Cutaneous T-Cell Lymphoma: Pathogenesis and Treatment

Review Article [1] | July 01, 2000
By Timothy M. Kuzel, MD [2] and Steven T. Rosen, MD [3]

Drs. Girardi and Edelson provide a concise discussion of current issues surrounding the management of patients with cutaneous T-cell lymphomas. They discuss a number of current theories regarding etiology and pathogenesis and provide a

Drs. Girardi and Edelson provide a concise discussion of current issues surrounding the management of patients with cutaneous T-cell lymphomas. They discuss a number of current theories regarding etiology and pathogenesis and provide a brief overview of the many therapies that are currently available to treat mycosis fungoides/Sézary syndrome—the most common form of patch/plaque cutaneous T-cell lymphoma (CTCL).

The importance of the authors' discussion regarding variant forms and presentations cannot be emphasized strongly enough. Mycosis fungoides/Sézary syndrome can manifest in a variety of ways, from isolated patches or plaques to involvement of the skin, lymph nodes, and peripheral blood. Regardless of the extent or stage of this disease, however, many of the same treatment approaches are appropriate.
In contrast, treatment of the non–mycosis fungoides/Sézary syndrome forms of CTCL—such as peripheral non-Hodgkin's T-cell lymphomas with skin involvement, human T-cell lymphotropic virus type 1 (HTLV-I)–related acute T-cell lymphoma/leukemia, or the CD30-positive family of lymphoproliferative disorders—often requires other modalities not commonly applied in the treatment of classic mycosis fungoides.
For this reason, we find it extremely helpful to evaluate these patients in the setting of a multidisciplinary clinic, with participation in diagnosis and management by dermatologists, dermatopathologists, hematopathologists, hematologists, and radiation oncologists. This allows for a complete review of pathologic material (including routine hematoxylin and eosin [H&E]-stained slides), immunohistochemistry or flow cytometry data, and gene rearrangement studies. With this approach, we can provide a consensus regarding therapy that is tailored to specific subtypes of CTCL.

Etiology of Mycosis Fungoides/Sézary Syndrome

The authors advance the theory that an as yet unidentified retrovirus infects the Langerhans cells of the skin. In turn, these professional antigen-presenting cells are stimulated to produce cytokines that activate T-helper cells, thereby resulting in the ultimate formation of the neoplastic cells of mycosis fungoides/Sézary syndrome. This theory represents speculation on the authors' part and requires significant basic scientific confirmation before it can be accepted.
Other theories have been advanced, including those with a role for infection/colonization of skin by staphylococcal organisms (some of which are able to stimulate T-helper lymphocytes) or exposure of skin to other agents that cause the release of cytokines from keratinocytes (which stimulate the proliferation of T-helper cells). Based on the cytokine profile expressed by the neoplastic T lymphocytes, studies of the T-helper cell subsets (TH1 and TH2) responsible for this disease are leading to new therapeutic strategies. No specific chromosomal abnormalities have been consistently noted that would associate a particular oncogene or suppressor gene with this disease. Finally, there are proponents of the theory that this disease does not result from stimulation of T lymphocytes at all, but rather, represents a lymphoaccumulative disorder caused by dysregulated apoptosis signaling in the neoplastic clone. This hypothesis has also stimulated the development of novel therapeutic interventions.

Shortcomings of Published Trials

Drs. Girardi and Edelson's discussion of therapy for mycosis fungoides/Sézary syndrome highlights alternative strategies and reflects the opinions of the authors. Unfortunately, much of the literature regarding the treatment of this disorder lacks the rigor of oncologic studies in other disease sites. Many published "trials" of agents used in this disease represent anecdotal outcomes of a handful of patients (often 5 to 10) treated in a sometimes nonuniform, uncontrolled fashion.
Until recently, very few adequate phase I or phase II trials have been performed for systemic agents

in mycosis fungoides/Sézary syndrome. Likewise, few randomized therapeutic trials have been performed, thereby limiting comparisons of active approaches. Thus, treatment decisions often reflect the biases of individual centers and do not represent a true "consensus" of all clinical investigators.

Managing Mycosis Fungoides/Sézary Syndrome

At Northwestern University, we agree with Drs. Girardi and Edelson that immunomodulatory approaches can affect the outcomes of patients with mycosis fungoides/Sézary syndrome. The presence of cytotoxic, infiltrating T lymphocytes in early-stage plaque lesions, along with their gradual loss with disease progression, suggest that indiscriminate suppression of the immune system may be counterproductive.

In addition, the authors' suggestion that photopheresis results in a specific cytotoxic response by the host immune system through "vaccination" or reinfusion is intriguing and, in fact, led us to the theory that psoralen plus ultraviolet A light (PUVA) therapy works via similar mechanisms. It has been suggested that the exposure of the T lymphocytes to photoactivated psoralen compounds in the presence of ultraviolet light induces apoptosis via cross-linking of DNA and inhibition of protein production. Given the systemic nature of this disease (even in early-stage patients) and the trafficking of cells within the lymph nodes and blood, neither approach would be expected to result in complete and durable remissions—unless secondary effects were beneficial. The exposure of components of apoptotic malignant clones to antigen-presenting cells may allow the host immune system to respond to novel antigens associated with the neoplastic population with a subsequent immune response.

This theory prompted us to test PUVA with systemic interferon administration, whereby we speculated that synergistic immune approaches would result in higher response rates and more durability. We have demonstrated that this combination results in approximately 90% response rates in advanced-stage, pretreated patients.[1] More recently, a European randomized trial demonstrated that the combination of PUVA plus interferon was associated with higher rates of response induction (80% vs 60%) than interferon plus a retinoid (acitretin [Soriatane]), thereby confirming our initial findings.[2]

We have, therefore, treated most patients with advanced disease with PUVA plus interferon, resulting in rapid response induction and often durable benefits. However, unanswered questions persist, for example, regarding the optimal duration of interferon therapy and whether similar benefits can be obtained with combinations of interferon and other topical modalities.

Once frontline treatment has failed, the progression of CTCL mimics that of low-grade B-cell lymphomas. Many treatment approaches demonstrate activity, but typical response rates and durability decrease with subsequent interventions. Unlike patients with low-grade B-cell lymphomas, CTCL patients are often symptomatic, requiring therapy to control infection and deal with cosmetic issues. Thus, many patients with CTCL are treated sequentially with palliative topical therapies, such as topical chemotherapy, limited or total skin electron-beam radiotherapy, and topical steroids or retinoids. Ultimately, many patients require systemic therapy.

Because we believe that immunosuppression is potentially harmful to patients with CTCL, we do not use any immunosuppressive or cytotoxic chemotherapy until late in the disease. A spectrum of single agents and combination regimens have demonstrated efficacy, but since only palliation can be achieved, the risk/benefit of each approach must be carefully weighed.

Due to their lympholytic effects, the purine analogs—fludarabine (Fludara), pentostatin (deoxycoformycin [Nipent]), and cladribine (chlorodeoxyadenosine [Leustatin])—have great theoretical appeal. However, they must be used with caution because of their immunosuppressive consequences and associated opportunistic infections.

Data from the National Cancer Institute's randomized clinical trial suggests that aggressive chemotherapy/radiation therapy combinations do not improve survival vs sequential palliative approaches with less toxicity.[3] These data have shifted our focus to clinical trials of novel therapies. Recent investigations of targeted approaches, including the diphtheria toxin—interleukin-2 (IL-2) fusion protein denileukin diftitox (Ontak) and new retinoids (eg, oral bexarotene [Targretin]), have led to the Food and Drug Administration (FDA) approval of agents with novel mechanisms of action. Our interest in manipulating T-lymphocyte subsets with cytokines such as IL-2 (Proleukin) and interleukin-12 remains a priority.

Finally, we are pursuing studies of the mechanisms of drug resistance in the neoplastic cells of patients with mycosis fungoides/Sézary syndrome. We hope to identify subsets of patients who are most likely to respond to cytotoxic chemotherapy. We are also using allogeneic bone marrow transplantation with donor lymphocyte infusions for the rare young patients with aggressive,

refractory disease who are fortunate to have a matched-related donor.
In summary, much remains to be defined regarding the management of patients with CTCL. Accrual to clinical trials remains a priority, to best define the use of current and potential agents.

References: 1. Kuzel TM, Roenigk HH Jr, Samuelson E, et al: Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sezary syndrome. J Clin Oncol 13:257-263, 1995.

2. Stadler R, Otte HG, Luger T, et al: Prospective randomized multicenter clinical trial on the use of interferon-2a plus acitretin versus interferon-2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood 92:3578-3581, 1998.

3. Kaye FJ, Bunn PA Jr, Steinberg SM, et al: A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. N Engl J Med 321:1784-1790, 1989.

Source URL:
http://www.physicianspractice.com/review-article/cutaneous-t-cell-lymphoma-pathogenesis-and-treatment-0

Links:
[1] http://www.physicianspractice.com/review-article
[2] http://www.physicianspractice.com/authors/timothy-m-kuzel-md
[3] http://www.physicianspractice.com/authors/steven-t-rosen-md