Gene Profiling Could Drive CTCL Management

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SAN FRANCISCO — Dermatologists and oncologists have long fretted over when to pull out the therapeutic big guns for patients with early-stage cutaneous T-cell lymphoma.

Gene expression profiling of lesional skin may provide the answer.

"We want to know who's going to progress in a high-risk way and who's not. And we're looking to see which patients will respond to which therapies. We think we can begin to do so by looking at some of these genes," Dr. Thomas S. Kupper said at the annual meeting of the American Academy of Dermatology.

The great majority of patients with stage IA and many with stage IB cutaneous T-cell lymphoma (CTCL) have indolent, skin-limited disease, but others have rapidly progressive and often fatal disease. Lesional skin gene expression profiling may eventually make it possible to employ, in proactive fashion, the more aggressive and toxic systemic therapies in selected high-risk patients with early-stage disease, according to Dr. Kupper, Thomas B. Fitzpatrick Professor of Dermatology at Harvard Medical School and chair of the department of dermatology at Brigham and Women's Hospital, Boston.

He and a multidisciplinary team profiled gene expression on 63 lesional skin biopsies from 62 patients with all stages of CTCL. Thirteen patients had stage IA disease—that is, limited patches and plaques over less than 10% of their body surface area—while 29 had stage IB CTCL, 8 had stage IIB, and 12 had stage III.

The investigators identified 593 markedly upregulated genes grouped within three distinct patterns or clusters of gene expression, with roughly one-third of patients falling within each cluster.

The dominant genes upregulated in cluster 1 included many genes involved in T-cell activation and the immune response, including the T-cell alpha and beta chains, interleukin-2 receptor, lymphocyte-specific protein kinase, CD8+ T-cell markers, tumor necrosis factor pathway genes, downstream members of the WNT signaling pathway, and several B-cell–related genes.

Cluster 2 was rich in upregulated genes involved in keratinocyte and epidermal differentiation and proliferation. All but two patients in cluster 2 had stage IA or IB disease. Cluster 2 patients were generally extremely treatment-responsive; indeed, all but three cluster 2 patients were maintained in remission or under good control with only topical therapies. The sole stage IIB patient in cluster 2 went into remission on PUVA alone.

Cluster 3 featured upregulation of several T-cell–specific genes as well as genes related to keratinocyte function. Like cluster 1, cluster 3 was distinguished by more aggressive, less treatment-responsive disease. Seven of 12 stage III patients fell into cluster 3, as did only 1 patient with IA disease.

During roughly 3 years of follow-up, there were seven deaths, three cases of disease progression despite systemic therapies, and one large-cell transformation.

None occurred in cluster 2 patients. In contrast, the event-free survival rate was 80% in cluster 3 and less than 60% in cluster 1. One cluster 1 patient with stage IA disease at the time of gene profiling progressed to large-cell transformation unresponsive to total skin electron beam therapy, denileukin diftitox (Ontak), and suberoylanilide hydroxamic acid.

Nine of 11 stage IB patients in cluster 2 were maintained on intermittent topical therapies. In contrast, the more difficult to treat stage IB patients tended to fall into clusters 1 and 3; indeed, 7 of 18 patients with IB CTCL in clusters 1 and 3 required systemic therapies after a variety of topical therapies failed. One stage IB patient in cluster 1 developed metastatic disease and died despite oral bexarotene, denileukin diftitox, total skin electron beam irradiation, interferon, photopheresis, and multiagent chemotherapy.

Prospective studies with larger numbers of CTCL patients will be required to characterize the gene profile clusters more fully and zero in on individual genes having particularly potent predictive power, Dr. Kupper said.

The gene profiling study was sponsored by the National Institutes of Health. ■

Rituximab Clears B-Cell Lymphoma Skin Lesions

SAN FRANCISCO — Intralesional rituximab appears to be an effective and nontoxic therapeutic option for patients with multiple noncontiguous lesions of CD20-positive primary cutaneous B-cell lymphoma, according to Dr. Marco Ardigo.

Rituximab (Rituxanin North America and Japan; MabTheraelsewhere) is a chimeric monoclonal antibody directed against the CD20 antigen. It is often administered intravenously for the treatment of primary cutaneous B-cell lymphoma (CBCL). But the investigational use of intralesional rituximab has several compelling advantages: Notably, it does not produce systemic immunosuppression, and the cost is far lower because a much smaller amount of drug is used and prophylactic antibiotics are not required to prevent severe infections, Dr. Ardigo said at the annual meeting of the American Academy of Dermatology.

He reported on two patients with follicular CBCL and one with marginal zone CBCL whose multiple noncontiguous skin lesions made the prospect of local radiotherapy or surgical excision problematic. All three patients were free of systemic involvement. Their 15 nodular lesions up to 2.5 cm in diameter were treated with 20 mg of rituximab injected subcutaneously into each lesion three times per week, 1 week per month for 2 months. The maximum cumulative dose was 120 mg per lesion, in contrast to the usual intravenous regimen of 375 mg/m^2 once weekly for 4 weeks or more.

Complete remission occurred by 2 months. The three patients have remained in remission through 10 months of ongoing follow-up.

No systemic side effects were noted, and no reduction in peripheral CD20-positive T cells occurred in the weeks following intralesional therapy. The only side effect reported was local pain during the injections, said Dr. Ardigo of the San Gallicano Dermatological Institute, Rome.

He noted that several other small case series have reported similarly favorable experiences with intralesional rituximab for primary CBCL, including one from the University of Zurich (Arch. Dermatol. 2000;136:374-8) and another from Geneva University (Br. J. Dermatol. 2006;155:1197-200).

Dr. Ardigo reported no financial conflicts of interest with commercial entities. ■

Skin Cancer Risk Behaviors Most Common in Adults Aged 18-29

SAN FRANCISCO — Recent findings that risk behaviors for skin cancer are most prevalent among 18- to 29-year-olds will be used to create a road map for efforts to curb the rising incidence of melanoma, which has climbed by 4% per year for the past 3 decades.

"We've got enough data epidemiologically now to really see where efforts have to be focused," Dr. Darrell S. Rigel said at the annual meeting of the American Academy of Dermatology. "In the next 10-15 years, we can begin to make an impact on the incidence of melanoma."

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DR. RIGEL

Dr. Rigel cited the findings of a landmark study at Fox Chase Cancer Center in Philadelphia, where researchers analyzed trends in skin cancer risk behaviors among 28,235 adults in the 2005 National Health Interview Survey.

The majority of Americans engage in multiple skin cancer risk behaviors. The most common were infrequent use of sun-protective clothing and infrequent use of an SPF-15 or stronger sunscreen.

The prevalence of these two risky behaviors was greatest among 18- to 29-year-olds. So, too, were rates of the other skin cancer risk behaviors tracked in the study: use of indoor tanning, staying in the sun when outside on a sunny day, and getting a sunburn within the past year, said Dr. Rigel of New York University. Indeed, more than 80% of 18- to 29-year-olds reported two or more of these behaviors, and nearly half engaged in three or more (Am. J. Prev. Med. 2008;34:87-93).

A profile emerged of adults at highest risk for skin cancer based on modifiable behaviors: individuals who were younger, male, white, living in the Midwest, smokers, risky drinkers, less educated, and with less sun-sensitive skin. This profile could be particularly helpful in primary care settings, where surveys indicate rates of assessment for skin cancer risk behaviors are low because of time pressure.

A particularly noteworthy study finding was that individuals aged 40-64 years who reported never having had a total skin exam were more than one-third more likely to engage in multiple skin cancer risk behaviors, compared with their contemporaries who had had a screening skin exam. The Fox Chase investigators argued that this observation lends support to recent calls for the creation of a national melanoma screening program targeting all white men aged 50 and older for a whole-body skin screening exam (Arch. Dermatol. 2006;142:504-7).

The Fox Chase team found that although skin cancer risk behaviors were associated with greater levels of physical activity, which often takes place outdoors, higher skin cancer risk is also associated with being overweight or obese. In an accompanying editorial, Dr. Martin A. Weinstock observed that this finding sets the stage for a potential conflict between two worthy goals: preventing skin cancer and maintaining a healthy body weight (Am. J. Prev. Med. 2008;34:171-2).

This conflict can be minimized by promoting the "Slip! Slop! Slap!" public health message developed in Australia in the early 1980s, said Dr. Weinstock, professor of dermatology at Brown University, Providence, R.I. ■