoma skin cancer were not available. Although the public health implication is uncertain because of the much lower absolute risk of skin cancer in blacks compared with whites, the findings suggest that sunlight exposure increases skin cancer risk in blacks.


Granulocyte-macrophage colony-stimulating factor (GM-CSF) enhances immune responses by inducing proliferation, maturation, and migration of dendritic cells (DCs) as well as expansion and differentiation of B and T lymphocytes. The potency of DNA vaccines can be enhanced by the addition of DNA encoding cytokines, acting as molecular adjuvants. We conducted a phase I/II trial of human GM-CSF DNA in conjunction with a multipeptide vaccine (gp100 and tyrosinase) in stage III/IV melanoma patients. Nineteen human leukocyte antigen (HLA)-A*0201+ patients were treated. Three dose levels were studied: 100, 400, and 800 microg DNA/injection, administered subcutaneously every month with 500 microg of each peptide. In the dose-ranging study, three patients were treated at each dose level. The remaining patients were then treated at the highest dose. Most toxicities were grade 1 injection-site reactions. Eight patients (42%) developed CD8+ T-cell responses, defined by a > or =3 SD increase in baseline reactivity to tyrosinase or gp100 peptide in tetramer or intracellular cytokine staining (ICS) assays. There was no relationship between dose and T-cell response. Responding T cells had an effector memory cell phenotype. Polyfunctional T cells were also demonstrated. At a median of 31 months follow-up, median survival has not been reached. Human GM-CSF DNA was found to be a safe adjuvant.


Ovarian manifestation of metastatic amelanotic melanoma is exceptionally rare and can lead to the clinical and even histological misdiagnosis of ovarian cancer. We report on a 35-year-old female patient who presented with bilateral adnexal masses, as well as massive ascites. She underwent laparascopy and multiple biopsies were taken. She was histologically diagnosed with malignant ovarian tumour and was referred for radical surgery. Postoperative final histological examination and immunohistochemical staining of the tumour revealed an amelanotic epithelioid melanoma. Despite the variety of this case, clinicians should be aware of this differential diagnosis when treating ovarian cancer. This report discusses the differential diagnosis and clinical management of both metastatic amelanotic malignant melanoma of the ovary and epithelial ovarian cancer.


BACKGROUND: Guidelines for follow-up of melanoma patients are not established. In 1987, a follow-up protocol was instituted at the Yale Melanoma Unit to improve upon the detection of disease recurrence in patients with American Joint Committee on Cancer Stage I-III cutaneous melanoma. The follow-up protocol consists of a
patient education program and a surveillance schedule based on stage of disease. METHODS: The authors retrospectively reviewed the records of 373 patients who were seen and followed according to the surveillance protocol in the Yale Melanoma Unit between January 1988 and December 1994 to determine 1) the time interval between the initial visit and recurrence; 2) the most common method of detecting recurrences; 3) whether the surveillance schedule or the patient detects more recurrences, i.e., asymptomatic recurrences versus symptomatic recurrences; 4) whether there is any survival difference between asymptomatic and symptomatic recurrences. RESULTS: The 5-year overall survival rates for Stage I, II, and III patients were 95%, 72%, and 52%, respectively. Of the 78 recurrences, 44 (56%) were detected by physician-directed surveillance examinations and 34 (44%) by patients. Most recurrences were found within the first (47%) or second (32%) year of follow-up. The estimated 6-month hazard rates for death or recurrence were 0.0044, 0.0088, and 0.0278 for Stage I, II, and III patients, respectively. The group of asymptomatic patients with recurrence had a survival advantage over the symptomatic recurrence group. In addition, patients with locoregional recurrence had better survival than those with distant recurrence. CONCLUSIONS: Although many recurrences arise rapidly and are recognized early by patients, in this study more than half were found by surveillance examinations before symptoms were manifest. Based on the hazard ratio for recurrences, the authors recommend the following surveillance schedules in addition to the patient education program for detection of recurrences: 1) Stage I, annually; 2) Stage II, every 6 months for Years 1-2 and annually thereafter; 3) Stage III, every 3 months for Year 1, every 4 months for Year 2, and every 6 months for Years 3-5; 4) at Year 6 and beyond, all patients should have surveillance annually, due to the risk of late recurrence and/or metachronous multiple primaries.


While high-dose bolus inpatient interleukin-2 is generally given on 8-week cycles, continuous infusion interleukin-2 could potentially allow for more rapidly repeated cycles. Fourteen (14) patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, having either kidney cancer (6) or melanoma (8), have been treated with continuous infusion (CIV) interleukin-2 (IL-2) 18 MIU/m2/24 hours for 72 hours. Cycles were repeated every 3 weeks up to 4 cycles, then every 3-4 weeks for 2 cycles, then every 6-8 weeks, until progression or intolerable toxicity. All patients received famotidine 20 mg intravenously (i.v.) twice per day during the 72-hour infusions. Patient characteristics included a median ECOG performance status of 1; median age = 63 (range: 25-79); most common metastatic sites: lung (9), bone (5), lymph nodes (5), and the liver (3). No patients with metastatic kidney cancer underwent a nephrectomy prior to interleukin-2. Median number of cycles received = 5 (1-9). No patients required Intensive Care Unit (ICU) admission. There have been no treatment-related deaths. Most common toxicities have been rigors, fever, nausea/emesis, and the reversible elevation of creatinine. One complete response and three partial responses (67% response rate; 95% confidence interval: 30%-90%) have been seen in kidney cancer, and two partial responses (25% response rate; 95% confidence interval: 7%-60%) have occurred in melanoma. Median survival has not been reached at >9+ months. Responding sites include the liver, bone, lung, lymph node and subcutaneous sites. Inpatient 72-hour continuous infusion interleukin-2 at this dose and schedule is well tolerated by patients with an ECOG performance status of 0 or 1 and has activity in kidney cancer and melanoma.


Six patients with either melanoma (3) or kidney cancer (3) who had experienced disease progression on outpatient interleukin-2 regimens were subsequently treated with inpatient bolus Interleukin-2 (IL-2) 36 MIU/m2 followed by continuous infusion IL-2 18 MIU/m2/day for 3 days. Cycles were repeated every 2 weeks up to four times, then every 3-4 weeks if tolerated and in the absence of disease progression. Two patients (one each with kidney cancer and melanoma) have achieved partial responses. One patient with kidney cancer and hepatic metastases has had a minor response. Interleukin-2 given at this dose and schedule shows some evidence of activity in patients who have received prior outpatient IL-2.


Twenty patients with either melanoma (7) or kidney cancer (13) were treated with outpatient bolus interleukin (IL)-2 18-22 MIU/m2 IVPB for 3
consecutive days for 6 consecutive weeks followed by a 2-week rest break (on an 8-week cycle). Patient characteristics included 16 males/4 females, eleven patients had received no prior systemic therapy, median ECOG performance status = 1, and most common disease sites being lung, lymph node, subcutaneous, bone, and liver. Two patients with melanoma (29% response rate) (95% CI: 8-64%) and two with kidney cancer (15%) (95% CI: 3-43%) have achieved partial responses. Two minor responses in kidney cancer were also seen. The most common toxicities were nausea, fatigue, rigors, fever, and myalgia/arthralgia. No cardiac events occurred, and no patients required hospitalization due to toxicity. IL-2 at this outpatient dose and schedule is well tolerated and displays some evidence of activity in melanoma and kidney cancer. Larger patient numbers are required to corroborate these response rates and to determine whether complete responses are possible.


The cytotoxic ability of T-cells against tumor cells may be increased by interleukin (IL-2). The infiltration of tumors by these cytotoxic T-cells may be enhanced by low-dose cyclophosphamide, which may also serve to deplete regulatory T-cells. Famotidine may increase IL-2 internalization by the IL-2 receptor on T-lymphocytes. We have treated 14 patients with either metastatic melanoma or kidney cancer, using CY 350 mg/M2 intravenously (i.v.) over 1 hour followed by a continuous infusion IL-2 9 MIU/M2/24 hours for 72 hours and famotidine 20 mg i.v. twice per day. All patients had received prior systemic therapy. Cycles were repeated every 4 weeks until disease progression. Patient characteristics: 8 with melanoma, 8 males, median age, 64, median Eastern Cooperative Oncology Group performance status: 1; most common metastatic sites: lungs, lymph nodes, bone, and liver. Median number of cycles received=2 (range, 2-4). Most common toxicities were fever, nausea/emesis, hypomagnesemia, hypophosphatemia, hyponatremia, and rigors. All patients were treated on an oncology inpatient unit. One (1) patient with kidney cancer has had a partial response in lung and lymph nodes for 5 months, while 1 patient with melanoma had a partial response in pulmonary metastases. Cyclophosphamide and IL-2 with famotidine has evidence of antitumor activity in previously treated kidney cancer and melanoma.


Lymphokine-activated killer (LAK) cells generated by high-dose continuous infusion interleukin-2 (IL-2) are able to nonspecifically lyse melanoma and kidney cancer cells. In vitro famotidine enhances cytotoxicity of LAK against tumor cells, possibly by increasing IL-2 uptake at the IL-2 receptor on lymphocytes. Outpatient IL-2 regimens typically have response rates of 15% or less, with most patients eventually experiencing progressive disease. Second-line therapy is, therefore, needed. We treated 11 patients (6 with metastatic melanoma; 5 having metastatic kidney cancer) who had previously experienced progressive disease on prior IL-2 regimens, with a combination of famotidine 20 mg intravenously (i.v.) twice per day and continuous-infusion IL-2 18 MIU/M2/24 hours x 72 hours, followed 24 hours later by a pulse IL-2 dose (18 MIU/M2 over 15 minutes). Cycles were repeated every 3 weeks. Patient characteristics were: 9 males, median age 63 years (range, 57-75), median Eastern Cooperative Oncology Group (ECOG) performance status: 1; most common metastatic sites: lungs, lymph nodes, and soft tissue/subcutaneous (s.c.); median number of cycles received: 4; most common toxicities were fever, nausea/emesis, hypophosphatemia, and hypomagnesemia. Five (5) patients (3 with melanoma, 2 with kidney cancer) have had partial responses. Two (2) patients with kidney cancer have been converted to complete responders with resection of residual disease, remaining without relapse at 5+ and 20+ months. Responding sites are lungs, lymph nodes, abdominal mass, and s.c. Median duration of response was 9.5 months. Median survival was 12 months. This combination has activity in patients with metastatic kidney cancer or melanoma who have received prior IL-2.


BACKGROUND: Occurrences of melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) have been associated with varying geography. Our goal was to evaluate differences in risk of these skin cancers according to residence at varying UV indices at 3 time points. METHODS: Prospective 1984-2002 study of 84 836 female nurses who lived in different UV index regions of the United States at birth and at 15 or 30 years of age. The outcome measure was diagnosis of melanoma, SCC, or BCC. RESULTS: During the 18-year study, 420
cases of melanoma, 863 cases of SCC, and 8215 cases of BCC occurred. At 30 years of age, age-adjusted risks for SCC were 1.47 (95% confidence interval [CI], 1.22-1.76) and 1.90 (95% CI, 1.51-2.36) for women residing in states with a UV index of 6 (medium) and 7 or more (high), respectively. Although elevated, the age-adjusted risk of BCC at 30 years of age associated with residence in these states was substantially less. Although the risk of melanoma was not elevated for women living in these states at 30 years of age, it was significantly elevated among women living in states with UV indices of 6 at birth and at 15 years of age. There was no material change in risk estimates with multivariate adjustment. For women who reported living in states with UV indices of 7 or more at all 3 time points, the multivariate risk of SCC was highest. CONCLUSIONS: The risk of SCC is independently affected by residence in locations with medium and high UV indices; the gradient of risk is weaker for BCC; and the risk of melanoma does not change significantly across this gradient.


BACKGROUND: The tissue of origin of the cell line MDA-MB-435 has been a matter of debate since analysis of DNA microarray data led Ross et al. (2000, Nat Genet 24(3):227-235) to suggest they might be of melanocyte origin due to their similarity to melanoma cell lines. We have previously shown that MDA-MB-435 cells maintained in multiple laboratories are of common origin to those used by Ross et al. and concluded that MDA-MB-435 cells are not a representative model for breast cancer. We could not determine, however, whether the melanoma-like properties of the MDA-MB-435 cell line are the result of misclassification or due to transdifferentiation to a melanoma-like phenotype. METHODS: We used karyotype, comparative genomic hybridization (CGH), and microsatellite polymorphism analyses, combined with bioinformatics analysis of gene expression and single nucleotide polymorphism (SNP) data, to test the hypothesis that the MDA-MB-435 cell line is derived from the melanoma cell line M14. RESULTS: We show that the MDA-MB-435 and M14 cell lines are essentially identical with respect to cytogenetic characteristics as well as gene expression patterns and that the minor differences found can be explained by phenotypic and genotypic clonal drift. CONCLUSIONS: All currently available stocks of MDA-MB-435 cells are derived from the M14 melanoma cell line and can no longer be considered a model of breast cancer. These cells are still a valuable system for the study of cancer metastasis and the extensive literature using these cells since 1982 represent a valuable new resource for the melanoma research community.


We studied the workload of the general practitioner after two skin cancer screening clinics in the Netherlands. Thirty-one physicians participated in the project. The numbers of patients presenting with benign and malignant skin lesions were recorded 2 weeks before and 6 weeks after the public campaigns. In the week immediately after the screening there was a small increase in the number of consultations for suspected skin cancer. Thereafter, the weekly number of malignant lesions decreased to precampaign levels. Subsequently to the campaigns the numbers of referrals for benign skin lesions decreased slightly. We conclude that the extra workload for the general practitioner generated by the screening campaigns has been negligible.


A lectin that can specifically bind to O-acetylsialic acids, found in glycoproteins and gangliosides, was purified to homogeneity from a crab Cancer antennarius (crab lectin) (Ravindranath, M. H., Higa, H. H., Cooper, E. L., and Paulson, J. C. (1985) J. Biol. Chem. 260, 8850-8856; Correction (1986) J. Biol. Chem. 261, 1983; Ravindranath, M. H., and Paulson, J. C. (1987) Methods Enzymol. 138, 520-527). We tested lectin binding to human melanoma cell lines to identify O-acetylsialylated gangliosides on the melanoma cell surface. The highest degree of binding of the crab lectin was demonstrated on a melanoma cell line, UCLASO-M25. To confirm that the binding was due to O-acetylsialic acid in the alkali-labile gangliosides, the gangliosides were isolated and purified from M25 cells and individually coated onto sheep asialoerythrocytes, which served as targets in an agglutination assay using the lectin. The crab lectin agglutinated the asialo-sheep erythrocytes coated with alkali-labile gangliosides, but the lectin failed to agglutinate the asialoerythrocytes coated with alkali-labile gangliosides, but the lectin failed to agglutinate the asialoerythrocytes coated with alkali-labile gangliosides, but the lectin failed to agglutinate the asialoerythrocytes coated with GM3, GD3, and base-treated gangliosides. Subsequently, the purified alkali-labile M25 ganglioside was base-treated and applied to TLC, and we found that it was converted to a slower migrating species identical to the disialolactosylerceramide (GD3). These results indicate that O-acetyl GD3 expressed on
the melanoma cell surface is recognized by the lectin. Because O-acetyl GD3 is not expressed on human normal tissues, we examined the capability of O-acetyl GD3 to induce immune responses in man. Sera from patients with melanoma were tested against M25 cells in an immunoadherence assay, and those positive to the M25 cell line were further tested for specificity to O-acetyl gangliosides. The presence of autoantibodies to O-acetyl-GD3 in melanoma sera was confirmed by blocking of the antigen sites on M25 cells by the lectin or preabsorption of the sera with erythrocytes bearing O-acetyl gangliosides. The data provide evidence that O-acetyl-GD3 may represent an important tumor marker for detection and treatment of human melanoma.


Cutaneous melanoma (CM) and nonmelanoma skin cancer (NMSC) have a high chance for cure if detected in an early phase of development. Patients who have these tumors may now be treated in the outpatient setting with a minimum of discomfort, inconvenience, and cost. Most skin cancer deaths are caused by CM. Until recently, CM incidence in the United States has been increasing faster than any other potentially lethal cancer, attributable at least in part to aggressive case detection and greater public awareness about the significance of risk factors and early warning signs of evolving tumors, resulting in increased numbers of curable tumors. Most CMs are discovered by patients or close acquaintances. Most CM deaths are related to patient delay in seeking medical care. Patient delay is attributed mostly to lack of knowledge rather than to fear and denial. In the United States, primary prevention of CM and NMSC has focused on encouraging sensible sun-exposure behaviors, while secondary prevention consists of a yearly national campaign that promotes skin awareness and self-examination and free examinations to detect evolving tumors, sponsored by the American Academy of Dermatology and the American Cancer Society. More attention is needed to encourage timely consultation for evolving tumors and predisposing risk factors and to focus screening and surveillance efforts of those people at greatest risk. Public education must continue to promote personal responsibility in the intervention process to reduce the morbidity and mortality associated with CM and NMSC.


We assessed the relationships between chronic arsenic (As) exposure, human papilloma virus (HPV) contact and non-melanoma skin cancer (NMSC) by means of a dermatology clinic-based case-control study (42 cases and 48 controls) in Region Lagunera, Mexico, where chronic As poisoning is endemic. Exposure was determined through detailed history of residence in the As-contaminated area and measurement of As levels in drinking water and urine. We used a consensus epitope from the central region of L1 protein of the HPV family to determine antibodies against HPV. A history of As exposure and HPV seropositivity were associated with increased NMSC risks. A history of exposure to high levels of As increased the risk for NMSC (OR = 4.53; P = 0.11) in the group of seronegative HPV patients. A positive response to HPV significantly increased the OR for NMSC to 9.04 (P = 0.01) when history showed exposure to low levels of As. Interestingly, the OR was significantly increased to 16.5 (P = 0.001) when both exposure to high levels of As and HPV seropositivity were present. In addition, the presence of NMSC increased the OR (5.45; P = 0.03) for a positive response to HPV when history showed exposure to low levels of As, but the OR was increased to 8.0 (P = 0.005) in the cases with high exposure levels. Thus, HPV infection could constitute an additional risk factor for NMSC development in humans chronically exposed to As. However, further studies with additional populations are needed to determine the interaction between HPV and As exposure in NMSC.


Accurate melanoma staging is critical in establishing management strategies and estimating disease relapse. Combined with assessment of comorbidities and understanding treatment toxicities, risk assessment is central to offering appropriate surgical or systemic therapies. The American Joint Commission on Cancer (AJCC) melanoma staging system provides survival estimates within anatomically defined disease categories. Newer prognostic factors and methods of prognostic analyses can augment predictions for the presence of micro-metastatic disease and further define the risk for relapse. This article highlights relevant changes, evidence supporting future incorporation of more recently defined prognostic variables, novel approaches used as adjuncts to the current staging
system, and future directions of the AJCC staging committee.


It is well established, at least in mice, that not only ultraviolet C (UVC) or ultraviolet B (UVB), but also ultraviolet A (UVA) is able to induce squamous cell carcinomas. Results from animal models, epidemiological studies, and clinical observations suggest that UVA might play an important role in the pathogenesis of malignant melanoma as well. In contrast to UVC or UVB, UVA is hardly able to excite the DNA molecule directly and produces only few pyrimidine dimers. Oxidative DNA base damage, generated indirectly through photosensitizers, might be responsible for the mutagenic and carcinogenic properties of UVA. This is supported by differences in mutation spectra induced by UVA and UVB in mammalian cells and tumors. Avoidance of natural and artificial UVA sources is recommended, especially for melanoma-prone individuals.


INTRODUCTION: CI-980 is a novel chemotherapeutic agent that inhibits polymerization of tubulin. Preclinical studies have indicated a high level activity of this agent against various tumor cell lines. METHODS: 13 malignant melanoma patients who had failed prior chemotherapy and/or immunotherapy and 13 hormone refractory prostate cancer patients, including 4 who had received prior chemotherapy, were treated in 2 separate NCI-supported clinical trials. Subjects received a recommended phase II dose of CI-980 of 4.5 mg/m2/day by continuous infusion for 72 hours every 3 weeks. RESULTS: No activity was seen in either study. Toxicity was tolerable with neutropenia being the most common, significant toxicity. Among the melanoma patients, 15% and 31% developed grade 3 and grade 4 neutropenia, while 7% and 38% of the prostate patients developed grade 3 and grade 4 neutropenia, respectively. CONCLUSIONS: CI-980 at this dose and schedule is ineffective against malignant melanoma and hormone refractory prostate cancer.


Autotaxin (ATX) promotes cancer cell survival, growth, migration, invasion and metastasis.
black American students. Danish students were more likely than Americans to use sunscreen, however, Americans were more likely to apply sun protective factor (SPF) 15 or greater. In conclusion, given that sunbathing and tanning bed use are associated with the development of precancerous lesions and skin malignancy, Danish teens are at increased risk. The rates of skin malignancy are relatively high in Scandinavia and efforts to improve understanding of exposure and cancer risks should be undertaken in adolescents.


When overexpressed, the stress protein heat shock protein 70 (HSP70) increases the oncogenic potential of cancer cells in rodent models. HSP70 also prevents apoptosis, thereby increasing the survival of cells exposed to a wide range of otherwise lethal stimuli. These protective functions of HSP70 involve its interaction with and neutralization of the adaptor molecule apoptotic protease activation factor-1, implicated in caspase activation, and the flavoprotein apoptosis-inducing factor (AIF), involved in caspase-independent cell death. We have shown previously that a peptide containing the AIF sequence involved in its interaction with HSP70 (ADD70, amino acids 150-228) binds to and neutralizes HSP70 in the cytosol, thereby sensitizing cancer cells to apoptosis induced by a variety of death stimuli. Here, we show that expression of ADD70 in tumor cells decreases their tumorigenicity in syngeneic animals without affecting their growth in immunodeficient animals. ADD70 antitumorigenic effects are associated with an increase in tumor-infiltrating cytotoxic CD8+ T cells. In addition, ADD70 sensitizes rat colon cancer cells (PROb) and mouse melanoma cells (B16F10) to the chemotherapeutic agent cisplatin. ADD70 also shows an additive effect with HSP90 inhibition by 17-allylamino-17-demethoxygeldanamycin in vitro. Altogether, these data indicate the potential interest of targeting the HSP70 interaction with AIF for cancer therapy.


Aberrantly expressed or mutated proteins in cancer cells evoke immune recognition, but host reactions are usually insufficient to prevent disease progression. Vaccination with irradiated tumor cells engineered to secrete granulocyte-macrophage colony stimulating factor (GM-CSF) augments host immunity through improved tumor antigen presentation by recruited dendritic cells and macrophages. By analyzing the immune response of a metastatic melanoma patient who achieved a long-term response to vaccination, we identified melanoma inhibitor of apoptosis protein (ML-IAP) as a target for immune-mediated tumor destruction. Vaccination stimulated a coordinated cellular and humoral reaction to ML-IAP that was associated with extensive tumor necrosis, whereas lethal disease progression was linked with the loss of ML-IAP expression and the absence of intratumoral lymphocyte infiltrates. These findings demonstrate that ML-IAP can serve as a tumor rejection antigen, although additional vaccine targets will be required to circumvent immune escape and tumor heterogeneity.


With marked increases in the annual incidence of non-melanoma skin cancer (NMSC) across the globe, its management is of increasing concern to dermatologists. This paper summarises the epidemiology and risk factors and provides an overview of treatment approaches in NMSC across Europe, including surgery, topical 5-fluorouracil and cryotherapy, in the context of the trade-offs that exist in finding optimal treatment outcomes. The paper will also briefly examine new approaches such as immunomodulators and the growing body of data on photodynamic therapy (PDT) using methyl aminolevulinate (MAL), including the authors' personal experience of the efficacy and cosmetic results obtained with these newer therapies.


BACKGROUND: In the past, recommendations on how to break the bad news of a cancer diagnosis have been based on expert opinion. Recently, consensus-based guidelines for medical practitioners have been developed. The objective of this work is to investigate patient preferences for communication practices and to identify any disparities between these guidelines, patient preferences and patient recollections of hearing their diagnosis. PATIENTS AND METHODS: A consecutive sample of 131 newly diagnosed melanoma patients were surveyed approximately 4 months after initial diagnosis to document their preferences and recollections of their communication experiences. RESULTS: Of the 'breaking bad news' recommendations investigated, patients did not strongly endorse the doctor helping tell others of the
diagnosis or telling the patient about cancer support services. Very few patients expressed a preference for having another health professional present. One communication feature, the patient feeling confident about getting the best treatment, was endorsed as "very important" but does not feature in published guidelines. The most notable disparities between guidelines and the reported experiences of patients related to perceived delays in receiving the diagnosis, and having adequate opportunity to ask their clinician questions. CONCLUSION: Current Australian recommendations on how to communicate a diagnosis of cancer were generally supported by the patients' expressed preferences, but several modifications are proposed. IMPLICATIONS: Suggestions are offered to help overcome the disparities identified between recommendations and patients' preferences when a diagnosis of cancer is being communicated. Schwartz, A. L., R. Malgor, et al. (2009). "Phenylmethylmazole decreases Toll-like receptor 3 and noncanonical Wnt5a expression in pancreatic cancer and melanoma together with tumor cell growth and migration." Clin Cancer Res 15(12): 4114-22.

PURPOSE: To evaluate whether (a) Wnt5a expression in pancreatic cancer and malignant melanoma cells might be associated with constitutive levels of Toll-like receptor 3 (TLR3) and/or TLR3 signaling; (b) phenylmethylmazole (C10), a novel TLR signaling inhibitor, could decrease constitutive Wnt5a and TLR3 levels together with cell growth and migration; and (c) the efficacy of C10 as a potential inhibitor of pancreatic cancer and malignant melanoma cell growth in vivo. EXPERIMENTAL DESIGN: We used a variety of molecular biology techniques including but not limited to PCR, Western blotting, and ELISA to evaluate the presence of constitutively activated TLR3/Wnt5a expression and signaling. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide-based technology and scratch assays were used to evaluate inhibition of cell growth and migration, respectively. TLR3 regulation of cell growth was confirmed using small interfering RNA technology. Nude and severe combined immunodeficient mice were implanted with human pancreatic cancer and/or melanoma cells and the effects of C10 on tumor growth were evaluated. RESULTS: We show that constitutive TLR3 expression is associated with constitutive Wnt5a in human pancreatic cancer and malignant melanoma cell lines, that C10 can decrease constitutive TLR3/Wnt5a expression and signaling, suggesting that they are interrelated signal systems, and that C10 inhibits growth and migration in both of these cancer cell lines. We also report that C10 is effective at inhibiting human pancreatic cancer and malignant melanoma tumor growth in vivo in nude or severe combined immunodeficient mice and associate this with inhibition of signal transducers and activators of transcription 3 activation. CONCLUSIONS: C10 may have potential therapeutic applicability in pancreatic cancer and malignant melanoma.


Doxorubicin (5 mg kg⁻¹) was administered intravenously to C57 mice bearing subcutaneous B16F10 melanomas, distributing into the tumour with an area under the concentration-time curve (0-48 h; AUC) of 8.7 micrograms h g⁻¹. Injection of doxorubicin-N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer conjugate, containing 5 mg of doxorubicin equivalent per kg, mediated an AUC for free doxorubicin (i.e. doxorubicin released from the conjugate) of 15.2 micrograms h g⁻¹ and for total doxorubicin (i.e. free plus conjugated) of 149.1 micrograms h g⁻¹. An increased dose of doxorubicin-HPMA copolymer conjugate (18 mg of doxorubicin equivalent per kg) produced AUC values of 40.1 micrograms h g⁻¹ and 671.7 micrograms h g⁻¹ for free and total doxorubicin respectively. Hence administration of doxorubicin-HPMA copolymer conjugate achieved rises of 1.7- to 4.6-fold in tumour AUC (free doxorubicin) and 17.19 to 77.0-fold in tumour AUC (total doxorubicin). HPMA copolymers bearing fluorescein isothiocyanate accumulated in vascularised stromal regions, particularly in new growth sites at the tumour periphery. Treatment of mice with doxorubicin-HPMA copolymer conjugate achieved treated/control lifespans up to 320% (three doses of 27 mg of doxorubicin equivalent per kg) compared with only 133% using aggressive regimens of free doxorubicin (3 x 5 mg kg⁻¹).


Despite increased sensitivity of PCR techniques, routine H&E histology and, in some cases, immunohistochemistry remain the gold standards for the detection of micrometastatic disease. Highly sensitive and specific molecular assays such as RT-PCR provide an ideal way to detect micrometastatic disease in tissues or blood at risk for metastases. RT-PCR has been shown to increase detection of micrometastases, especially in patients with breast cancer and melanoma. These assays have the potential to provide valuable tumor staging and progression information and thus determine the need for further
surgery, adjuvant chemotherapy, and antigen-specific immunotherapy. As investigators gain more experience using molecular assays, the results of these assays will be more likely to guide clinical staging and decision making.


BACKGROUND: With recent advances in the diagnosis and management of ocular and periocular melanoma, many of which are based on results from randomized control trials, there is an increasing need for an evidence-based review of the literature for the Australasian population. The Australian Cancer Network has recently redeveloped the evidence-based Clinical Practice Guidelines for the Management of Melanoma, including a chapter on ocular melanoma. These are the first evidence-based guidelines on ocular melanoma to be created by the Australian Cancer Network. METHODS: The primary research questions were formed and a detailed literature search was undertaken. Each relevant article was assessed and graded I-IV according to the level of evidence. Articles were grouped into bodies of evidence which were then assessed. RESULTS: A total of 107 relevant articles were identified and grouped into 12 bodies of evidence. Guidelines based on this analysis were formulated and graded. These are presented below. CONCLUSIONS: The management of ocular melanoma has benefited from recent advances in imaging, molecular biology and cytogenetics, and tumours today are detected earlier and with greater accuracy than 25 years ago. With improved treatment ocular and periocular melanomas can be controlled locally, with good preservation of vision in many patients. However, there remains no cure for metastatic disease.


Photodynamic therapy (PDT) is based on the association of a light source and light sensitive agents in order to cause the selective death of tumor cells. To evaluate topical 5-aminolaevulinic acid (5-ALA) and diode laser photodynamic single session therapy single session for non-melanoma skin cancer (NMSC), a long-term follow-up was performed. Nineteen Bowen's disease (BD) and 15 basal cell carcinoma (BCC) lesions were submitted to 6-h topical and occlusive 20% 5-ALA plus DMSO and EDTA, and later were exposed to 630 nm diode laser, 100 or 300 J cm(-2) dose. At 3 months tumor-free rate was 91.2% (31/34) whereas at 60 months, 57.7% (15/26), slightly higher in BCC (63.6%; 7/11). The relation between the reduction of the clinical response and the increase of tumor dimension observed at 18 months was lost at 60 months. The sBCC recurrence was earlier compared to the nBCC one. ALA-PDT offered important advantages: it is minimally invasive, an option for patients under risk of surgical complications; clinical feasibility; treatment of multiple lesions in only one session or lesions in poor healing sites and superior esthetical results. However, the recurrence rate increase after ALA-PDT diode laser single session can be observed at long-term follow-up, and the repetitive sessions, an additional advantage of the method, is strongly recommended. The clinical response and recurrence time seem to be related to the laser light dose and NMSC types/subtypes, thickness and dimension, which must be considered for the choice of the ALA-PDT.


Basal cell and squamous cell carcinomas comprise the majority of non-melanoma skin cancers. Whereas the incidence of skin cancer is equivalent to that of all other cancers combined, non-melanoma skin cancer receives a disproportionate share of attention because mortality is relatively low. However, the impact on public health is striking. This review is intended to update readers on the current findings in research on the prevention of these diseases. Topics covered include preventive strategies targeting high-risk populations, chemoprevention (including treatment of intraepithelial neoplasia), and an overview of recent and ongoing clinical and preclinical studies involving new chemopreventive agents.


The mitogen-activated protein kinase (MAPK) pathway is frequently activated in human cancers, leading to malignant phenotypes such as autonomous cellular proliferation. Here, we demonstrate a novel role of the activated MAPK pathway in immune evasion by melanoma cells with the mutation of BRAF, which encodes a MAPK kinase (BRAF(V600E)). MEK inhibitor U0126 or RNA interference (RNAi) for BRAF(V600E) decreased production of the immunosuppressive soluble factors interleukin (IL)-10, VEGF, or IL-6 from melanoma cells to levels comparable to those after signal inhibition.
transducer and activator of transcription (STAT)3 inactivation. The suppressive activity of the culture supernatants from the melanoma cells on the production of inflammatory cytokines IL-12 and tumor necrosis factor alpha by dendritic cells upon lipopolysaccharide stimulation was markedly reduced after transduction with BRAF(V600E) RNAi, comparable to the effects observed with STAT3 RNAi transduction. No additive or synergistic effects were observed by the simultaneous transduction of RNAi for both BRAF(V600E) and STAT3. Furthermore, specific DNA binding and transcriptional activity of STAT3 were not affected by down-regulation of the MAPK signaling with the BRAF RNAi. These results indicate that the MAPK signal, along with the STAT3 signal, is essential for immune evasion by human melanomas that have constitutively active MAPK signaling and is a potential molecular target for overcoming melanoma cell evasion of the immune system.


Melanoma-associated antigen (MAGE) genes are cancer-testis antigen genes that serve as immunotherapy targets in several human cancers. Previous studies have revealed that the forced expression of MAGE genes induces a paclitaxel-resistant phenotype. In the present study, we examined whether the expression of MAGE-A1 could predict the response of advanced and recurrent gastric cancers (GCs) to taxan (docetaxel or paclitaxel)-based chemotherapy. The expression of MAGE-A1 was analyzed by immunostaining in 41 primary GC samples. DNA demethylation was assessed by methylation-specific polymerase chain reaction and the effect of the forced expression of MAGE-A1 on drug resistance to taxan drugs was monitored by MTT assay. The expression of MAGE-A1 in primary GC was observed in 4 (9.8%) of 41 cases. All 4 patients with MAGE-A1-positive GC showed progressive disease, whereas MAGE-A1 expression was not detected in any of the 23 patients showing partial response (P=0.0302). There was no association between MAGE-A1 gene demethylation and response to chemotherapy (P=0.7245). The forced MAGE-A1 expression in the TMK-1 GC cell line increased the sensitivity to paclitaxel and docetaxel. These results suggest that although MAGE-A1 does not participate directly in the drug-resistant phenotype, the expression of MAGE-A1 could be a marker for the prediction of resistance to taxan-based chemotherapies in patients with GC.


Malignant melanoma is a neoplasm with an often unpredictable course and metastases potentially affecting all organs of the human body. Metastases into the gall bladder are rare. The role of hormonal background in the development and progression of malignant melanoma has not been established. The authors present a case of a 63-year-old man who had initially undergone long-term hormone therapy for the treatment of prostate cancer, and later presented with melanoma metastatic to the gall bladder.


c-fos is a member of the proto-oncogene family and is implicated in the modulation of cell proliferation and differentiation. Previous studies have shown that the c-fos gene expression is regulated in a tissue specific manner. In order to clarify the role of the c-fos gene in human epidermis, we have investigated c-fos mRNA expression in both normal skin and non-melanoma skin cancer. In normal skin the intensity of the c-fos mRNA expression in spinous cells was found to be stronger than that observed in basal cells. In lesions of solar keratosis and Bowen's disease the spinous cells also showed stronger c-fos mRNA expression than in basal cells. In two of four cases of Bowen's disease some upper spinous cells showed very strong mRNA expression of the c-fos gene. In squamous cell carcinomas studied there was considerable variation in the intensity of c-fos mRNA expression. Our findings indicate that the degree of c-fos mRNA expression is related to the degree of dysplasia present. In all cases of basal cell carcinoma examined the c-fos mRNA expression was markedly decreased. These results suggest that c-fos expression may be involved in the differentiation of human keratinocytes in vivo rather than in the neoplastic process itself.


Identification of antigenic peptides expressed on cancer cells enables us to treat cancer patients with peptide-based immunotherapy. Although optimal protocols for peptide-based vaccines have not yet been elucidated, boosting the immune system could be a better approach than priming the immune system to elicit prompt and potent peptide-specific T-cell
responses in cancer patients. With this possibility in mind, the authors undertook a clinical trial in which cancer patients were vaccinated with peptides (maximum 4) after confirmation of pre-existing peptide-specific cytotoxic T-lymphocyte (CTL) precursors in the periphery. Fourteen patients (seven with melanoma and seven with other types of cancer) positive for either HLA-A24 or HLA-A2 were enrolled in this study. Fourteen and 16 peptides were used to screen for HLA-A24+ and HLA-A2+ patients, respectively. The vaccination was well tolerated, and the only adverse effects were local pain and fever. Kinetic analysis revealed that peptide-reactive CTLs increased after peptide vaccination in 7 of 14 patients. Immunoglobulin G (IgG) reactive to the administered peptides was detected in 2 patients before vaccination, although it became detectable in 8 of the other 12 patients after the peptide vaccination. Stable disease for more than 6 months was observed in five patients (one with melanoma and four with other types of cancer); all of these patients showed increased levels of peptide-specific IgG. These results indicate that peptide vaccination of patients showing evidence of pre-existing peptide-specific CTL precursors can be applied in further clinical trials aimed at the treatment of melanoma and other types of cancer.


Sentinel node mapping reduces surgical morbidity and allows the use of more accurate tumour staging techniques. Radionuclide studies are preferentially performed using small colloids, which have limited availability in our country. The possibility of using phytate for sentinel node mapping was raised because of the similarity between its biodistribution and that of nanocolloids in the reticuloendothelial system. In this paper we evaluated the use of 99mTc-phytate for sentinel node mapping, correlating the histopathological results with the status of the rest of the lymph node chain in different malignant tumours. A total of 100 patients were studied. Group 1 consisted of 62 patients with breast cancer, group 2 of 20 patients with melanoma and group 3 of 18 patients with vulvar carcinoma. Lymph node scintigraphy was carried out after injecting 99mTc-phytate subdermally, and the sentinel node projection was marked on the skin. After 18-24 h, intraoperative sentinel node localisation was performed using a gamma probe (combined with visual localisation using patent blue dye) in 75 patients, and lymph node dissection was then carried out. Radionuclide scintigraphy identified the sentinel node in 98% of all studies. Intraoperative detection using the gamma probe was equally efficient: group 1=93% (38/41), group 2=95% (18/19) and group 3=100% (15/15). The sentinel node was involved in 41%, 31% and 20% of cases in groups 1, 2 and 3, respectively. Among the patients with positive nodes, the sentinel node was the only one affected in 53% of group 1, 50% of group 2 and 67% of group 3 cases. The method's negative predictive value was 91% in group 1 and 100% in the other groups. One false-negative study occurred in a patient who had a multifocal tumour and an intraparenchymatous lymph node; another occurred in a patient with a macroscopically affected node found during surgery. There were no side-effects related to the 99mTc-phytate. It is concluded that scintigraphic and intraoperative sentinel node identification was satisfactorily performed using 99mTc-phytate. The results were comparable to those previously described in the literature using other radiopharmaceuticals. Easy availability and low cost justify the use of phytate in our practice.


PURPOSE: Deregulation of phosphatidylinositol 3-kinase/Akt and Ras/Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase kinase/extracellular signal-regulated kinase pathways occurs in melanoma and breast cancer, deregulating normal cellular apoptosis and proliferation. Therapeutic cocktails simultaneously targeting these pathways could promote synergistically acting tumor inhibition. However, agents with manageable toxicity and mechanistic basis for synergy need identification. The purpose of this study is to evaluate the preclinical therapeutic efficacy and associated toxicity of combining sorafenib with nanoliposomal ceramide. Sorafenib and nanoliposomal ceramide synergistically inhibited cultured cells by cooperatively targeting mitogen-activated protein kinase and phosphatidylinositol 3-kinase signaling. A 1- to 2-fold increase in cellular apoptosis and 3- to 4-fold decrease in cellular proliferation were observed following combination treatment compared with single agents, which caused synergistically acting inhibition. In vivo, an approximately 30% increase in tumor inhibition compared with sorafenib treatment alone and an approximately 58% reduction in tumor size compared with nanoliposomal ceramide monotherapy occurred by doubling apoptosis rates with negligible systemic toxicity. CONCLUSIONS: This study shows that nanoliposomal ceramide enhances effectiveness of
sorafenib causing synergistic inhibition. Thus, a foundation is established for clinical trials evaluating the efficacy of combining sorafenib with nanoliposomal ceramide for treatment of cancers.


In the present study we evaluated the response rate and the immunorestorative properties of interferon alpha 2b (IFn alpha 2b) administered to patients with advanced renal cell carcinoma (RCC), melanoma (MEL) or colorectal cancer (CC). We studied the immune status and correlated it with clinical responses. Thirty-five patients with advanced RCC, and 14 with MEL were treated with recombinant INF alpha 2b. The dose was increased progressively from 5 x 10(6) IU/day in the first week (three times every week) to 10 x 10(6) IU/day in the second week and thereafter to 15 x 10(6) IU/day subcutaneously. In patients with CC INF alpha 2b was given at 5 x 10(6) IU/day every other day (three times every week); these patients also received (together with INF) leucovorin 200 mg m-2 day-1 in a 1-h i.v. infusion every week, and mid-infusion 400 mg/m2 5-FU was administered as an intravenous bolus every week. The response rate was as follows: for RCC, 6 patients achieved partial response (PR), 10 stable disease (SD), and 21 progressed (PD); for MEL, 5 patients achieved PR and 9 PD; for CC, 6 achieved PR, 5 SD, and 9 PD. In all patients blood was withdrawn prior to INF alpha 2b treatment and then monthly. T lymphocytes, after isolation from peripheral blood, were tested for proliferation in the autologous mixed-lymphocyte reaction and allogeneic mixed-lymphocyte reaction, interleukin-2 (IL-2) production, expression of IL-2 receptors during the allogeneic-mixed-lymphocyte reaction, and the production of IL-1 by peripheral blood monocytes. Striking increases were demonstrated in all parameters 2 months after treatment with INF alpha 2b. In comparison to normal controls, all patients with the malignant neoplasms presented decreased (> 45%) mean values of the immunological parameters under investigation (P 0.0001). Responders (patients with RCC, MEL, and PR) presented lower mean values of all the parameters studied than did non-responders (P 0.0001). Patients with CC presented the lowest mean values of the parameters than did the other patients (RCC, MEL) (P 0.0001). After therapy with INF alpha 2b, patients with RCC experiencing PR showed a mean increase of more than 30% (P 0.0001). Patients with SD showed a mean increase of about 20% (P 0.0001), and those with PD showed a 6% increase in the immunological parameters under investigation. Patients with MEL experiencing PR showed a mean increase of more than 30% and patients with PD a decrease of more than 10% (P 0.0001). All patients, regardless of the clinical response, achieved an increase of more than 60% (P 0.0001). Administration of IFN alpha 2b resulted in a marked potentiation of a deficient cellular immune response in vitro in those patients with RCC and MEL who responded to the treatment. On the other hand, non-responders demonstrated a decrease in the examined parameters and, in some, deterioration of the already depressed immunological functions was observed. This observation can have prognostic significance regarding clinical response of INF. In contrast, our findings show that the immune stimulation associated with INF alpha treatment in all our CC patients did not predict an improved clinical outcome. There are several theoretical explanations for this discrepancy.


Sentinel lymph node biopsy (SNLB) is a new method for staging regional node fields in patients with cancers that have a propensity to metastasise to lymph nodes. The majority of early experience has been obtained in patients with melanoma and breast cancer. The technique requires the close cooperation of nuclear medicine physicians, surgical oncologists and histopathologists to achieve the desired accuracy. It involves: (i) identification of all lymph nodes that directly drain a primary tumour site (the sentinel nodes) by the use of pre-operative lymphoscintigraphy, (ii) selective excision of these nodes by the surgeon, guided by pre-operative blue dye injection and a gamma detecting probe intra-operatively and (iii) careful histological examination of the sentinel nodes by the histopathologist using serial sections and immunohistochemical stains. If the nodes are normal it can be inferred with a high degree of accuracy that all nodes in the node field are normal. This means that radical dissections of draining node fields can be avoided in patients with normal lymph nodes. A further advantage of lymphatic mapping is that drainage to sentinel nodes in unusual locations is identified, leading to more accurate nodal staging than could be achieved with routine dissection of the closest node field.

Cancer/testis (CT) antigens are potential targets for cancer immunotherapy, with NY-ESO-1 being among the most immunogenic. In several clinical trials in malignant melanoma (MM) patients, NY-ESO-1 protein/peptides showed clear evidence of inducing specific immunity. However, little is known about NY-ESO-1 expression in primary and metastatic MM and its relationship to disease progression. We analyzed NY-ESO-1 expression immunohistochemically in a series of primary and metastatic MMs and its relation to prognostic parameters and survival. We studied 61 primary and 63 metastatic MM specimens (from 61 and 56 patients, respectively). The prevalence of NY-ESO-1 expression was significantly higher in metastatic versus primary tumors [18/56 (32%) versus 8/61 (13%), P = 0.015]. There was a significant association between initial stage at presentation and NY-ESO-1 expression [stage I (3.45%), stage II (9.52%) and stage III (45.45%), P = 0.0014]. Primary MMs expressing NY-ESO-1 were significantly thicker than NY-ESO-1 negative cases (median thickness 4.7 mm versus 1.53 mm respectively, P = 0.03). No significant difference was seen in overall survival. In conclusion, NY-ESO-1 is more frequently expressed in metastatic than in primary MM and its expression is associated with thicker primary lesions and a higher frequency of metastatic disease, indicative of a worse prognosis. Our study suggests that patients with metastatic MM who express NY-ESO-1 may benefit from NY-ESO-1-based immunotherapy.


Melanoma is a disease which has been shown to be responsive to immune intervention. This has been suggested by reports of spontaneous responses of metastatic disease with strong immune infiltrates, and supported by recent data correlating clinical response after IFNalpha treatment with development of generalized autoimmunity. Since the identification of melanoma-associated tumor antigens, many groups have performed clinical trials to take advantage of this discovery with melanoma-specific cancer vaccines. These trials, in which multiple antigen delivery strategies have been tested in hundreds of patients, have demonstrated that these vaccines are safe, immunogenic, and yield a low frequency of objective clinical responses. The ability to perform careful immunological monitoring has allowed important insights into the nature of the anti-tumor immunity generated by these vaccinations. While many trials have found that the absolute frequency of T cells specific for a vaccine-encoded antigen are a marker of immunization, it does not correlate with objective clinical response. Induction of broad immunity to multiple tumor antigens, taking advantage of cross-reactive T cells and activation of persistent T cells may be more important. Harnessing additional modes of amplifying immune responses (lymphodepletion, cytokine support, inhibition of negative immune self-regulation) are now being tested and should improve clinical responses from 5% to 10% complete response seen currently.


PURPOSE: This phase I clinical trial evaluated safety, feasibility, and efficiency of nonviral intratumoral jet-injection gene transfer in patients with skin metastases from melanoma and breast cancer. EXPERIMENTAL DESIGN: Seventeen patients were enrolled. The patients received five jet injections with a total dose of 0.05 mg beta-galactosidase (LacZ)-expressing plasmid DNA (pCMVbeta) into a single cutaneous lesion. Clinical and laboratory safety monitoring were done. Systemic plasmid clearance was monitored by quantitative real-time PCR of blood samples throughout the study. All lesions were resected after 2 to 6 days. Intratumoral plasmid DNA load, DNA distribution, and LacZ expression was analyzed by quantitative real-time PCR, quantitative reverse transcription-PCR, Western blot, immunohistochemistry, and 5-bromo-4-chloro-3-indolyl-beta-D-galactoside staining. RESULTS: Jet injection of plasmid DNA was safely done in all patients. No serious side effects were observed. Thirty minutes after jet injection, peak plasmid DNA levels were detected in the blood followed by rapid decline and clearance. Plasmid DNA and LacZ mRNA and protein expression were detected in all treated lesions. Quantitative analysis revealed a correlation of plasmid DNA load and LacZ-mRNA expression confirmed by Western blot. Immunohistochemistry and 5-bromo-4-chloro-3-indolyl-beta-D-galactoside staining showed LacZ-protein throughout the tumor. Transfected tumor areas were found close and distant to the jet-injection site with varying levels of DNA load and transgene expression. CONCLUSION: Intratumoral jet injection of plasmid DNA led to efficient LacZ reporter gene expression in all patients. No side effects were experienced, supporting safety and applicability of this novel nonviral approach. A next step with a therapeutic gene product should determine antitumor efficacy of jet-injection gene transfer.


The present study describes sun exposure and sun protection behaviors of northern Australian outdoor workers with previous non-melanoma skin cancer (NMSC). In 1999 a cross-sectional study of northern Australian men with previous NMSC was conducted by self-administered questionnaire. Compared to other men, outdoor workers spent more time in the sun on average working days and days off (P < 0.0001, respectively), and outdoor workers with sun-sensitive skin reported that more skin lesions had been removed (P = 0.0461). The workplace did not reinforce sun-safe practices of 36.8% of workers who spent half their time or more outdoors. Sun-protective behaviors were not different between in- and outdoor workers. Outdoor workers experienced high levels of sun exposure, however, sun-protective behavior was similar to other workers. Workplaces should be targeted to reinforce sun-safe policies.


OBJECTIVE: To identify predictors of recent sunburn in north Australian men with a history of non-melanoma skin cancer (NMSC). METHODS: A survey of men with previous NMSC was conducted (n = 300, response rate 62%). RESULTS: Fifty-four percent of participants reported recent sunburn. Predictors included younger age, belief that NMSC is caused by childhood sun exposure, belief that sun protection will not help prevent further NMSC, wearing of casual clothes, and use of shade as the main sun-protection strategy. CONCLUSION: Health promotion messages should emphasize the importance of sun protection throughout life and the use of stringent sun-protection measures.


The cultivated mycelium of a Cordyceps sinensis (Cs) fungus was sequentially extracted by petroleum ether (PE), ethyl acetate (EtOAc), ethanol (EtOH) and hot water. All solvent extracts except hot water extract showed a significant and dose-dependent inhibitory effect on the proliferation of four cancer cell lines, MCF-7 breast cancer, B16 mouse melanoma, HL-60 human promyelocytic leukemia and HepG2 human hepatocellular carcinoma, with IC(50) values below 132 microg/ml. The EtOAc extract, in particular, had the most potent effect against all four cancer cell lines, with IC(50) between 12 microg/ml (on B16) and 45 microg/ml (on MCF-7). In contrast, it had much lower cytotoxicity against normal mouse bone marrow cells. The EtOAc extract contained carbohydrates, adenosine, ergosterol and trace amount of cordycepin, of which ergosterol and related compounds were identified as a major class of active constituents contributing to the in vitro cytotoxicity. In an animal test, the EtOAc extract showed significant inhibiting effect on B16-induced melanoma in C57BL/6 mice, causing about 60% decrease of tumor size over 27 days. Our results suggest that the EtOAc extract of Cs fungal mycelium has strong anti-tumor activity and is a potential source of natural anti-tumor products.


BACKGROUND AND OBJECTIVES: We surveyed expression of melanoma antigen-encoding genes in lung cancer because of promising implications for immunotherapy. METHODS: We studied 57 human lung carcinoma specimens using the reverse transcription-polymerase chain reaction (RT-PCR). RESULTS: In the samples, the expression of melanoma antigen-encoding genes 1, 2, and 3 was observed in 9/43 (20.9%), 13/43 (30.2%), and 22/48 (45.8%), respectively. In 28 cases in which all three messenger RNAs were sought, 18 (64.3%) showed expression of at least one gene, 10 (35.7%) showed expression of two or three genes, and 10 (35.7%) were negative for all three genes. In a clinicopathologic analysis, melanoma antigen-encoding genes 1 and 3 were frequently expressed in squamous cell carcinomas (P = 0.0543) and in cases with regional lymph node metastasis (P = 0.0572), respectively. CONCLUSIONS: The high incidence of melanoma antigen-encoding gene expression in lung cancer indicates the possibility of a future specific immunotherapy for this disease.

References


9/2/2012