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ORIGINAL ARTICLE

Treatment of classic Kaposi sarcoma with a nicotine dermal patch: a phase II clinical trial

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Novelty and impact: This randomized trial used a novel design (lesion, rather than patient, as the primary unit of measure), novel drug (nicotine), novel delivery system (transdermal patch) and novel validation method (masked reading of digitized photographs).

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Abstract

Background Kaposi sarcoma (KS), a malignancy of dermal endothelial cells that is caused by human herpesvirus 8 (HHV8) infection, is sensitive to perturbations of immunity. Nicotine might be effective against KS because of its immunologic and vascular effects and because smoking is associated with a low risk of KS.

Objective and study design We conducted a masked, randomized phase 2 clinical trial of transdermal nicotine and placebo patches to assess the safety and efficacy of nicotine against classic KS (cKS).

Subjects and methods Three cKS lesions, predominantly nodules, in each of 24 non-smoking patients were randomly assigned to 15 weeks continuous treatment with nicotine patch (escalated to 7 mg), identical masked placebo patch or no patch. Changes in lesion area and elevation from baseline through six follow-up visits, by direct measurement and by two independent readers using digital photographs of the lesions, were compared using non-parametric and regression methods. Changes in longitudinal levels of HHV8 antibodies and DNA in blood cells were similarly assessed.

Results There were no systemic or serious adverse events, and compliance was good. One patient resumed smoking and discontinued patches, and two patients withdrew at week 12 for unrelated indications. Six (29%) of the remaining 21 suspended use of patches to relieve local skin irritation; four of these six completed the trial at reduced dose. Treatment assignment was not associated with significant or consistent changes in cKS lesion area or elevation, HHV8 viral load or antibodies.

Conclusion Transdermal nicotine and placebo patches caused no serious toxicities but had no demonstrable effect on nodular cKS lesions or HHV8 levels.

Introduction

Classic Kaposi sarcoma (cKS), a low-grade malignancy of endothelial cells, initially manifests as one or a few reddish patches on the skin. Over months to years, new cKS lesions appear, darken, thicken into plaques and nodules, and disseminate to regional lymph nodes and occasionally to viscera. Spontaneous regressions can occur, probably reflecting the sensitivity of this disease to perturbations of immunity. AIDS-associated KS is strongly associated with worsening immunity, whereas approximately 80% of stage 0 (e.g. non-visceral) AIDS KS patients have tumour responses when treated with highly active antiretroviral therapy (HAART) without specific cancer chemotherapy.[1,2]

Human herpesvirus 8 (HHV8), the primary cause of KS,[3] is endemic in the Mediterranean region, where approximately 1 in 3000 HHV8-seropositive men and 1 in 7500 HHV8-seropostive women develop cKS per year.[4] Because cKS patients are often elderly, and because the malignancy tends to be indolent, initial treatment of limited disease is conservative, with observation supplemented when appropriate by radiotherapy or intralesional vincristine or vinblastine.[5,6] Advanced or rapidly progressing cKS is treated with systemic vincristine or vinblastine, reserving other medications for cases with severe symptoms or vital organ involvement.[7–9]

To identify novel, low-toxicity treatments for cKS, we investigated nicotine administered via transdermal patch applied directly over selected lesions. Based on the extraordinary sensitivity of KS to perturbations of immunity, we postulated that the immunologic effects of smoking underlie the observed fourfold lower risk of cKS risk among cigarette smokers.[10] We speculated that a similar smoking-related immunologic mechanism might induce regression of early stage KS lesions. Among the many components of cigarette smoke, nicotine per se induces well-defined alterations of immunity likely relevant to dermal KS. Nicotine affects the functions of dendritic cells and alters production of interferon gamma as well as several other cytokines and growth factors.[11–13] These are intimately related to the propagation of KS both *in vivo* and *ex vivo*.[14,15] In addition to its immunologic effects, the vasoconstrictive properties of nicotine might also be therapeutic, in view of the vascularity of KS and the efficacy of elastic stockings against KS-associated lymphedema.[16] Transdermally administered nicotine has minimal toxicity, is an effective treatment for active ulcerative colitis[17,18] and has induced responses in several dermatologic vascular conditions.[19–23]

Our primary hypothesis was that nicotine, at levels achievable in the dermis when administered by transdermal patch,[24,25] would induce regression of cKS lesions. There were two secondary hypotheses. First, identical placebo patches would retard the growth of cKS lesions by altering the microflora and respiration of the underlying skin. And second, systemic levels of nicotine, which are obtained from transdermal patches, would alter HHV8 viral load or antibody levels associated with KS progression or regression.[26]

Materials and methods

Patient and lesion inclusion criteria

We recruited patients with histologically confirmed cKS. Inclusion criteria were ages 18 to 78 years; non-smoker for ≥ 1 years; HIV seronegative; no life-threatening condition; maximum of one Eastern Cooperative Oncology Group (ECOG) common toxicity criteria grade > 0 (and no grade > 1); no recent (within 90 days) or anticipated need (within 15 weeks) for systemic cKS treatment; and ≥ 3 cKS lesions of specified diameter (minimum, 0.5 cm; maximum, 3 cm) and separation interval (minimum, 6 cm), including at least two such lesions on a body site to which a patch could be readily applied. Three eligible lesions (A, B and Z) were selected in each patient and served as the primary unit of measure.

The protocol was approved by the local and US institutional review boards. Each patient provided written informed consent before enrolment.

Treatment regimens

Single lots of unlabelled, low-dose (7 mg) Nicoderm-CQ™ and indistinguishable placebo patches were provided gratis by the manufacturer (GlaxoSmithKline Consumer Healthcare, Parsippany NJ). Lesions A and B were assigned to nicotine or placebo by coin toss. All investigators remained blinded to treatment assignment. The intention was to treat lesions A and B continuously for 15 weeks; lesion Z was assigned to no treatment.

Nicotine side effects (nausea, lightheadedness, headache and sleep disturbance) are common with initial exposure and high peak levels (10–20 s after inhaled tobacco smoke), but they are rare with nicotine patches, which have a very slow rate of drug absorption. Nonetheless, dose escalation was used to reduce risk. Specifically, each A and B lesion was treated with 1/4-size patches for weeks 1 to 2, then ½-size patches for 2 weeks, and full-size patches for weeks 5 to 15. Treatment was continuous, with fresh patches applied every second morning and recorded on a calendar. At each visit, the patient was questioned to assure that the A and B assignment had not been confused. Adherence was assessed by counting the patches.

Dose modifications

For skin toxicity that was moderate (intense erythema) or severe (ulceration) or for any ECOG common toxicity criterion grade > 2, use of the patches was immediately suspended. If resolved (minimal or no erythema, ECOG grade ≤ 1) by the next visit, the patches were restarted at the previously tolerated dose. Patches were permanently discontinued for persistent or recurrent moderate or severe toxicity.

Patient and lesion assessments

Toxicity and adverse events were noted by physical examination, questionnaire, complete blood counts and

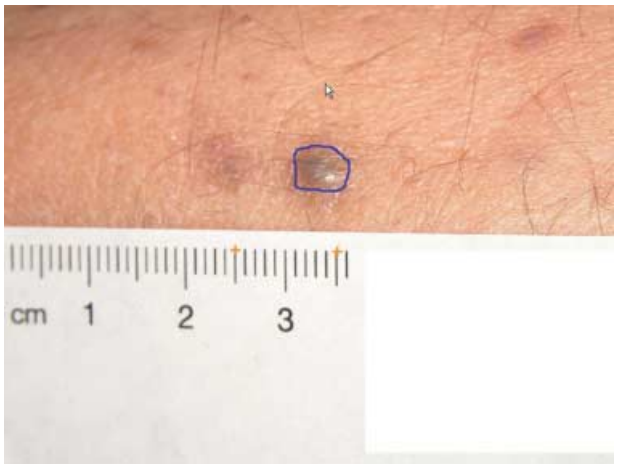

fig. 1 De-identified digital photograph in which area of the selected nodular KS lesion was quantified by multiplying pixels in the circumscribed lesion (blue) by the 1-cm interval scored on the internal ruler (gold + s).

serum chemistry data collected on standardized forms. Non-smoking was confirmed by carbon monoxide breathalyser.

Dermatology collaborators measured the perpendicular bidimensional diameter and assessed the elevation [ordinal scale from 0 (no elevation) to 4 (massive)] of each selected lesion at seven visits (weeks 0, 2, 4, 6, 9, 12, 15). Digital photographs were taken with an adjacent identification label and ruler.

De-identified photograph files (fig. 1) were uploaded in random order into the NIH National Library of Medicine Boundary Marking Tool (http://archive.nlm.nih.gov/bmt),[27] with which two independent readers (JJG, BMD) circumscribed the lesion and marked 1.0 cm on the internal ruler. Pixels between the ruler marks were used to quantify the area of the circumscribed lesion in cm^2.

Efficacy criteria

Change in lesion area from visits 1 to 7 in the clinic measurements, corroborated by the photographic readings was the primary end point. Complete response (CR) was defined as complete disappearance, partial response (PR) as ≥ 50% decrease in area, minor response as > 30% to 50% decrease in area, progression as > 30% increase in area; and others (–30% to +30% change) as no response (NR). Changes in lesion elevation and from visits 1 to 5, for which data were complete, were similarly assessed.

Viral loads and antibodyttiters

Blood from the first 20 patients was collected in acid-citrate dextrose anticoagulant, separated into components, frozen in aliquots and shipped frozen to Frederick, MD, USA. HHV8 load in blood cells was determined by TaqMan PCR using primers targeting the *HHV8 K6* gene, standardized to the human *ERV3* gene.[28] Epstein–Barr virus (EBV) was similarly quantified using primers to the *EBV pol* gene.[28] Antibodies against HHV8 recombinant proteins (K8.1 lytic-phase and ORF73 latent-phase) were quantified by enzyme immunoassays using twofold plasma dilutions starting at 1 : 20 (for K8.1) or 1 : 100 (for ORF73).[28]

Statistical methods

Correlations between the clinic and photo reader measurements were assessed with Pearson's *R*. Absolute and proportional (%) changes in lesion area from visits 1 to 5 and visits 1 to 7 were calculated, and response and progression rates were described. Changes in area and elevation (on the 0–4 ordinal scale) by treatment assignment (nicotine, placebo, no patch) were compared using the non-parametric median score test [PROC NPAR1WAY, Statistical Analysis System (SAS) version 9.1, Cary, NC, USA]. To account for correlations between lesions of the same individual, we used a permutation approach. We randomly assigned treatment labels to each lesion within each person and then computed the test statistic for the permutated dataset. The permutation distribution function, with 5000 repetitions of the test statistic, was used to find the *P*-values. Linear mixed models (PROC MIXED, SAS 9.1) were fit to the natural log-transformed areas from all visits to test for difference in area change by treatment assignment. Mixed models were repeated with the data truncated at visit 5, adjustment for sex and age, and no patch vs. either patch (nicotine and placebo combined). To assess treatment effects on smaller vs. larger lesions, analyses were stratified by the visit 1 lesion size (below vs. above median). Linear regression (PROC REG, SAS 9.1) was used to assess change in antibody titres and viral loads over time (visits 1, 5 and 7).

Results

Twenty-four patients, each of whom had at least three cKS lesions that met the inclusion criteria, were enrolled between 17 October and 29 November 2005. They were elderly and 79% were male (Table 1). None had received systemic KS therapy. Total dermal KS lesions ranged from 3 to 40, with a large range in maximum lesion size (Table 1). Duration of KS was not recorded. In each patient, lesions A, B and Z were measured and photographed. Lesions A and B were randomly assigned to masked treatment with nicotine or placebo patch.

Table 1 Patient characteristics

Characteristics	Value
Enrolled (no.)	24
Male (no.)	19
Previous systemic KS therapy	0
Current smoker (no.)	0
Current age [median (range)]	67.5 (57–77) years
Total number of KS lesions [median (range)]	11 (3–40)
Largest KS lesion [median (range)]	6 (0.2–132) cm^2
Completed visit 6 (no.)	24*
Completed visit 7 (no.)	22

*One patient withdrew for elective mitral valve surgery. A second patient withdrew to receive systemic chemotherapy for rapid progression of KS on unpatched dermal sites (e.g. palms). One nicotine-patched lesion was excised for persistent bleeding at visit 6 and thus not evaluated at visit 7.

Follow-up, adherence, and toxicity

All adverse events and changes in the size of each selected lesion were reported to the Data and Safety Monitoring Board immediately after each visit. Twenty-two patients were followed through visit 7. The other two patients withdrew after visit 6: one for elective mitral valve replacement surgery, the other for systemic chemotherapy to treat rapid progression of KS on unpatched dermal sites (e.g. both palms). No other patient had evident changes in the extent or severity of their overall KS burden during the study.

There were no deviations from treatment assignment. The number of used patches recorded on each patient's calendar matched the opened and unopened foil packets. None of the 24 patients required modifications of treatment through visit 3. Planned escalation from ½-size to full-size patches was delayed from visits 4 to 5 in two patients: one because of systolic hypertension (155–175 mm Hg) and one because of an accidental fall. One patient resumed smoking, after lying about when he had quit. He had no toxicity, discontinued patches after visit 4, and remained in follow-up for intention-to-treat analysis.

To relieve severe local skin erythema, 6 (29%) of the 21 non-smoking patients who were followed through visit 7 suspended use of patches. Four of these six suspended use of both patches at visit 4; all of them restarted the patches and completed follow-up at a lower dose. The fifth patient suspended both patches for the final interval (visits 6–7). The sixth patient suspended patch A (masked nicotine) at visit 4 and had this lesion excised at visit 6 for persistent bleeding.

No systemic or serious adverse events were attributed to the use of patches by the local clinical investigators or by the independent Data and Safety Monitoring Board.

Efficacy, clinic measurements

By assessment in the clinic, there were four CRs among 65 lesions evaluated at the end of the trial, including two treated with nicotine, one with placebo, and one with no patch (Table 2). There were 11 PRs: 4 with nicotine, 5 with placebo, and 2 with no patch. However, the majority of lesions in each treatment group had NR (No. = 26) or progressed (No. = 23).

As shown in Table 3, cross-sectional area of the lesions at visit 1 did not differ by treatment assignment (nicotine, 0.36 cm^2; placebo, 0.50 cm^2; no patch, 0.34 cm^2; $P = 0.11$). Comparing area at visit 1 to area at the completion of the trial (visit 7), untreated lesions had increased more than did nicotine-treated lesions (17% more in medians, 60% more in means), but this was not statistically significant. Specifically, change in area did not differ by treatment assignment for all 72 lesions evaluated at visit 5 ($P = 0.26$) nor for the 65 lesions evaluated at visit 7 ($P = 0.74$). No difference by treatment assignment was confirmed by modelling all measurements from all visits (fig. 2).

At visit 1, median lesion elevation was level 2 (moderate nodule) for all three treatment assignments. No change was seen in median elevation in the placebo or untreated lesions at visit 5 or 7. Lesions assigned to nicotine patch decreased non-significantly in elevation by ½ level at visit 5 ($P = 0.88$) and by 1 level at visit 7 ($P = 0.11$).

Table 2 Responses of KS lesions at visit 7 (week 15), by treatment assignment

	Number of lesions at visit 7					
Treatment	Missing data*	Complete response	Partial response	Minor response	No response	Disease progression
Nicotine	3	2	4	0	8	7
Placebo	2	1	5	1	9	6
None	2	1	2	0	9	10

*Following visit 6 (week 12) two patients withdrew and the nicotine-treated lesion was excised in a third patient.

Table 3 Median size and change in size of KS lesions during 15 weeks of observation, by treatment assignment and observer

Treatment	Area at visit 1	Area change (%) visits 1 to 5	Area change (%) visits 1 to 7
Clinic measurement			
Nicotine	0.36 cm^2	−0.02 cm^2 (–13%)	0 cm^2 (0%)†
Placebo	0.50 cm^2	0.03 cm^2 (5%)	0.03 cm^2 (5%)
None	0.34 cm^2	0 cm^2 (0%)	0.06 cm^2 (13%)
P-value*	0.11	0.26	0.74
Photograph reader 1			
Nicotine	0.39 cm^2	0.03 cm^2 (12%)	−0.03 cm^2 (–13%)†
Placebo	0.51 cm^2	0.02 cm^2 (4%)	−0.04 cm^2 (–7%)
None	0.26 cm^2	0.01 cm^2 (3%)	0.05 cm^2 (30%)
P-value*	0.07	0.85	0.92
Photograph reader 2			
Nicotine	0.48 cm^2	0.04 cm^2 (11%)	0.07 cm^2 (34%)†
Placebo	0.51 cm^2	0 cm^2 (0%)	0.06 cm^2 (9%)
None	0.34 cm^2	0.05 cm^2 (13%)	0.05 cm^2 (20%)
P-value*	0.31	0.61	0.31

*Permutation-based *P*-values for any difference in area change (%) among treatment groups.
†Data missing for one lesion that was excised at visit 6 due to bleeding.

Efficacy, photographic corroboration

Correlation between each photograph reader and the clinic was high ($R = 0.62–0.64$, $P < 0.0001$ for each). Moreover, overall correlation between the two photograph readers, who were masked to each other, was very high ($R = 0.90$, $P < 0.0001$).

As shown in Table 3, proportional change in lesion area from visits 1 to 7 was variable (range, 13% decrease to 34% increase) and did not differ significantly by treatment assignment ($P = 0.31–0.92$). Considering all measurements at all visits, treatment assignment was unrelated to change in lesion area ($P = 0.92–1.00$, example in fig. 2). Adjustment for sex and age quartile yielded similar null results ($P = 0.90–0.94$). Likewise, adjusted for sex and age quartile, change in lesion area across all visits was unrelated to no patch vs. either patch (nicotine and placebo combined, $P = 0.56–0.87$).

In post hoc subgroup analyses across all visits, growth of larger lesions (area above median at visit 1) was associated with treatment assignment in the photograph readings ($P = 0.02–0.04$), specifically with a trend toward more growth with no patch compared with either patch ($P = 0.05–0.15$). This was not seen with clinic measurements of the larger lesions ($P = 0.60–0.82$) or with the smaller lesions by any measurement method ($P = 0.51–0.97$).

Viral loads and antibody titers

HHV8 and EBV DNA were each detected in 15 (26%) of 58 frozen peripheral blood cell specimens from the first 20 patients. Both HHV8 and EBV were detected in four specimens (kappa = 0.01). The *ERV3* control gene was detected and quantified in all specimens. HHV8 and EBV detection and levels did not change significantly across visits 1, 5 and 7 ($P = 0.33–0.44$).

Median antibody titres in these 58 plasma specimens were 1 : 640 and 1 : 800 against the HHV8 K8.1 and ORF73 antigens, respectively. As with viral DNA, these antibody titres did not differ significantly across visits 1, 5 and 7 ($P = 0.35$ for K8.1 and $P = 0.92$ for ORF73).

Discussion

KS is a complex tumour that arises from HHV8-infected endothelial cells in the setting of immune activation, growth factors and pro-inflammatory cytokines, especially interferon gamma.[14,15] Whereas HHV8 and expression of *HHV8* genes are absolutely required,[3] exogenous factors that regulate the development, maintenance and dissemination of the neoplasm are unknown. Also by unknown mechanisms, HAART- or chemotherapy-induced regression of KS can be paralleled by a decline in or disappearance of HHV8-infected peripheral blood cells.[26] We investigated whether such changes could be induced by nicotine through its immunologic or vascular actions. In the current study, 15 weeks of continuous use of a transdermal patch, either with or without nicotine, did not significantly affect the size of cKS lesions, HHV8 viral load or HHV8 antibody titres.

New treatments for KS are needed, especially for AIDS-associated KS that has become the most common of all

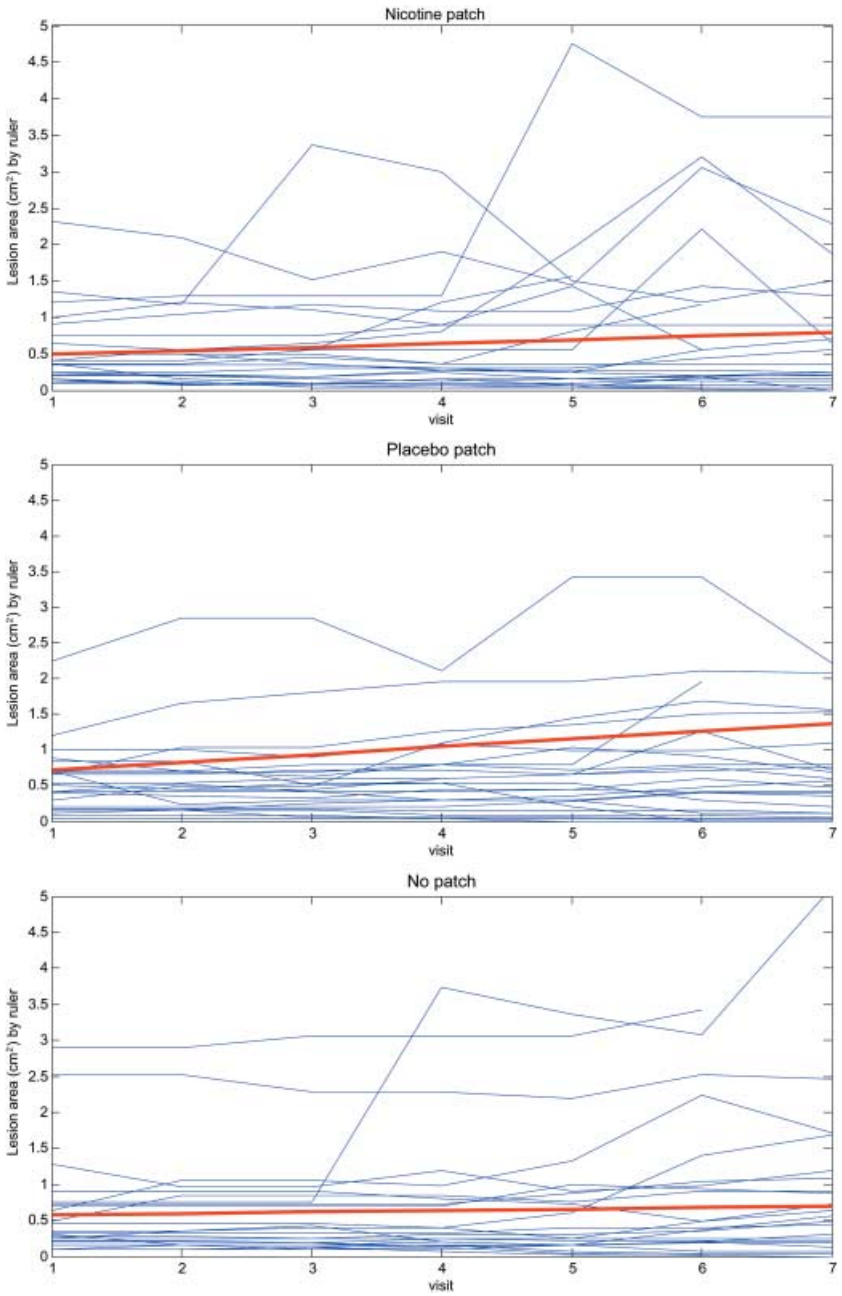

fig. 2 Changes in lesion area using clinic measurements from all seven visits, by treatment assignment. Area of the largest 'No patch' lesion, which ranged from 6.90 to 7.68 cm^2, is not shown. The red line is the average change (slope) derived by multivariable mixed models procedures, including treatment assignment and measurements from all visits; the interaction of those two variables (slope comparison) was not significant for visits 1 through 5 ($P = 1.00$) or visits 1 through 7 ($P = 1.00$).

malignancies in several sub-Saharan African countries.[29,30] HAART is first-line therapy for AIDS-KS, but treatment failures are common especially with visceral or massive lymphatic disease.[1,2] An easily administered medication with efficacy against KS and limited interactions with HAART would be highly desirable. We studied transdermal nicotine because of its safety profile, likelihood of high drug levels throughout the selected tumours, and likelihood to favourably alter the dermal inflammation, immunity and vascularity believed to foster the dissemination of HHV8 and the growth of KS lesions.[11–13,16–25] We studied cKS patients because they have fewer health complications and medication requirements than do AIDS KS patients.

The patients' advanced age and underlying conditions presented minor difficulties for this clinical trial, delaying dose escalation in two patients and requiring withdrawal for elective surgery in one. There were no systemic toxicities and no serious adverse events attributed to the use of patches. However, significant local erythema did occur

with both nicotine and placebo patches, requiring nearly one third of the patients to remove them. Most patients who suspended the patches successfully completed the study with smaller (lower dose) patches.

Topical 0.1% alitretinoin (9-*cis*-retinoic acid) gel is effective for dermal AIDS-KS lesions and is licensed for this use.[31–33] Only two cases of cKS treated with alitretinoin gel have been reported: one with many small nodules had a CR; one with large plaques and nodules had NR.[34,35] As with our transdermal patches, alitretinoin gel causes local dermatitis and occasional local ulceration. Treatment with oral 9-*cis*-retinoic acid, which induces regression of AIDS-KS in approximately 38% of patients, also is limited by skin toxicity as well as by headache.[36,37]

We postulated that the growth of cKS lesions could be affected by occlusion of the epidermis with the placebo patches. With no serious toxicity, occlusion of the skin with duct tape may accelerate resolution of common warts, presumably by altering local immunity or inflammation.[38,39] This is not implausible, as occlusion substantially alters not only water evaporation and carbon dioxide emission from the skin, but also keratinocyte growth, epidermal microbial flora, and even dermal histology including Langerhans cells.[40] Unfortunately, 15 weeks of occlusion with placebo patches had no effect on cKS lesions.

The current study had several limitations that might have contributed to the null results. It was large enough to detect a large effect. We had 80% statistical power (one-sided $\alpha = 0.05$) to detect a 131% difference in area change between 24 treated and untreated lesions; we observed less than half that difference (60%). Regarding duration, major responses of AIDS KS lesions to alitretinoin gel were observed within 12 weeks in two studies,[31,32] but prolonged HAART may be needed to observe some responses.[2] Thus, 15 weeks of treatment in our study may have been insufficient. We studied small cKS lesions, but nearly all of them were nodules that had been present for months to years. Some nodular KS lesions seem to be clonal malignancies,[41,42] which hypothetically may be less responsive to alterations of the tumour milieu than would patch stage lesions. Similarly, smoking is associated with a low risk of developing KS,[10,43] but whether smoking affects KS progression is unknown. Finally, staging and assessment of response is difficult with KS. Our use of three independent measures of tumour area at each clinic visit is a strength of our study because together they provided an unbiased representation of changes in area over time. Additional strengths include estimation of lesion elevation, good adherence to assigned treatments, and the use of masked, indistinguishable nicotine and placebo patches.

In summary, nicotine had no consistent effect on nodular cKS lesions, despite administration via transdermal patch to achieve high local concentration of the drug. Future investigations of other diseases should consider the transdermal patch to deliver medications, as we observed high compliance and no adverse effects except local erythema that abated with removal of the patch.

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