

## T/NK-Cell Lymphomas/Leukemias: Shedding New Light on These Rare Diseases

This issue of *Cancer Control* is devoted to a rare but biologically interesting group of lymphoid disorders: mature T-cell and natural killer (NK)-cell lymphomas/leukemias. A majority of these malignancies were not well characterized or even recognized as distinct clinicopathologic entities until the introduction of immunophenotyping to clinical practice at the end of 20th century. The World Health Organization (WHO) classification of lymphoid malignancies recognized 13 distinct mature T/NK-cell leukemias/lymphomas that account for 12% to 15% of all lymphoid malignancies diagnosed in Western countries.<sup>1</sup> More recently, two lymphoma classification organizations, WHO and the European Organization for Research and Treatment of Cancer (EORTC) issued a consensus classification of cutaneous lymphomas, discussed elsewhere in this issue.<sup>2</sup>

T/NK-cell lymphomas/leukemias have many similar clinical and laboratory characteristics due to an origin from a common T/NK-cell precursor. In contrast to B-cell lymphomas and leukemias, the cytomorphology of malignant T and NK cells often has poor correlation with prognosis, an immunophenotype is commonly overlapping, and genotype is frequently unrevealing. A lack of clonality markers in NK-cell diseases then makes it difficult to differentiate indolent malignancies from benign reactive expansions of NK cells. Thus, clinical presentation remains one of the most important features contributing to accurate diagnosis and directing therapeutic decision. The role of an expert hematopathologist and dermatopathologist in the initial diagnosis is invaluable. Since T/NK-cell lymphomas/leukemias are rare diseases, progress in laboratory and clinical research was until recently in the shadow of advances achieved in diagnosis and therapy of more common systemic B-cell lymphomas. Principles of therapy were often derived from uncontrolled single institutional studies, retrospective reviews, and historical clinical trials that included both B-cell and T-cell non-Hodgkin's lymphomas. For this reason, outcome of therapy, especially in the group of aggressive T/NK-cell lymphomas/leukemias, is unsatisfactory with no standard therapy established for the majority of these entities. However, recent increased interest in this group of diseases resulted in the development and clinical testing of several promising, novel targeted therapeutics,

including immunotherapy with monoclonal antibodies against common T/NK-cell markers such as CD2, CD4, CD25, CD30, and CD52. These immunotherapeutics follow denileukin diftitox, an interleukin-2 diphtheria toxin fusion protein that was the first biological agent approved by US Food and Drug Administration (FDA) for therapy of cutaneous T-cell lymphomas. Retinoids and histone deacetylase inhibitors also are promising groups of agents tested in clinical studies dealing with distinct T-cell malignancies. Two agents, bexarotene and vorinostat, were already approved for therapy of cutaneous T-cell lymphomas.

In this issue of *Cancer Control*, a group of scientists and clinicians with specific interest in T/NK-cell malignancies discuss advances in diagnosis and therapy of a majority of these diseases.

Dr Sotomayor, head of the Lymphoma Section at Moffitt Cancer Center, has delineated in his commentary the role of NIH NCI-designated cancer centers in the diagnosis, therapy, and research of rare diseases such as T/NK-cell malignancies. Multidisciplinary teams, rare disease networks, tumor banking, and tumor registries are only some examples of new concepts in this field.

Dr Keehn and a team led by Dr Glass discuss the most common entity in the group of cutaneous T-cell lymphomas (CTCL), mycosis fungoides, and its aggressive leukemic subtype, Sézary syndrome. Although mycosis fungoides belongs to a group of indolent T-cell lymphoproliferative disorders, multimodal therapy is often necessary to control advanced and refractory disease. Recent progress in management of these disorders is critically reviewed.

Dr Reznia and coauthors review the classification and treatment of rare and aggressive types of peripheral T-cell and NK-cell lymphomas of the skin with a focus on cytomorphology, immunophenotype, molecular markers, and novel therapeutic agents. Some of these rare entities still have provisional status in the WHO/EORTC classification.<sup>2</sup>

We are fortunate to have an internationally recognized expert in T/NK-cell lymphomas, Dr Marshal Kadin, as a senior author on a manuscript by Dr Droc and colleagues dealing with CD30+ lymphoproliferative disorders. These diseases comprise a spectrum of lymphoid malignancies with distinct biological behav-

ior and prognosis ranging from benign disease (such as lymphomatoid papulosis) to aggressive disease (such as systemic anaplastic large T-cell lymphomas). These authors provide an up-to-date review of molecular pathogenesis and management of these disorders.

We invited Drs Yasunaga and Matsuoka from Japan to discuss adult T-cell lymphomas/leukemias (ATLL), the first human hematologic malignancy caused by retrovirus, human T-cell lymphotropic virus-1 (HTLV-1). This condition is endemic in Japan, the Caribbean Islands, and South America but is rare in the United States. The Japanese Clinical Oncology Group (JCOG) has tested several combined chemotherapy regimens in clinical studies in aggressive T-cell lymphomas including ATLL with limited success. It is hoped that a better understanding of pathobiology of this disease will result in the development of novel targeted agents that increase the response rate and overall survival of patients who currently have a poor prognosis.

Dr Alekshun and I review a fascinating group of T/NK-cell malignancies: diseases of large granular lymphocytes (LGL). At least four different subtypes of LGL leukemias can be recognized according to laboratory features and clinical presentation. Novel agents targeting important pathogenic signaling pathways or T/NK-cell surface antigens, currently being tested in clinical trials, are discussed in detail.

Peripheral T-cell lymphoma, unspecified (PTCL-u) is the most common type of aggressive mature T-cell lymphomas in the United States. The prognosis of patients with advanced-stage PTCL-u treated with conventional chemotherapy regimens is inferior to patients with diffuse large B-cell non-Hodgkin's lymphomas, with a 5-year overall survival rate of only 25% to 30%. A team headed by Dr Ayala discusses pathobiology of this entity along with rare subtypes of specified aggressive T-cell lymphomas/leukemias. These authors focus on the role of consolidation with high-dose chemotherapy followed by hematopoietic stem cell rescue in the first remission in patients with poor prognostic factors.

Ms Behera and a team headed by an international authority in the field of evidence-based medicine (EBM), Dr Djulbegovic, applied EBM principles to clinical research of rare diseases such as T/NK-cell lymphomas/leukemias. The primary objectives of this article are how to select optimal therapy for patients with rare diseases in the absence of randomized clinical trials and how to recognize and avoid most common biases affecting clinical studies.

We believe that continuous refinement of the classification of T/NK-cell malignancies, along with a better understanding of molecular pathogenesis of each entity, will accelerate the development of new therapeutic targeted approaches for these diseases. We hope that readers will find this set of articles interesting and useful in their daily clinical practice.

We would also like to draw attention to the three articles included in this issue's ongoing department, "Cancer, Culture and Literacy." In the first article, Dr Kelly and colleagues discuss their interesting findings concerning colorectal cancer screening in Appalachian Kentucky. Then, Dr Mojica and coworkers point out the significant differences in the time needed for different hospitals to resolve questions about abnormal mammograms in low-income patients. It is likely that some systems are at fault, so this should be capable of being corrected. Finally, Dr Teschendorf and colleagues shed some light on what approaches might be developed to assist and minimize stress in that most important cancer caregiver: the family.

Lubomir Sokol, MD, PhD

Malignant Hematology Program  
H. Lee Moffitt Cancer Center & Research Institute  
Tampa, Florida  
E-mail: lubomir.sokol@moffitt.org

L. Frank Glass, MD

Cutaneous Oncology Program  
H. Lee Moffitt Cancer Center & Research Institute  
Tampa, Florida  
E-mail: fglass@health.usf.edu

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