CD26 in T-Cell Lymphomas: A Potential Clinical Role?

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T-cell non-Hodgkin's lymphomas are a heterogeneous group of diseases that differ markedly in terms of their clinical behavior and prognosis. In recently developed classification systems, the sites of initial disease

An important change in the lymphoma classification systems occurred recently with the publication of the Revised European-American Classification of Lymphoid Neoplasms (REAL).[1] The REAL classification advocates the initial division of all lymphomas into two groups based on cell type, namely, T-cell and B-cell lymphomas. This modification circumvents the rather troublesome situation associated with the use of the previously accepted morphology-based Working Formulation, in which T-cell lymphomas that occur less frequently and have a worse prognosis are included in a number of different groups (diffuse-mixed, large cell, or lymphoblastic) and are treated in the same manner as their B-cell counterparts.

In addition to morphology, biological observation and clinical experience are used to identify specific entities of the REAL classification. While most of the REAL classification entities were recognized in the prior Working Formulation classification, new subtypes are also described.[2]

The REAL Classification System

The REAL classification divides T-cell lymphomas into two major groups based on the maturation stage of the malignant T cells: (1) precursor T-cell neoplasms, and (2) peripheral T-cell and natural killer (NK) cell neoplasms.[1] Peripheral T- and NK-cell neoplasms are further subdivided into 10 categories (1 provisional), with some containing provisional subtypes. Despite these instances of uncertainty, the REAL classification is a major step forward in delineating lymphoma entities, especially those of T-cell lineage. It recognizes another important aspect of T-cell lymphomas: the site of presentation is one of the cornerstones of distinction, ie, extranodal lymphomas are intrinsically different from their nodal counterparts.

Subsequent analyses have confirmed that the REAL classification indeed defines clinical entities that can be diagnosed by expert hematopathologists and that can predict the patient's clinical course and prognosis, thus making them useful in prescribing and devising therapies. The largest of these studies, the Non-Hodgkin's Lymphoma Classification Project (NHLCP), found the prevalence of T-cell lymphoma to be about 12%, with the peripheral (T-cell) lymphoma group representing the largest majority (7%).[3] In this analysis, however, the peripheral T-cell lymphoma group comprised 5 of 10 T-cell lymphoma subgroups as defined in the REAL classification. Anaplastic large T-/null-cell lymphoma and precursor T-lymphoblastic lymphoma subgroups each represented 2% of cases. Overall, the newly described entities of the REAL classification comprised approximately 20% of all cases.

The WHO Classification System

Since the advent of the REAL classification, significant new data have been generated for some lymphoma subgroups, allowing for the clarification and proper classification of provisional entities, especially among T-cell lymphomas. The World Health Organization (WHO) Classification for Neoplastic Diseases of the Lymphoid Tissues, which has been in development for the last few years, is based on the REAL classification and incorporates several additional modifications.[4] In addition to precursor T-cell neoplasms, the proposed WHO classification recognizes 14 subgroups among mature T- and NK-cell neoplasms. Disease site assumes a more prominent role in subgroup delineation, allowing subgroups to be easily separated as predominantly leukemic, nodal, extranodal, or cutaneous (Table 1).

Predominantly Leukemic Group
The predominantly leukemic group consists of four entities. T-cell prolymphocytic leukemia...
comprises up to 20% of all prolymphocytic leukemia cases. It is characterized by malignant cells that express CD2, CD3, CD5, and CD7, and that have prominent nucleoli and abundant cytoplasm. Cells that are smaller in some cases and that might be called T-cell chronic lymphocytic leukemia comprise 1% of all chronic lymphocytic leukemia cases. T-cell prolymphocytic/chronic lymphocytic leukemia is more aggressive than its B-cell counterpart and is rarely curable.

Large granular lymphocytic leukemia has been divided in the WHO classification into two subgroups: T- and NK-cell leukemias. These are associated with lymphocytosis and neutropenia. The T-cell type usually has more adverse features, such as anemia, splenomegaly, and complications secondary to cytopenia. Although the disease is indolent, an occasional case is associated with Epstein-Barr virus (EBV) and follows a more aggressive course. Sézary syndrome is the leukemic variant of mycosis fungoides (described later), although it can arise de novo. Patients usually also present with erythroderma and lymphadenopathy. Expected survival is less than 1.5 years, especially if extracutaneous disease is present.

**Predominantly Nodal Group**
The predominantly nodal group also combines four entities. Peripheral T-cell lymphoma, unspecified, is the most common of all the T-cell subgroups. It typically contains a mixture of small and large atypical cells that are difficult to subclassify. Patients are usually adults with aggressive, generalized disease. Relapse is common and the prognosis is poor.

Angioimmunoblastic T-cell lymphoma, a rare disease with a generally poor outcome, is composed of small cells, immunoblasts, and characteristic clear cells. Patients usually present with generalized lymphadenopathy, constitutional symptoms, and rash. Polyclonal hypergammaglobulinemia is often present.

Adult T-cell leukemia/lymphoma is caused by the human T-lymphocyte virus-1, which is transmitted either by infected cells via semen, blood products, needles, or breast milk, or by transplacental migration. The incubation period often ranges from 20 to 30 years. Four clinical types are recognized, the majority being acute with a median survival duration of less than 1 year. Moreover, autologous stem-cell transplantation appears to provide little benefit for adult T-cell leukemia patients.

Primary nodal anaplastic large T-/null-cell lymphoma is characterized by the presence of large blastic cells that in most cases express CD30 and have a characteristic chromosomal abnormality (see below). While patients often present with systemic disease and extranodal involvement (40% to 70%), treatment with aggressive chemotherapy results in excellent response in many cases.

**Primary Extranodal Lymphomas**
The modern definition of primary extranodal lymphomas includes only cases with limited stage IE and IIE disease, the majority of which are of B-cell origin. Many cases of extranodal T- and NK-cell lymphomas are associated with EBV and occur with increased frequency in immunosuppressed patients, especially after organ transplantation. Each of the four types comprise less than 1% to 2% of the total number of lymphoma cases but still account for approximately 25% of all T-cell lymphoma cases.

Nasal NK-/T-cell (angiocentric) lymphoma usually presents with destructive nasal or midline facial tumor, is EBV-positive, and is much more common in Asia. Although the disease is often localized, chemotherapy is generally administered in conjunction with radiotherapy. However, the relapse rate is high and the prognosis is generally poor. A common clinical complication is a hemophagocytic syndrome.

Primary Intestinal Lymphomas
Approximately 10% to 25% of primary intestinal lymphomas have a T-cell phenotype. These lymphomas are usually associated with celiac disease and are also called enteropathy-type intestinal T-cell lymphomas. The majority of patients present with a short history of abdominal pain and weight loss, or are treated with emergency surgery owing to small-bowel perforation or obstruction. While a tumor mass is frequently absent, the clinical course is aggressive and the outcome is poor.

Subcutaneous panniculitis-like T-cell lymphoma is usually manifested by subcutaneous nodules affecting the extremities. Malignant T cells are CD8 positive and can have either the alpha-beta or gamma-delta T-cell receptor. Hemophagocytic syndrome is a frequent complication that leads to death in the majority of patients, who often present with fever, pancytopenia, and hepatosplenomegaly. A bone marrow aspirate showing macrophages containing phagocytosed erythrocytes confirms the diagnosis.

Hepatosplenic gamma-delta T-cell lymphoma is considered a more systemic disease. Patients usually present with hepatosplenomegaly and bone marrow involvement but without lymphadenopathy. The majority of patients are young males. Clinically, this disease is aggressive, with a median survival of
less than 3 years.

**Primary Cutaneous Lymphomas**

The definition of primary cutaneous lymphomas includes diseases that manifest exclusively in the skin with no evidence of extracutaneous disease at the time of diagnosis or within the first 6 months after diagnosis. More than 80% of all primary cutaneous lymphomas are of T-cell origin.

There are two major types, and the prognosis for both is generally good. Mycosis fungoides is a low-grade lymphoma of mature T cells, characterized by three phases of evolution: patch, plaque, and tumor. All three lesions can occur simultaneously in the same patient.

In rare instances, mycosis fungoides can progress to its leukemic variant, Sézary syndrome. This syndrome is characterized by the loss of the pan-T-cell marker CD7 on CD4-positive malignant T cells. Extracutaneous disease and the extent and type of skin involvement are the most important prognostic indicators.

The predominantly cutaneous T-cell lymphoma subgroup also incorporates rare primary cutaneous anaplastic large-cell lymphoma, which has an excellent prognosis. It usually occurs in older patients and presents as a solitary mass with an ulcerated surface. Treatment generally consists of excision with or without radiation. In one-fourth of patients, the skin lesions spontaneously regress, either partially or completely. Primary cutaneous anaplastic large-cell lymphoma and lymphomatoid papulosis have overlapping histologic and clinical features, and are considered to represent a continuous spectrum of the disease.

**Prognostic Factors**

Many recent reports have provided additional data on various lymphoma subgroups, including clinical aggressiveness, prognostic factors, immunophenotype, and molecular genetics. The NHLCP analysis of the clinical aggressiveness of different lymphoma groups (Table 2) provided contrasting results with regard to different T-cell lymphoma subgroups[5]: the anaplastic large-cell lymphoma group clearly had the best prognosis (77% overall 5-year survival rate), while the T-cell lymphoblastic lymphoma (26%) and peripheral T-cell lymphoma (25%) groups had the poorest prognosis.

Other studies confirmed that the T-cell phenotype in itself is an important prognostic factor. Independent of the International Prognostic Index (IPI), the T-cell phenotype signifies a shorter disease-free interval, shorter overall survival, or both (except for CD30-positive anaplastic large-cell lymphoma) as compared with B-cell lymphomas.[6,7] In addition, the T-cell phenotype appears to confer a greater likelihood of advanced disease, B symptoms, and elevated lactate dehydrogenase.[6]

The IPI project did not evaluate the influence of immunophenotype on overall survival. However, subsequent studies used the IPI to stratify T-cell lymphoma patients into prognostic groups. This was done mostly to compare outcomes between groups with the same IPI but different immunophenotypes (T-cell vs B-cell).

Recently, Gisselbrecht et al[6] reported that the IPI could indeed stratify T-cell lymphoma patients into statistically significant prognostic groups. However, Armitage et al[5] used the IPI to stratify patients in every major lymphoma subgroup and found no correlation between the T-cell lymphoma subgroups (peripheral T-cell lymphoma, anaplastic large-cell lymphoma, and lymphoblastic lymphoma).

**Molecular Genetics**

Similarly, the significance of the molecular genetics of T-cell lymphomas is less well understood.[8] It has been established that a large number of T-cell lymphomas are characterized by chromosomal abnormalities that involve the T-cell receptor genes. A notable exception is CD30-positive anaplastic large-cell lymphoma, with respect to both its chromosomal abnormality and our understanding of its molecular genetics.

Anaplastic large-cell lymphoma is recognized by a strong, but not specific, association with a t(2;5) translocation that fuses the nucleophosmin gene from 5q35 to a tyrosine protein kinase (anaplastic lymphoma kinase) gene on 2q23. Activation of anaplastic lymphoma kinase results in an unregulated mitogenic signal, ie, cell proliferation. The translocation is present in most cases of primary nodal, but not primary cutaneous, anaplastic large-cell lymphoma. The subset of CD30-positive anaplastic large-cell lymphomas that are anaplastic lymphoma kinase-positive appears to have the most favorable outcome.[9]
CD26

In view of the heterogeneity of T-cell lymphomas in terms of clinical behavior and prognosis, there is a constant search for new prognostic factors and molecular markers. One example involves research examining the potential role of CD26 in human T-cell lymphoma. CD26 has been extensively characterized as a molecule with an essential function in human T-cell physiology. It performs a number of diverse functions, and has been described as an alternative pathway of T-cell activation, an exopeptidase with dipeptidyl peptidase IV enzymatic activity, a functional collagen receptor, and a molecule involved in thymic ontogeny.[10-16] Notably, CD26 has also been identified as the adenosine deaminase (ADA) binding protein that is expressed on the cell surface along with ADA. Adenosine deaminase is a key enzyme in purine salvage that regulates intracellular adenosine levels through the irreversible deamination of adenosine and deoxyadenosine.[17] Widely distributed in mammalian tissues, ADA displays the highest activity in lymphoid tissues, particularly in normal circulating T cells. The vital role of ADA in human lymphocytes is demonstrated by the fact that congenital deficiency of ADA enzymatic activity is associated with a defect in the maturation and function of lymphocytes, resulting in severe combined immunodeficiency disease. Although most ADA is found in the cytosol, it also appears on the surface of lymphocytes. Recently, in vitro studies have demonstrated that ADA cell-surface expression is dependent on CD26 surface expression and that coexpression of ADA with CD26 on the cell surface can block the inhibitory effect of accumulated adenosine on T-cell proliferation.[15] Other studies have shown that the expression of both ADA and CD26 increases significantly upon T-lymphocyte activation, while the absence of ADA expression causes anergy.[17] These data identified a potential new, nonenzymatic role for cell surface ADA as a costimulatory molecule in conjunction with CD26 in T cells.

CD26 in Human Lymphomas

While the basic role of CD26 in T-cell function is understood,[10-15] its potential involvement in the development of human lymphomas is only recently being examined. Italian researchers[18] showed that CD26 was expressed mostly on CD30-positive anaplastic large-cell lymphoma (12 of 17 cases) irrespective of antigenic phenotype, and on T-cell lymphomas (7 of 15 cases). CD26 was not detected among 26 B-cell lymphomas other than B-cell anaplastic large-cell lymphoma, and was rarely found in Hodgkin’s disease (2 of 23 cases). In addition, it was reported that, in contrast to normal T lymphocytes, CD26 and CD40 ligand were mutually exclusive in human T-cell lymphomas/leukemias.[19]

CD26 expression was restricted mainly to aggressive diseases, such as T-cell acute lymphoblastic leukemia (12 of 23 cases) and T-cell CD30-positive anaplastic large-cell lymphoma (5 of 8 cases), whereas CD40 ligand was expressed on relatively indolent diseases such as mycosis fungoides (11 of 21 cases). Within aggressive subgroups, CD26 expression appeared to confer a poorer prognosis. Interestingly, the expression of CD26 was found to be significantly decreased in all 20 patients with adult T-cell leukemia/lymphoma compared with healthy individuals.[20] Additional evidence supporting the role of this molecule in the pathogenesis of T-cell malignancies has recently been published.

Extensive immunophenotypic characterization of T-acute lymphoblastic leukemia cells revealed a close association between CD26 enzymatic activity, features of T-cell immaturity (ie, lack of CD3 cell-surface expression), and proliferative activity.[21] Of interest is the fact that CD26 expression increases in relatively mature human thymocytes.[10] Furthermore, CD26 enzymatic activity varied with the stage of differentiation, as well as activation of human alloreactive T-cell subsets.[22]

Similar observations were made in abnormal T cells, in which the presence (or intensity) of cell-surface CD26 expression was separable from the level of its intracellular enzymatic activity.[23] These data suggest that CD26 cell-surface expression and its enzymatic activity may have independent roles in the pathogenesis of T-cell malignancies. The significance of CD26 expression and function in CD26-positive U937 lymphoma cells has been assessed in a study by Reinhold et al.[24] which suppressed CD26 enzymatic activity by specific inhibitors. Inhibition of both DNA synthesis and cellular proliferation, as well as modulation of cytokine production, was observed, suggesting an important role for the enzymatic activity of CD26 in the biology of U937 lymphoma cells.

CD26 and Other Neoplasias

Recent findings suggest that CD26 may play an important role in the development of other neoplasias as well. For example, it is tightly regulated during the process of neoplastic transformation of melanocytes, as indicated by its expression on normal melanocytes but not on
melanoma cells.[25] When melanocytes are transformed in vitro in defined steps, loss of CD26 expression occurs concomitantly with the emergence of growth independence and the appearance of specific chromosomal abnormalities. CD26 has also been shown to be (1) a novel marker for differentiated thyroid carcinoma[26]; (2) expressed on glioma[27] and neuroblastoma[27]; and (3) a marker capable of distinguishing adenocarcinoma from other histologic types of lung cancer.[28] CD26 is aberrantly expressed in human hepatocellular carcinoma, as compared with normal liver tissue,[29] and is markedly reduced in metastatic prostate cells, as compared with primary prostate malignant or benign cells.[30] As an adhesion molecule, CD26 may also have a significant role in the metastatic dissemination of breast cancer, because it interacts with breast cancer cell surface-associated polymeric fibronectin.[31]

The Potent Inhibitor—Pentostatin

Pentostatin (Nipent) is a potent inhibitor of ADA that has proven to be a potent antitumor agent in several hematologic malignancies. Pentostatin is a purine analog with particularly significant activity in hairy cell leukemia.[32] It is also active in chronic leukemias and low-grade lymphomas, although not as active as other purine analogs.[33,34] By inhibiting ADA enzymatic activity, pentostatin causes an enhancement in the local concentration of adenosine and an increase in intracellular deoxyadenosine triphosphate, resulting in cytotoxicity and growth inhibition.[25] Other cellular events that have been reported following treatment with pentostatin include inhibition of S-adenosylhomocysteine hydrolase, single-strand breaks in DNA, and activation of caspase-dependent apoptosis.[35-37]

Several reports have suggested that pentostatin may have activity against T-cell malignancies as well, including T-lymphoblastic leukemia, cutaneous T-cell lymphoma (CTCL), Sézary syndrome, and adult T-cell lymphoma.[33] Assessment of the response rate in these studies has been limited by the relatively small number of patients, the heterogeneity of patient populations, and the variability in the dose and schedule of pentostatin (Table 3). Higher doses of pentostatin (10 mg/m²/d for 5 days) caused a number of side effects, including severe renal toxicity and central nervous system depression.[32] Lower doses were tolerated much better, and in the majority of reported studies, a dose of up to 5 mg/m²/d was administered for 3 to 5 days.[32,33]

New Trial of Pentostatin in Relation to CD26 Expression

To translate our knowledge of the basic biology of ADA and CD26 into clinical practice and to be able to develop targeted, specific treatment for T-cell lymphomas based on CD26 expression, novel experimental venues are needed. Taking advantage of the fact that pentostatin is a potent inhibitor of ADA and that CD26 expression is integral to ADA cell-surface expression and function, our trial at M. D. Anderson Cancer Center will examine the effect of pentostatin on relapsed/refractory T-cell lymphomas in relation to CD26 expression. Response rates will be evaluated separately for CD26-positive and CD26-negative T-cell lymphomas, in view of the potential differences in their biology and the possible differences in their response to pentostatin. A pentostatin dose schedule of 5 mg/m²/d for 3 days every 4 weeks appears to be optimal and is the starting dose for this trial. Knowledge gained from this trial will clarify the role of CD26 as a potential target in the treatment of T-cell lymphomas, as well as delineate a more precise role for pentostatin in the treatment of these diseases.

References:


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