

Journal Watch

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Second lymphomas and other malignant neoplasms in patients with mycosis fungoides and Sezary syndrome: evidence from population-based and clinical cohorts

Huang KP, Weinstock MA, Clarke CA, McMillan A, Hoppe RT, Kim YH.

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The risk of developing second malignancies in cases of mycosis fungoides (MF) and Sezary syndrome (SS) was assessed in this retrospective study. Two cohorts of patients with a diagnosis of MF or SS were studied: 1798 patients from nine population-based cancer registries, the Surveillance, Epidemiology, and End Results Program (SEER-9) and a cohort of 429 patients from Stanford University referral centre.

The mean age of MF and SS patients in the SEER cohort was 59 years (range 10-88 years); 1081 patients were males and 717 were females. After a mean follow-up time of 5.6 years, 197 second cancers were observed. The mean time to development of malignancy was 4.1 years. The overall standardized incidence ratio (SIR) was 1.32 (95% confidence interval (CI): 1.15-1.52). The incidence of various cancers were significantly increased: melanoma (10 cases; SIR: 2.60; 95% CI: 1.25-4.79); urinary cancers (21 cases; SIR: 1.74; 95% CI: 1.08-2.66); Hodgkin's lymphoma (HD 6 cases; SIR: 17.14; 95% CI: 6.25-37.26); non-Hodgkin's lymphoma (NHL 27 cases; SIR: 5.08; 95% CI: 3.34-7.38).

In the Stanford cohort, patients with MF or SS were diagnosed at a mean age of 55 years. After a mean follow-up period of 7.8 years, 37 second

cancers were observed (SIR: 1.04; 95% CI: 0.76-1.44). The incidence was significantly increased for HD (3 cases; SIR: 27.27; 95% CI: 5.35-77.54) and biliary cancer (2 cases; SIR: 11.76; 95% CI: 1.51-42.02). The total incidence of HD and NHL (all lymphomas) was also significantly increased (7 cases; SIR: 5.11; 95% CI: 2.06-10.40). The mean time to development of second malignancy was as follows: 4 years (all types), 6 years (HD), 1 year (NHL), 9 years (biliary cancer). There was no relationship between stage at diagnosis of MF and time to onset of second cancers.

It was therefore concluded that these findings confirmed earlier reports of an increased risk of lymphoma in patients with MF or SS.

Psoriasis and pustular dermatitis triggered by TNF- α inhibitors in patients with rheumatologic conditions

de Gannes GC, Ghoreishi M, Pope J, Russell A, Bell D, Adams S, et al.

Arch Dermatol 2007;143:223-31.

Fifteen cases of exacerbation or new-onset of psoriasis after treatment with tumour necrosis factor- α (TNF- α) inhibitors were reported. To test the hypothesis that TNF- α inhibition leads to increased interferon- α (IFN- α) production by plasmacytoid dendritic cells, the levels of interferon- α in psoriatic lesions was estimated by immunohistochemical staining for myxovirus-resistance protein A (MxA), which was produced in response to type I IFNs (IFN- α and IFN- β).

Fifteen patients (11 women, 4 men, age range: 19-78 years) were reported. New-onset psoriasis occurred in 13 cases after TNF- α inhibitor therapy (etanercept: 6 cases; infliximab: 5 cases; adalimumab: 4 cases). These cases were treated by TNF- α inhibitors for two to 62 months prior to onset of skin disease. Palmoplantar pustulosis occurred in most cases (9/15). Other clinical presentations included guttate and plaque-type psoriasis. Histopathology specimens were available in five cases, all of which were consistent with psoriasis. Thirteen cases were able to continue TNF- α inhibitor therapy for their rheumatological diseases; of these, topical treatment was able to control psoriasis in four cases while the skin disease remained persistent in nine cases. Two cases stopped TNF- α inhibitor therapy and skin disease cleared completely in one case but remained persistent in another despite topical psoriatic treatment. One case developed psoriasis as well as a lupus-like reaction (positive ANA and pericarditis) under infliximab treatment.

Although epidermal staining for MxA was seen for both TNF- α inhibitor induced psoriasis and psoriasis vulgaris, there was a significantly increased immunostaining for MxA in TNF- α inhibitor-induced psoriasis (n=4) compared to that of idiopathic psoriasis vulgaris (n=2).

It was concluded that TNF- α inhibitors could induce an exacerbation or new-onset psoriasis. The finding of increased IFN- α production was a possible mechanism for this phenomenon.

Childhood bullous pemphigoid: clinical and immunological findings in a series of 4 cases

Martinez-De Pablo MI, González-Enseñat MA, Vicente A, Gilaberte M, Mascaró JM.
Arch Dermatol 2007;143:215-20.

A series of four cases of childhood bullous pemphigoid (BP) was reported to delineate the

clinical and immunological features of this condition. All cases were boys, age four to 12 months. The disease duration before presentation was two to four months. The hands and feet were involved in all cases. There was generalized involvement in three cases but neither mucosal disease nor scarring was observed. All cases resolved with systemic steroids (prednisolone 1-2 mg/kg/day) in less than six months. At a follow-up time ranging from six to 27 months, all cases were in remission.

Direct immunofluorescence revealed basement membrane zone (BMZ) linear deposits of IgG and C3 in all cases and faint IgA staining on BMZ in two cases. Immunological studies were performed in available sera from three cases. Indirect immunofluorescence studies revealed circulating IgG antibodies to BMZ in all cases and IgA antibodies to BMZ in one case. IgA antibodies to the NC16A domain of bullous pemphigoid 180-kDa antigen (BP 180) were detected in all three cases on immunoblotting and IgG antibodies to this domain were present in two of these cases. Autoantibodies IgG and IgA to the NC16A domain of BP180 were detected in two cases using enzyme-linked immunosorbent assay (ELISA). Only one case had IgG antibodies to the carboxyterminal domain of BP 180 on immunoblotting.

The authors suggested that the presence of IgA and IgG autoantibodies to BP180 in these cases raised the question about the relationship between BP and linear IgA bullous dermatosis.

Efficacy of topical pimecrolimus in the treatment of chronic vulvar pruritus: A prospective case series - a non-controlled, open-label study

Sarifakioglu E, Gumus II.
J Dermatol Treatment 2006;17:276-8.

This is a single-centre, non-controlled, open-label

study to assess the efficacy of topical pimecrolimus in the treatment of chronic vulvar pruritus since topical steroid can be associated with side effects such as cutaneous atrophy or steroid resistance after long term use. Fifteen patients (30 to 60 years of age) diagnosed to have chronic vulvar pruritus with normal physical examination and skin biopsy were recruited. Those with diabetes mellitus, liver/renal disease, vaginitis, vaginal candidiasis, contact dermatitis, atopic dermatitis, anxiety and depression were excluded. The duration of disease ranged from 4 months to 20 years (median 4 years). They were treated with 1% pimecrolimus cream twice daily for 4 weeks. No other drugs or disinfectants were applied topically during the study period. The patients were assessed at baseline, 7, 14, 21 and 28 days by grading the intensity of pruritus (scores ranging from 1 (slight) to 4 (very intense)) and symptoms status (scores ranging from 1 (persistence) to 4 (total regression)). At baseline and on day 28, the patients were asked to give a self-assessment control score, ranging from 1 (unsatisfactory) to 4 (excellent).

At baseline, ten patients graded pruritus as very intense (score: 4), four reported intense pruritus (score: 3) and one reported moderate pruritus (score: 2). Two patients defaulted and 13 reported improvement. Comparing scores at baseline and on day 28, the mean intensity of pruritus score changed from 3.5 to 0.2 ($p < 0.001$), the mean symptom status score changed from 1.1 to 3.8 ($p < 0.001$) and the overall self-assessment control score changed from 1.0 to 3.5 ($p < 0.001$). The clinical response was noted within 2 to 4 weeks. Ten patients scored 4 and three scored 2 in the self-assessment control score at day 28. Three cases reported slight burning after application of pimecrolimus which lasted for 2 to 3 days. A telephone follow-up was conducted 3 to 6 months post-study for 10 patients. They all remained in remission.

The authors concluded that topical pimecrolimus was an effective treatment for chronic vulvar

pruritus and might be considered as a second line treatment. They recommended controlled studies for further evaluation.

How much of a topical agent should be prescribed for children of different sizes?

Nelson AA, Miller AD, Fleischer Jr AB, Balkrishnan R, Feldman SR.

J Dermatol Treatment 2006;17:224-8.

This study aimed to devise a simple guideline for topical steroid usage in infants, children, adolescents and adult. The authors used the body surface area (BSA) to determine the quantity of steroid needed. The BSA was calculated using the equation derived by Gehan and George based on body height and weight. The height and weight of children (both sexes) aged 6 months, 6 years, 12 years and 20 years were determined by the standard growth and development charts from the United States Centre for Disease Control and Prevention. They used a concentration of 2 mg of topical agent per cm^2 of BSA to estimate the amount of medication needed for a total body application.

To determine how much a specific body part corresponded to the percentage of total BSA, the authors did not use the "rule of nines" because it was more appropriate for adults. They adopted the Lund and Browder method to determine the BSA of body parts for paediatric patients. The percentage of different anatomic areas varied according to patient's age.

The BSA of the average (50th percentile) male and female for different ages were determined. A 20-year-old male needed 37.6 gm of topical steroid to cover the total BSA (1.88 m^2) once whilst a 20-year-old female required 32.6 gm. A 6-month-old boy required only 8 gm to cover the body once (BSA 0.4 m^2) whereas 7.6 gm was needed for a 6-month-old girl (BSA 0.38 m^2).

A 6-year-old boy needed 16.8 gm (BSA 0.84 m²) and the female counterpart needed 16.2 gm (0.81 m²) to cover the body once. A 12-year-old male required 26.2 gm to cover the total BSA (1.31 m²) whilst 26.6 gm was needed for the female counterpart (BSA 1.33 m²). Roughly, infants, children and adolescent require one-fifth, two-fifths and two-thirds of adult doses respectively. The required amount for each body parts were also calculated using the Lund and Browder method.

They concluded that a simple guideline for how much topical steroid to prescribe could avoid potential side effects such as overdosing or undertreatment. This might help to achieve better clinical outcomes.

Blood concentrations of pimecrolimus in adult patients with atopic dermatitis following intermittent administration of pimecrolimus cream 1% (Elidel) for up to 1 year

Van Leent EJM, De Vries HJC, Ebelin M, Burtin P, Scott G, Bos JD.

J Dermatol treatment 2007;18:19-22.

This is an open-label, multiple topical dose study in adults with moderate to severe atopic dermatitis (AD). It aimed to determine the blood concentrations of pimecrolimus during long term intermittent use, to investigate any drug accumulation and to assess long-term safety.

Adults of more than 18 years old with AD affecting $\geq 20\%$ total body surface area (TBSA) were recruited. Exclusion criteria included females who were pregnant or breastfeeding, history or presence of malignancies, exposure to radiotherapy, and systemic cytotoxic or immunosuppressive drugs within 24 weeks before the study. Phototherapy or conventional systemic therapy for AD (such as oral steroid or

cyclosporine) had to be discontinued for one month before study. No other systemic or topical treatment for AD was allowed during the study period except: emollients and/or antihistamine, oral steroid up to 2 administrations and topical steroid of ≤ 2 weeks were allowed to treat acute flares of AD not controlled by study medication. The patients were instructed to apply pimecrolimus 1% cream twice daily on all their lesions including face and neck for up to 12 months. They could stop the treatment when AD was in remission and restart when recurred. They were assessed at screening, day 1, weeks 1, 3 and 6 of treatment, and then monthly for 12 months and at study completion. Blood samples were taken at each visit at a site there no pimecrolimus cream was applied 0, 2 and 4 hours after drug application. Only one sample was taken when the patient was not under treatment at the time of visit. The serum pimecrolimus level was measured using a radioimmunoassay with a limit of quantitation of 0.5 ng/ml.

Forty patients of age 19 to 59 years old were recruited into the study. Only 13 completed 1 year and 20 completed only 6 months in the study. Among the 27 who did not complete the study, 22 discontinued because of unsatisfactory therapeutic response, 2 due to adverse events (application site burning and worsening of pigmentation disorder) and 3 were lost to follow up. A total of 918 blood samples were analyzed. 98% (900) of them had pimecrolimus level below 0.5 ng/ml. The maximum concentration observed was 0.8 ng/ml. Blood level remained low even in those with largest TBSA treated (up to 61.5% of TBSA). There was no evidence of systemic accumulation.

Three cases received > 2 administration of oral steroid and one received two oral doses for flaring of AD. Fourteen required topical steroid over 1-10 days and 29 took oral antihistamine during the study period. Twenty-five reported adverse events related to pimecrolimus. The most frequently reported event was application site

burning. The others were application site reaction, pruritus and dry skin.

The authors concluded that long term intermittent treatment with pimecrolimus cream 1% in adults with moderate to severe extensive AD was associated with minimal systemic exposure and no evidence of drug accumulation.

High-potency steroid use in children with vitiligo: a retrospective study

Kwintar J, Pelletier J, Khambalia A, Pope E.
J Am Acad Dermatol 2007;56:236-41.

This study was a retrospective one carried out in a tertiary academic health sciences center. It reviewed 101 children with the clinical diagnosis of vitiligo and who were solely treated with topical corticosteroids alone.

There were 58 females and the mean age at presentation to clinic was 7.06 years (range: 0.42-16.08 years). Age of vitiligo onset was predominantly distributed in the age-range of 3 to 10 years (77%). The most frequent location was the head and neck region (n=68, 67%), followed by extremities (n=67, 66%). Trunk involvement was seen in 50 patients (49%). At first visit, high-potency topical corticosteroids were prescribed in 83% of the patients and 17% were treated with moderate-potency corticosteroids. At first follow-up visit (mean: 81.7 +/- 44 days), 64% of patients (n=45) had repigmentation of their lesions, 11% (n=8) were worse than at the initial presentation, and 24% (n=17) had no change. There were no statistically significant differences in clinical outcomes between patients treated with high- (n=59) versus moderate- (n=11) potency corticosteroids (p=0.31). Local steroid side-effects were noted in 25% of patients, including striae (8 of 101), atrophy (5 of 101), telangiectasia (5 of 101) and others such as skin infections and acne. Laboratory tests were done

at a median of 14 days after commencement of treatment and 29% (21 of 73) had abnormal cortisol levels. Children with abnormal cortisol levels were not significantly different from those with normal cortisol levels by the potency and regimen of the corticosteroid used. Children with head and neck involvement were 8.26 times more likely to have abnormal cortisol levels.

It was concluded that the use of high potency corticosteroid was efficacious in the treatment of pediatric vitiligo but the potential for systemic absorption should be noted and monitored regularly especially in those with head and neck vitiligo.

Pityriasis lichenoides in childhood: a retrospective review of 124 patients

Ersoy-Evans S, Greco MF, Mancini AJ, Subasi N, Paller AS.
J Am Acad Dermatol 2007;56:205-10.

This study is a retrospective chart view of pityriasis lichenoides (PL) in childhood in the author's institution between 1993 and 2003. A total of 124 pediatric patients who were diagnosed clinically (39%) or histologically (61%) to have PL were recruited. The parents of eighty patients were interviewed by telephone to supplement the clinical information available by chart review and to determine their current disease status.

Forty-six patients (37%) had pityriasis lichenoides chronica (PLC), 71 (57.3%) had pityriasis lichenoides et varioliformis acuta (PLEVA) and seven had clinical features of both. The age of onset peaked at 2-3 years (24.8%) and 5-7 years (32%). A history of medication intake or infection three weeks prior to onset was noted in 11.2% and 30% of patients. Majority of them (74.2%) had a diffuse involvement and 20.2% had a peripheral involvement (over the upper and lower limbs) and the rest had central involvement (over face and trunk). Pruritus, fever and arthralgia were

noted in 59%, 6% and 3% of patients respectively. Fever and arthralgia were more common in patients with PLEVA. Majority of them (77%) were chronic and relapsing. The median duration of all forms of PL, PLC and PLEVA were 18.5, 20 and 18 months respectively. There were no statistically significant differences between PLC and PLEVA in terms of patient demographic data, history of infection, drug history, distribution of lesions and disease recurrence. Of 24 patients with known information on seasonal flaring, 76% had flares in winter but improved in the summer. Topical corticosteroids were given alone or in combination with other therapies in 58% of the patients. Majority of the patients (79.7%) were given oral erythromycin (30-50 mg/kg/d) alone or in combination with topical corticosteroids. For 57 patients whose follow-up data on response to erythromycin was available, the response rate to erythromycin was 66.6% and complete remission was seen in 61% of the patients who showed a response.

The authors concluded that in childhood, PL occurred mainly in the preschool and early school-age years. Majority of the PL were chronic and relapsing and erythromycin was an effective treatment.

Basal cell carcinoma on the trunk is associated with excessive sun exposure

Neale RE, Davis M, Pandeya N, Whiteman DC, Green AC.

J Am Acad Dermatol 2007;56:380-6.

This study reviewed 1621 participants in the context of a community-based follow-up study. It aimed to compare the phenotypic and sun exposure characteristics of participants who had a first BCC of the head or trunk with those without the diagnosis of BCC. All participants were required to complete a questionnaire to assess their propensity to burn or tan and their life-time occupational and recreational sun exposure.

There were 977 histologically confirmed basal cell carcinoma (BCC) in 373 patients between 1992 and 2004. About half (51%) of patients with BCC were men and the mean age was 54 years. Half of the patients (n=187) had only one BCC and for patients with multiple BCC, the mean and median number of BCC per patient were four and three respectively. The number of solar keratoses was found to be the strongest predictor of BCC at both trunk and head. It was observed that BCC of the trunk were more strongly associated with sun burns than BCC of the head. Patients with more than 10 sunburns had more than two times the risk of developing BCC on the trunk than those patients with no experience of sunburns. Moderate to severe elastosis of the skin of the back of the neck was also a strong and significant predictor of head and trunk BCC. Moreover, facial telangiectasia, a measure of long-term facial sun-exposure, was significantly associated with BCC of the face but not the trunk. There was a stronger association between solar lentigines and truncal BCC than that between solar lentigines and head BCC.

It was thus concluded that because of the strong association between truncal, compared with head, BCC and lifetime sunburns and solar lentigines on the trunk, sunburns are more important in the etiology of truncal BCC than head BCC.

An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema

Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ.

Br J Dermatol 2007;156:346-51.

This is an open-label, dose-ranging, single centre prospective study to assess the safety and efficacy of oral methotrexate in 12 adults with moderate-to-severe atopic eczema over a 24-week treatment period. They all had disease refractory to optimized topical steroid and emollient therapy

and had previously tried at least one form of second line treatment.

Methotrexate 10 mg weekly (after a 5 mg test dose) was used for each patient and the dose was increased by 2.5 mg every fourth week until either a clear clinical response or a maximum of 22.5 mg weekly was achieved. Blood tests were performed weekly for the first 4 weeks and 2-4 weekly thereafter depending on the stability of the blood result. Assessment using six area six sign atopic dermatitis (SASSAD) score, percentage body surface area (BSA) affected (measured using the 'rules of nines') and patient assessed itch and loss of sleep score were performed at baseline, 4 weekly interval during treatment period and 12 weeks after completion of therapy. Dermatology Quality of Life Index (DLQI) was assessed before treatment and at week 24.

There was a mean improvement in disease activity (SASSAD) of 19 units (52%; CI (confidence interval) 45-60%) from an average baseline of 35 units. Percentage BSA affected reduced in all patients with a mean improvement of 62% (CI 50-73%). A significant improvement in self reported itch and sleep loss score and DLQI were observed. The majority of improvement was seen by week 12, and patients who had not responded well over this period despite reaching a dose of 15 mg weekly failed to improve with further dose escalation. Only one patient experienced nausea and recurrent cutaneous herpes simplex infection and withdrew from the study at week 16. Another two patients had transient liver derangement and one patient developed nausea at 15 mg weekly which prevents him from further increase in dose.

The author therefore concluded that methotrexate was an effective, well tolerated treatment for moderate-to-severe atopic eczema, and response appeared to compare favourably with other second-line therapies.

Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up

Tschen EH, Wong DS, Pariser DM, Dunlap FE, Houlihan A, Ferdon MB and the phase IV ALA-PDT actinic keratosis study group.
Br J Dermatol 2006;155:1262-9.

This study was a multicentre (11 private practice clinics), open-label, phase IV study of patients with actinic keratoses (AKs) on the face and scalp. In this study, the efficacy and safety of topical aminolaevulinic acid-based photodynamic therapy (ALA-PDT) was evaluated. Patients with six to twelve thin or moderately thickened AKs on face or scalp were enrolled. Two AK lesions were biopsied at baseline and the remaining lesions (target lesions) were treated with ALA-PDT at baseline and in the second month, if required, and were followed-up for 12 months. ALA-PDT was administered by using 20% topical ALA solution and 10 J/cm² visible blue light delivered by BLU-U® Photodynamic Therapy illuminator.

One hundred and ten patients with a total of 968 lesions were enrolled and 101 patients completed the study, 87% were male, 95% were white-skinned and their ages ranged from 43 to 89 years (mean±SD: 67.0±9.8). The clinical diagnosis of AKs was confirmed histologically in 91% of cases. The remaining were squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and other benign non-AK diagnoses. The percentage of target AKs in the study group that cleared completely in the first and second months following a single ALA-PDT treatment were 76% and 72% respectively. Sixty percent of all patients received a second ALA-PDT treatment when target AKs were still present in month 2. The percentage of treated target

lesions that cleared completely peaked at 86% at month 4 then decreased gradually over time to 78% at month 12. The overall recurrence rate for all lesions that had been cleared at some time during the follow-up was 24% (162 lesions). Of these 162 lesions, 16 were lost to follow-up, seven cleared spontaneously and 139 were biopsied. Histology results for the biopsied recurrent lesions were AKs (91%), SCC (7%), BCC (0.7%) and other non-AK diagnoses (1%).

Erythema, edema, stinging or burning, hypopigmentation or hyperpigmentation, blistering or crusting were reported in some

patients. Most of the side effects disappeared by 1 month of study. Eight percent of patients (9/110) discontinued the study, either due to patient request (n=7) or to therapeutic failure (n=2).

The author thus concluded that ALA-PDT was a safe and effective therapy for the treatment of AKs of the face and scalp, with more than 80% of the AKs clearing completely after one to two ALA-PDT treatments and an overall recurrence rate of 24% within the 12 month follow-up time. This research was sponsored by DUSA Pharmaceuticals Inc.