

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Clara D. Bloomfield, MD

## Advances in the Treatment of Primary Cutaneous T-cell Lymphoma

Steven T. Rosen, MD  
Genevieve Teuton Professor of Medicine  
Director  
Robert H. Lurie Comprehensive Cancer Center  
Northwestern University  
Chicago, Ill.

### **H&O** What is the incidence of cutaneous T-cell lymphoma?

**SR** The incidence of cutaneous T-cell lymphoma (CTCL) is approximately 0.36 cases per 100,000 in the United States yearly, which equals 1,000–2,000 newly diagnosed patients. The prevalence is approximately 16,000–20,000 patients in this country. The median age of diagnosis is 50 years, and there is a slight male predominance. Blacks seem to have a higher incidence than whites or Asians. These demographics and incidences have remained relatively stable over the last decade.

### **H&O** Could you discuss the heterogeneity of CTCL?

**SR** An article was published in *Blood* in 2005 detailing the World Health Organization-European Organisation for Research and Treatment of Cancer (WHO-EORTC) classification of CTCL. The disease is divided into two major groupings, indolent and aggressive. The indolent form of the disease comprises mycosis fungoides and its variants, which make up approximately half of all cutaneous lymphomas, and the CD30-positive lymphoproliferative diseases, including two subsets that can be difficult to distinguish: anaplastic large-cell lymphoma and lymphomatoid papulosis. Together, these CD30-positive subtypes make up another 20% of all cutaneous lymphomas. Lymphomatoid papulosis in particular can have a waxing and waning course and spontaneous remis-

sions. The 5-year survival rates of these indolent forms of the disease are in general very good, above 90% altogether. Still indolent, but slightly more aggressive, are the subcutaneous panniculitis-like T-cell lymphomas and the CD4-positive small- to medium-sized pleomorphic T-cell lymphomas, constituting 1–2% of all cases of cutaneous lymphomas. The most frequent aggressive form is Sézary syndrome, the leukemic variant of mycosis fungoides, which has a 5-year survival rate between 25% and 50%. The other aggressive entities are very rare. CTCL constitutes 80% of all cutaneous lymphomas, the rest are B-cell lymphomas. The three main types of CTCL to focus on in this discussion are mycosis fungoides, the CD30-positive lymphoproliferative diseases, and Sézary syndrome.

### **H&O** What are the principal clinical characteristics of CTCL?

**SR** Patients present with patch plaque or tumor lesions, or, in the case of Sézary syndrome, exfoliative erythroderma, which is a cosmetic problem as well as life-threatening. Pruritis can also be a significant problem with some of the other variants. All the forms of CTCL are postthymic T-cell malignancies that express CD4, meaning they are in the helper phenotype. They tend to have a Th<sub>2</sub> cytokine profile, with the secretion of some specific interleukin (IL)-2 molecules including IL-4, -5, -6, -10, -17, -18. The characteristic histology seen on a skin biopsy is an epidermal band-like infiltrate of atypical lymphocytes and epidermotrophism, wherein the malignant cells enter the epidermis. The fascinating question regarding CTCL is one of why these malignant cells home to the skin. We know that a patch on the shoulder has the same clonal lymphocytes as a patch on the thigh and yet there is very little internal involvement. This process is thought to be the result of skin-homing ligands on the malignant cell recognizing receptors on either keratinocytes, dendritic cells, or endothelial cells. Some of those ligand receptors include the common lymphocyte antigen LFA1 and cytokine receptors CCR-4 and -10. In CTCL, there is no characteristic chromosomal abnormality; however, using genomic profiling, all the patients do have abnormalities and there are some aberrations that are more common than others. Looking at gene-expression profiles, there are

certain distinct patterns that are beginning to be identified in CTCL.

### **H&O** How is prognosis evaluated in CTCL?

**SR** The skin manifestations of CTCL often are associated with patients' prognosis. Patients with limited patch plaques (<10% of body surface) have a life expectancy nearly the same as that of the general population. More extensive disease in the skin, tumors, or erythroderma are associated with worse prognosis. Nodal involvement is associated with a median survival of less than 5 years, and those patients who have organ involvement at presentation or during the course of the disease typically have poor survival (1–2 years).

### **H&O** Could you discuss therapeutic advances in CTCL?

**SR** This disease has been a paradigm for biologic therapy. Chemotherapy has activity in this disease, but it is not a curative therapy. The typical therapies have been either skin-directed or systemic, and sometimes a combination of both approaches. Effective palliative skin therapies, depending on disease stage and extent, include topical steroids, topical chemotherapy (eg, nitrogen mustard), topical retinoids (eg, bexarotene [Targretin, Ligand] gel) for isolated lesions, phototherapy using narrow-band UV-B or a psoralen compound plus UV-A (PUVA), and either total-skin or site-directed radiation therapy. Systemic therapies include steroids, interferon, bexarotene capsules, and, more recently approved by the US Food and Drug Administration, the histone deacetylase inhibitor vorinostat (Zolinza, Merck) and the IL-2 receptor–targeted recombinant toxin denileukin diftitox (Ontak, Ligand). The CD52-directed humanized monoclonal antibody alemtuzumab (Campath, Genzyme) and the CD4-directed fully human antibody zanolimumab (HuMax-CD4, Genmab) have been used in this setting with success, though neither has yet achieved regulatory approval in CTCL. Alemtuzumab appears most promising in patients with Sézary syndrome. Some clinicians believe that interferon, which is the most effective single agent in the treatment of this disease, may work through its immunologic mechanism, but this hypothesis remains unproven, as interferon also has antiproliferative effects against the tumor. Clinicians have also used a variety of traditional chemotherapy drugs to treat CTCL; two of the most active are gemcitabine (Gemzar, Lilly) and pegylated doxorubicin (Doxil, Ortho Biotech). Extracorporeal photopheresis has also been employed for patients who are erythrodermic with circulating low levels of malignant cells. The final option used in patients refractory to standard therapy is allogeneic stem cell transplantation.

### **H&O** How does a clinician choose which therapy to use in a patient presenting with CTCL?

**SR** Each therapy has its own distinct toxicity profile. Selection of which therapy to use is in part based on judging what is needed to induce remission versus potential side effects. These considerations can change over the course of the disease. Comorbidities must also be factored into the decision of which therapy to use. The traditional approach at Robert H. Lurie Comprehensive Cancer Center for patients with disease at a stage greater than 1a is to begin treatment with interferon and PUVA; for patients who progress, depending on clinical circumstances and the nature of the disease, alemtuzumab is then used for Sézary syndrome and bexarotene with or without PUVA or UV-B light for mycosis fungoides. Many patients will ultimately receive an assortment of the different proven approaches. Clinicians attempt to sequence the therapies in a way that maximizes response and minimizes toxicity.

### **H&O** Do any agents now in preclinical testing appear promising in this setting?

**SR** One interesting agent is enzastaurin (Lilly), a protein kinase C inhibitor. Preclinical research shows that enzastaurin, at clinically achievable concentrations, induces apoptosis and downregulates Akt activity and its downstream effectors GSK3beta and ribosomal protein S6. Though not yet used clinically in CTCL, enzastaurin has shown clinical activity in other types of lymphoma.

### **H&O** What are directions of future research into therapies for CTCL?

**SR** As with many other hematologic malignancies, as a better understanding of the signaling pathways within the malignant cell is developed, researchers will identify small molecules or antibodies that target some of the key mediators of proliferation. This is a disease in which stimulating an immune response against the cancer may be an effective strategy in the future. Presently, we do see a graft-versus-CTCL effect with allogeneic transplantation.

### **Suggested Readings**

- Querfeld C, Rosen ST, Guitart J, et al. Phase II trial of subcutaneous injections of human recombinant interleukin-2 for the treatment of mycosis fungoides and Sézary syndrome. *J Am Acad Dermatol.* 2007;56:580-583.
- Querfeld C, Rizvi MA, Kuzel TM, et al. The selective protein kinase C beta inhibitor enzastaurin induces apoptosis in cutaneous T-cell lymphoma cell lines through the AKT pathway. *J Invest Dermatol.* 2006;126:1641-1647.
- Querfeld C, Rosen ST, Guitart J, Kuzel TM. The spectrum of cutaneous T-cell lymphomas: new insights into biology and therapy. *Curr Opin Hematol.* 2005;12:273-278.
- Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. *Dermatol Ther.* 2006;19:264-271.
- Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa-2b (Intron-A) for patients with cutaneous T-cell lymphoma. *Cancer.* 2007 Mar 15;[Epub ahead of print].