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Critical Reviews in Oncology/Hematology 72 (2009) 125–143

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Molecular classification of T-cell lymphomas

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Accepted 9 January 2009

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Abstract

T-cell neoplasms encompass a heterogeneous group of relatively rare disease entities. This review, focused on lymphoblastic tumors (T-ALL/LBL) and nodal-based peripheral T-cell lymphomas (PTCL), summarizes recent advances in the molecular characterization of these diseases. In T-ALL/LBL, molecular subgroups delineated by gene expression profiling correlate with leukemic arrest at specific stages of normal thymocyte development and different oncogenic pathways, and seem to be of interest for prognosis prediction. Angioimmunoblastic T-cell lymphoma (AITL), one of the most common PTCL entities, comprises neoplastic cells with a molecular signature similar to normal follicular helper T cells, and this cellular derivation might account for several of the peculiar aspects of this disease. Except in ALK-positive

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1040-8428/$ – see front matter
doi:10.1016/j.critrevonc.2009.01.002

anaplastic large cell lymphoma, defined by *ALK* gene fusions, chromosomal translocations are otherwise rare in PTCLs, but some recurrent rearrangements might be associated with distinct lymphoma subtypes. In PTCL, not otherwise specified (PTCL, NOS), novel molecular biomarkers of potential therapeutic interest have been recently identified.

Keywords: T-cell lymphoma; Lymphoblastic; Peripheral; Angioimmunoblastic; Anaplastic; Gene expression profiling; Molecular signature; Cytogenetics; Translocation; Comparative genomic hybridization; Review

1. Introduction

T-cell malignancies are segregated into two major groups: precursor T-cell lymphoblastic neoplasms, derived from maturing thymocytes, and peripheral T-cell lymphomas (PTCL), arising from mature post-thymic T cells. The latter comprise numerous entities listed according to the clinical presentation of the disease, as disseminated, predominantly extranodal or cutaneous, or predominantly nodal (Table 1), altogether accounting for less than 15% of all non-Hodgkin lymphomas (NHL) worldwide [1]. In comparison with B-cell malignancies, T-cell neoplasms are relatively rare and importantly, are overall characterized by an inferior treatment outcome.

In the WHO classification, the definition of disease entities relies on a combination of parameters including morphology, immunophenotype, genetic and molecular features, clinical presentation, and if possible the normal cell of origin. Yet, strikingly, many T-cell lymphoma entities encompass a wide range of clinical, biological and/or pathological heterogeneity. In PTCLs, immunophenotype lacks specificity and is of limited interest for classification, and – with the notable exception of anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma – specific genetic alterations have so far not been documented for most of these diseases. Over the past decade, high-throughput genome-wide analytical methods, such as gene expression profiling using DNA or oligonucleotide microarrays and array-based comparative genomic hybridization (aCGH), have emerged as powerful tools to globally characterize the molecular and genetic features of cancers, and have proven to add important information for lymphoma biology, classification and prognosis. Although the study of T-cell neoplasms is hindered by the rarity of these disorders and the difficulty in collecting homogeneous and well-characterized case series, several investigators have now reported on the molecular and genetic profiling of different T-cell lymphoma entities. In this review, we will summarize these results and discuss their relevance to classification and diagnosis, and their pathobiological and clinical implications.

Table 1
WHO 2008 classification of T-cell neoplasms.

Precursor T-cell neoplasms
Precursor T acute lymphoblastic leukemia (T-ALL)/lymphoma (T-LBL)
Mature T-cell neoplasms
Leukemic or disseminated
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Adult T-cell lymphoma/leukemia (HTLV1-positive)
Systemic EBV-positive T-cell lymphoproliferative disorders of childhood
Extranodal
Extranodal NK/T-cell lymphoma, nasal type[a]
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Extranodal–cutaneous
Mycosis fungoides
Sezary syndrome
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma[b]
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma[b]
Primary cutaneous small/medium CD4+ T-cell lymphoma[b]
Nodal
Angioimmunoblastic T-cell lymphoma (AITL)
Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative[b]
Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)

[a] Most cases are derived from NK cells and only a minority from T cells.
[b] Provisional entities.

2. T-cell lymphoblastic leukemia/lymphoma

Precursor T-cell lymphoblastic neoplasms are aggressive diseases that mainly develop in children, especially adolescent males, but can also affect adults. The disease most often manifests with extensive marrow and blood involvement (acute T-cell lymphoblastic leukemia, T-ALL), or less commonly as a mass lesion (often in the thymus/anterior mediastinum, but also in lymph nodes and rarely a variety of extranodal sites) with ≤25% marrow blasts (T-cell lymphoblastic lymphoma, T-LBL). T-ALL is less common than B-ALL, accounting for approximately 15% of childhood and 25% of adult ALL, while conversely T-LBL comprises 85–90% of LBL [2].

T-cell lymphoblastic neoplasms are composed of small to medium-sized blast cells with round to irregular or convoluted nuclei and a high mitotic activity. By immunophenotyping, the lymphoblasts in T-ALL/LBL usually express nuclear terminal deoxynucleotidyl transferase (TdT), and can be stratified into different stages of thymocyte development according to the expression of the T-cell receptor