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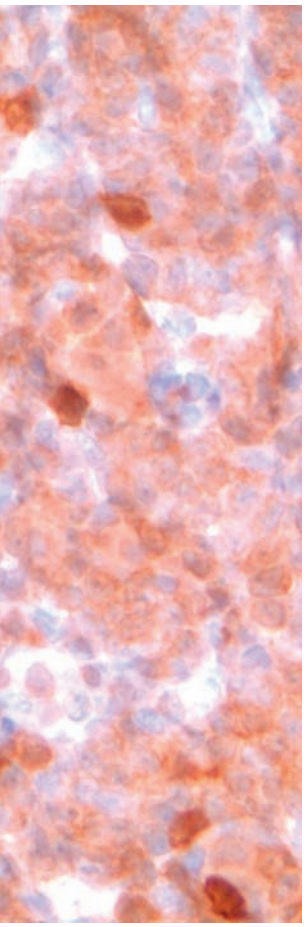

T-Cell and B-Cell Non-Hodgkin's Lymphoma Revisited: Therapeutic Paradigms and Advances

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GOAL

The goal of this activity is to provide medical oncologists and hematologists with the latest developments in T-cell and B-cell non-Hodgkin's lymphoma (NHL), including the pathophysiology of T-cell NHL, recent therapeutic advances in peripheral T-cell and B-cell, and clinical data on the treatment of cutaneous T-cell NHL.

TARGET AUDIENCE

The educational design of this activity addresses the needs of hematologists and medical oncologists involved in the treatment of patients with hematologic malignancies.

STATEMENT OF NEED

Non-Hodgkin's lymphoma (NHL) is any of a large group of cancers of the immune system, which can occur at any age and are often marked by enlarged lymph nodes, fever, and weight loss. NHL can be divided into aggressive (fast-growing) and indolent (slow-growing) types and can be classified as either B-cell or T-cell NHL. B-cell NHLs include Burkitt lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma. T-cell NHLs include mycosis fungoides, anaplastic large cell lymphoma, and precursor T-lymphoblastic lymphoma. Prognosis and treatment depend on the stage and type of disease.

According to the National Cancer Institute, an estimated 74,340 new cases of lymphoma have occured in 2008 in the U.S., with 66,120 of those being NHL. Of those new cases of NHL, it is estimated there will be 19,160 deaths. NHL is the fifth most common cancer in males and females in the United States. The age-adjusted incidence of NHL rose by 79 percent from 1975 to 2005. Approximately 2.4 cases per 100,000 people occur in 20- to 24-year-old individuals. The rate increases more than 19 times to nearly 46.2 cases per 100,000 persons by age 60 to 64, and more than 48-fold to more than 116.1 cases per 100,000 persons at ages 80 to 84. Although some of this increase is due to AIDS-related NHL, most cases of lymphoma have no known cause.

The T-cell lymphomas represent a very heterogeneous and challenging group of hematologic malignancies. Given the rarity of these diseases, there is little to no consensus regarding the management of patients either in the front line or relapsed state. One of the major difficulties with the management of these malignancies is the fact that there have been very few T-cell-'centric' drugs that have found their way into the standard treatment regimens. Most treatments used in T-cell lymphoma have been adopted based on the use of drugs active in the treatment of B-cell lymphomas (i.e., cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone [CHOP], Interleukin Converting Enzyme [ICE] based).

Over the past few years, however, there have been a number of major breakthroughs in the identification of novel targets and agents with activity in T-cell lymphoma. Gemcitabine, a deoxycytidine analogue, has proven to be a very active drug in a variety of T-cell lymphomas including cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL). Another promising small molecule with activity in T-cell lymphoma is pralatrexate, a 10-deazaaminopterin and investigational agent. In ongoing clinical trials, this compound has demonstrated an overall response rate of 50% or more in patients with relapsed or refractory disease.

Another class of drugs with unusual activity in T-cell lymphomas is the histone deacetylase inhibitors. Vorinostat (previously known as SAHA), has been approved for CTCL. Depsipeptide, a naturally occurring histone deacetylase activity (HDAC) inhibitor has demonstrated an overall response rate of about 30% in patients with CTCL and PTCL, with very durable responses despite their chemotherapy refractory nature. Another agent, LBH589, a potent hydroxamic acid derivative, has similarly demonstrated marked activity in patients with CTCL.

Despite improved treatment options and outcomes for patients with NHL, there are numerous unmet needs. NHL is a heterogeneous disease with patients often presenting additional treatment complexities due to co-morbidities, contraindications with existing medications, and various health effects that may occur as a result of treatment. With the growing number of novel agents and recent therapeutic advances in B-cell and peripheral T-cell lymphoma, it is imperative that clinicians be given the opportunity to develop clinical insights into understanding the risks, benefits, and tradeoffs associated with differing treatment approaches and the recent clinical trials and treatments.

LEARNING OBJECTIVES

At the end of this activity, participants should be able to:

- Review the pathophysiology of T-cell lymphomas
- Interpret current treatment options for optimal management of peripheral T-cell lymphoma
- Explain how to integrate emerging treatment options into the clinical management of patients with cutaneous T-cell lymphoma
- Describe recent clinical advances in the treatment of gastric mucosa-associated lymphoid tumors (MALT) lymphoma
- Translate recent advances in the management of central nervous system lymphoma

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Randy D. Gascoyne, MD, does not have any relevant financial disclosures.

Eric D. Hsi, MD, does not have any relevant financial disclosures.

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Lauren E. Abrey, MD, does not have any relevant financial disclosures.

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INTRODUCTION

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This issue of ***Grand Rounds in Hematology*** covers a number of diverse topics related to the diagnosis and treatment of both B-cell and T-cell lymphomas and highlights an evening educational session at the recent American Society of Hematology meeting in San Francisco. Several key opinion leaders in the field gathered to present their thoughts on a number of topics, including the pathophysiology of T-cell lymphoproliferative disorders, current treatment options for patients with peripheral T-cell lymphomas (PTCL), treatment strategies for patients with cutaneous T-cell lymphomas (Mycosis fungoides and Sézary syndrome), an overview of the biology and treatment options for extranodal gastric marginal zone lymphomas of mucosal-associated lymphoid tissue (MALT), and finally approaches to the treatment of primary central nervous system lymphomas (PCNSL).

Dr. Eric Hsi, a hematopathologist and head of Hematopathology at the Cleveland Clinic, provided a concise overview of T-cell ontogeny and how knowledge of T-cell development adds texture to the classification scheme used in the new 2008 World Health Organization (WHO) classification for PTCLs. Through the use of illustrative case examples, he walked the audience through the steps required to render an accurate diagnosis for this uncommon group of tumors.

Dr. David Straus from Memorial Sloan-Kettering Cancer Center in New York discussed conventional and new treatment approaches to this group of aggressive tumors. Patients with PTCLs are typically more difficult to treat than age- and stage-matched patients with diffuse large B-cell lymphoma. Newer treatment strategies include both novel chemotherapy agents and a growing list of biological agents, including monoclonal antibodies. In contrast to the great strides made in improving the lives of patients with diffuse large B-cell lymphoma following the addition of rituximab to conventional chemotherapy, the treatment of PTCL patients is clearly in need of significant improvements.

Dr. Steve Rosen, head of the Robert H. Lurie Comprehensive Cancer Center at Northwestern in Chicago, has enjoyed a career-long interest in cutaneous T-cell lymphomas (CTCL). By using clinical vignettes, he nicely covered the breadth of treatment choices for patients with this disfiguring form of cancer, with emphasis on practical approaches to the myriad of complications experienced by these patients.

Dr. Pier Luigi Zinzani from the Institute of Hematology and Oncology in Bologna, Italy, discussed both the pathogenesis and treatment options for patients with gastric MALT lymphomas. He explored a number of therapeutic options for gastric MALT lymphoma including antibiotic therapy, surgery, radiation, and newer immunochemotherapy alternatives that include anti-CD20 (rituximab) in combination with conventional chemotherapy.

Lastly, Dr. Lauren Abrey from Memorial Sloan-Kettering Cancer Center in New York, a well recognized expert in the field of PCNSL, discussed an approach to the diagnosis and treatment options for patients with these disorders. Choices of treatment strategies were supported by numerous survival curves that clearly supported her conclusions for both standard therapy and emerging novel approaches to the treatment of PCNSL.

Update on the Pathophysiology of T-Cell Lymphomas

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INTRODUCTION

T-cell lymphomas have been characterized as either precursor T-lymphoblastic or peripheral (mature) T-cell–derived based on phenotypic similarities to normal T-cell counterparts. An overview of this process as it is currently understood is presented here, along with descriptions of some newly identified mature T-cell lymphomas included in the recently published World Health Organization (WHO) lymphoma classification system. This review also includes case presentations of some common lymphomas.

OVERVIEW OF T-CELL DEVELOPMENT

T-cell lymphomas are categorized on the basis of their maturational state, which is determined by their development from either precursor T-cells or peripheral T-cells (Figure 1). Precursor T-cells develop in the thymus from bone marrow derived prothymocytes, which migrate to the thymus in early development and become double-negative ($CD4^-/CD8^-$) precursor T-cells. These precursor cells undergo scripted maturation beginning with rearrangement of their δ and γ T-cell receptor gene loci. If the rearrangement is successful the cells mature, express γδ–T-cell receptor, and migrate into the periphery to become γδ–T-cells, located primarily in mucosal sites and the skin. If rearrangement of the γ or δ T-cell genes is unsuccessful, further rearrangements occur in the α and β T-cell receptor genes as cells become CD4/CD8 double positive and express pre–T-cell receptors. Successful selection results in single-positive $CD4^+$ or $CD8^+$ cells that then populate the peripheral lymphoid system as CD4 or CD8 SP effector or memory T-cells. These αβ peripheral T-cells are at the stage of maturation that will correspond to the majority peripheral T-cell lymphomas such as peripheral T-cell lymphoma not otherwise specified (PTCL NOS) since most nodal T-cell lymphomas are of αβ T-cell type. Classification of peripheral T-cell lymphomas is largely based on characteristic clinicopathologic features rather than known biologic subsets. However, this may change as more is learned about T-cell lymphoma and its biologic or functional features. For example, follicular helper T-cells, which function in germinal center organization, are also thought to have malignant counterparts because of phenotypic similarities with some lymphomas, such as angioimmunoblastic T-cell lymphoma (AITL) and some rare cases of follicular T-cell lymphomas. The γδ–T-cell also gives rise to certain lymphomas that tend to follow the natural anatomic distribution of these cells, such as primary cutaneous γδ–T-cell lymphoma.

In addition to the genotypic changes that occur in TCR genes during the stages of maturation, phenotypic changes

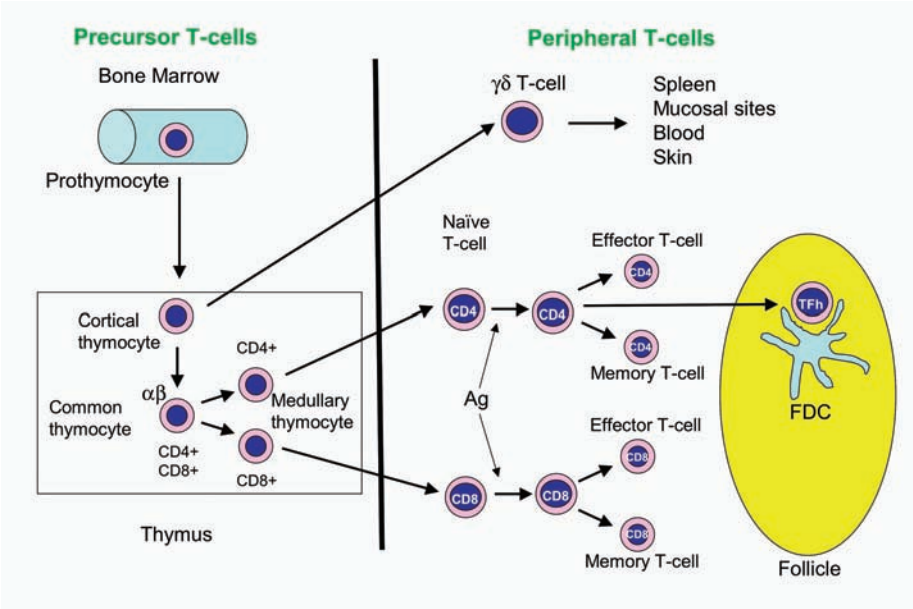

Figure 1. T-cell development. Acute lymphoblastic lymphoma of T-cell phenotype and precursor T-lymphoblastic lymphoma develop from precursor T-cells, whereas mature or peripheral T-cell lymphomas, the most frequently seen lymphomas, develop from mature or peripheral T-cells.

occur that enable pathologists to help diagnose and subclassify these lymphomas. For example, deoxynucleotidyl transferase (TdT) is expressed early in T-cell development and is present in precursor thymic T-cells but is lost as cells develop into mature T-cells, and so we would expect TdT to be absent in the peripheral or mature T-cell lymphomas but present in precursor T-cell neoplasms (T-lymphoblastic leukemia/lymphoma). CD7 is a very early T-cell antigen that is present before CD3 is expressed in thymocytes and thus is a very good marker for precursor T-cells, even very immature ones, in which cytoplasmic CD3 has not yet developed. The expression of surface CD3 occurs much later, along with T-cell–receptor expression, in very late medullary thymocyte stage, and both remain expressed in mature peripheral T-cells.

PERIPHERAL OR MATURE T-CELL LYMPHOMAS

Peripheral or mature T-cell lymphomas occur primarily in adults. The incidence varies by geographic region, which may have very different relative frequencies of T- and B-cell neoplasms. In the United States, according to National Cancer Institute SEER (Surveillance, Epidemiology and End Results) data, the incidence of T-cell neoplasms is 2.6 per 100,000 persons. These diseases are relatively more common in Asia, not only because of increased numbers of T-cell neoplasms overall, but also because of the decreased frequency of B-cell lymphomas in that population. In Asia, viral exposure is a very important factor in T-cell lymphoma etiology; human T-cell leukemia virus type 1 is associated with adult T-cell leukemia and lymphoma in endemic areas, and the Epstein-Barr virus (EBV) is associated with neoplasms such as the natural killer (NK)-cell lymphomas, in particular nasal NK/T-cell lymphoma.

Although T-cell lymphomas are uncommon, familiarity with the most commonly occurring subtypes is prudent. A recent study by the International T-cell Lymphoma Project showed that AITL and PTCL NOS make up the bulk of the lymphomas, followed by anaplastic large cell lymphomas (ALCLs) and then lymphomas such as adult T-cell lymphoma/leukemia and NK-cell lymphoma, which are particularly seen in Asia. In cases investigated by expert hematopathologists, only 2.5% of T-cell lymphomas were unclassifiable [1]. Thus, with the proper tools and well-trained diagnosticians, the vast majority of T-cell neoplasms can be classified within a modern classification system.

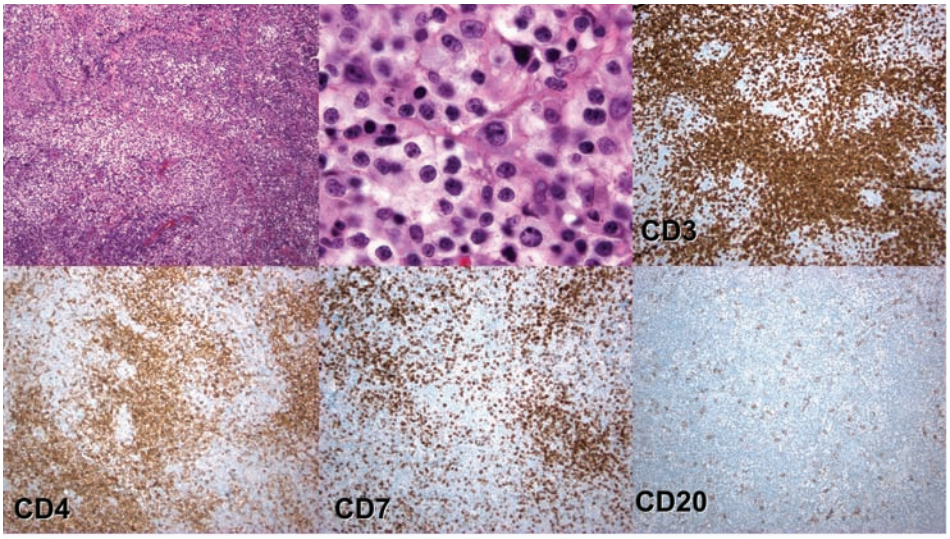

Figure 2. Case 1: angioimmunoblastic T-cell lymphoma. Cells viewed on low magnification were very pale with a washed-out look, an appearance attributable to the large quantity of clear cytoplasm (upper left). Immunostains revealed predominantly T-cells (upper center). CD3 and CD4 staining results were positive, with a very similar pattern. CD7 was decreased, suggesting actual loss of CD7 from the patient's T-cells. CD20 stain revealed a few scattered B-cells.

NEW WHO LYMPHOMA CLASSIFICATION

The new WHO classification of lymphomas was recently published [2]. Within the T-cell neoplasms, 2 major updates are present. The first is the inclusion of the updated 2005 WHO/European Organization for Research and Treatment of Cancer classification of primary cutaneous T-cell lymphomas [3]. The second is the recognition of new systemic T-cell lymphoproliferative diseases. This includes systemic EBV-positive T-cell lymphoproliferative disease of childhood and hydroa vacciniforme–like lymphoma. In the new classification of ALCL, 2 specific types are now recognized: anaplastic lymphoma kinase (ALK) positive and ALK-negative. Since the cutaneous T-cell lymphomas have been described in the 2005 WHO/EORTC update and classification of non-mycosis fungoides type cutaneous T-cell lympomas have been shown applicable in series from North America, we will focus on the new systemic diseases.

Systemic EBV-Positive T-Cell Lymphoproliferative Disease of Childhood

Systemic EBV-positive T-cell lymphoproliferative disease of childhood lymphomas present in children, most commonly of Asian, Native American, or Latin American descent [4]. These lymphomas have gone by many different names, such as fulminant EBV-positive T-cell lymphoproliferative disease of childhood, fatal infectious mononucleosis, fatal EBV-associated hemophagocytic syndrome, and severe chronic active EBV infection. All of these names point to the fact that this is a severe, life-threatening illness characterized by a clonal EBV-driven proliferation of cytotoxic T-cells.

Patients are previously healthy but then

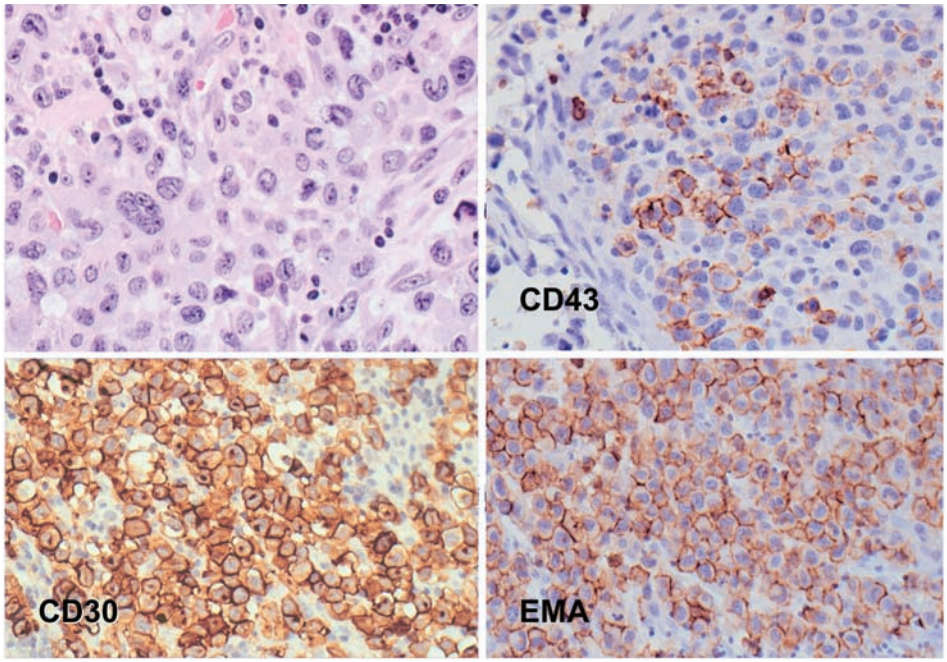

Figure 3. Case 2: anaplastic large-cell lymphoma (ALCL). Histological analysis in this patient revealed a very large atypical infiltrate, with lymphocytes 20 times normal size (upper left). Some of the cells expressed the T-cell–associated marker CD43, and some were positive for CD30 and epithelial membrane antigen (EMA).

present with acute onset of fever and malaise subsequent to organomegaly and lymphadenopathy over a span of weeks to months. The patients develop cytopenias and organ failure and have very high titers of EBV or high viral load. In some cases the illness is associated with a prodrome of more indolent or chronic active Epstein-Barr virus infection (CAEBV).

The pathological presentation of infiltration is quite subtle, usually with small T-cells that lack substantial cytologic atypia. The sinusoidal infiltrate occurs in extranodal sites, including the spleen, liver, and bone marrow. The lymph node architecture is preserved, and the presence of large numbers of EBV-positive T-cells is revealed only by special studies for EBV. The T-cells involved are monoclonal mature T-cells that are positive for T-cell–receptor beta, CD3, either CD4 or CD8, and by definition EBV-encoded small RNA.

This is an aggressive disease with fatal outcome and unknown underlying pathogenesis. Some reports describe patients with perforin mutations predisposing them to CAEBV, but in general this disorder appears to be due to an abnormality in immune response to EBV. The differential diagnosis would include CAEBV infection, but that is a more indolent disease. Also, with any type of EBV-positive lymphoproliferative disorder in children there is the possibility, particularly in boys, of X-linked lymphoproliferative disorder. This possibility can be ruled out with genetic tests for well-described mutations in certain genes such as SAP [5]. Another possibility is aggressive NK-cell leukemia/lymphoma, but this disease usually occurs in adults.

Hydroa Vacciniforme–Like Lymphoma

Hydroa vacciniforme–like lymphoma is a rare EBV-associated cutaneous lymphoma of NK- or T-cells that occurs in children from Asia or South and Central America [6]. This lymphoma mimics hydroa vacciniforme, a hypersensitivity to UV light that manifests as vesicular and cutaneous eruptions with scarring. Patients with hydroa vacciniforme–like lymphoma present with these lesions on sun-exposed areas of the skin, including the face, but they may develop systemic symptoms later in the disease, such as organomegaly and lymphadenopathy. This lymphoma may be associated with hypersensitivity to insect bites. When this occurs, it is often of the NK-cell type.

Examination of tissue under the microscope reveals an epidermal or dermal subcutaneous infiltrate of T- and NK-cells. Ulceration is also seen, but as with the previous EBV-positive entity these cells are small to medium sized without significant atypia. There is an angiocentric pattern with necrosis. EBV is by definition positive, and cytotoxic T-cells are monoclonal.

The clinical course of hydroa vacciniforme–like lymphoma is somewhat variable. In general it starts out as an indolent disease with recurrent skin lesions that may manifest over years, and when it finally does become systemic, it is a very aggressive disease with poor outcome.

CASE PRESENTATIONS OF THE MORE COMMON LYMPHOMAS

Case 1: Angioimmunoblastic T-Cell Lymphoma

This case patient, a 55-year-old man, presented with generalized adenopathy, B symptoms, and skin rash. Cells viewed on low magnification were very pale with a "washed-out" look, an appearance attributable to the large quantity of clear cytoplasm. Immunostains revealed predominantly T-cells, CD3 positive and CD4 positive, with a decrease in CD7 staining, suggesting abnormal loss of CD7 from the patient's T-cells. CD20 stain revealed a few scattered B-cells (Figure 2). Vessels with ovoid cells around them were visible in some areas where pale cells were visible, and a CD21 stain demonstrated that these ovoid cells were follicular dendritic cells in an abnormal location. All of these characteristics are classic features of AITL, a common type of peripheral T-cell lymphoma that is encountered in clinical practice. These lymphomas occur in middle-aged and elderly adults, and the ratio of affected men to women is

roughly equal. Patients suffer lymphadenopathy, fever, and weight loss and have polyclonal hypergammaglobulinemia and skin rash. Other common manifestations include hemolytic anemia, serous effusions, and arthritis. Laboratory tests reveal immune abnormalities such as circulating immune complexes, rheumatoid factor, and anti–smooth-muscle antibodies. These features all indicate an abnormality in the immune system. In fact, 20 to 30 years ago, these lymphomas were initially thought to be abnormal or atypical immune reactions rather than neoplasms and were given names such as angioimmunoblastic lymphadenopathy; we now know that most of these cases were likely AITLs. Some of the cellular features observed in this patient—the effaced nodal architecture that causes the hypocellular, depleted look and the reactive germinal centers—can be seen early in the disease but are usually absent later. Increased vascularity and abnormal follicular dendritic cells remain characteristic findings.

Phenotypic studies have recently reveled that the immunophenotype of the abnormal follicular dendritic cells resembles that of follicular helper T-cells, CD10-positive T-cells expressing the chemokine CXCL13, and large EBV-positive B-cells are present in the infiltrates. Genotyping reveals a monoclonal T-cell proliferation, but some cases show rearranged immunoglobulin in heavy chain genes as well, which is probably a manifestation of the EBV-driven B-cells, which are proliferating and are also monoclonal. Sometimes these EBV-positive B-cells proliferate and become the dominant feature of a biopsy specimen. In such cases, the underlying T-cell lymphoma is obscured, and the specimen may appear as an EBV-positive large B-cell lymphoma.

The normal counterpart of this lymphoma is postulated to be the follicular helper T-cell with a phenotype similar to AITL (T-cell, $CD4^+$, $CD10^+$, $CXCL13^+$, $PD1^+$). Recent gene expression studies have shown that the profile of these lymphoma cells is similar to that of normal follicular helper T-cells. Expression of the chemokine CXCL13 may be responsible for the follicular dendritic cell proliferation and the B-cell recruitment into the lymphoma, which is one of the normal functions of the CXCL13 chemokine [7].

Case 2: Anaplastic Large-Cell Lymphoma

The second case, a 32-year-old man with inguinal lymphadenopathy, involves another kind of lymphoma that clinicians are likely to encounter even though it is somewhat uncommon—systemic ALCL. A possible source of confusion is that a primary skin lymphoma, cutaneous anaplastic large-cell lymphoma, shares this name, but they are different lymphoma entities.

Histological analysis in this patient revealed a very large atypical infiltrate, with lymphocytes 5 times normal size. Some of the cells expressed the T-cell–associated marker CD43, and some were positive for CD30 and epithelial membrane antigen (Figure 3). In this case, immunostain results were positive in both cytoplasmic and nuclear locations, confirming the diagnosis of ALCL.

ALCL has a biphasic age distribution attributable to the combination of what are now recognized in the WHO 2008 classification system to be 2 different entities. The disease that occurs more frequently in younger patients is ALK-positive ALCL, but in older patients ALK-positive ALCL is less frequent. The 2 diseases are now considered separate largely on the basis of a recently reported study [8] showing a different outcome for ALK-positive versus ALK-negative ALCL versus PTCL NOS.

ALK-positive and ALK-negative ALCLs are both T-cell lymphomas, so they may express pan–T-cell markers, but they are almost by definition CD30 positive and clusterin positive in a majority of cases. ALK-positive lymphomas have a good prognosis, associated with an ALK translocation, whereas ALK-negative disease has a relatively poor prognosis (5-year survival 80% versus 30%, respectively). We now know that in addition to the classic t(2;5)(p23;q35) involving NPM and ALK of ALCL (85% of cases of ALK-positive ALCL), there are other

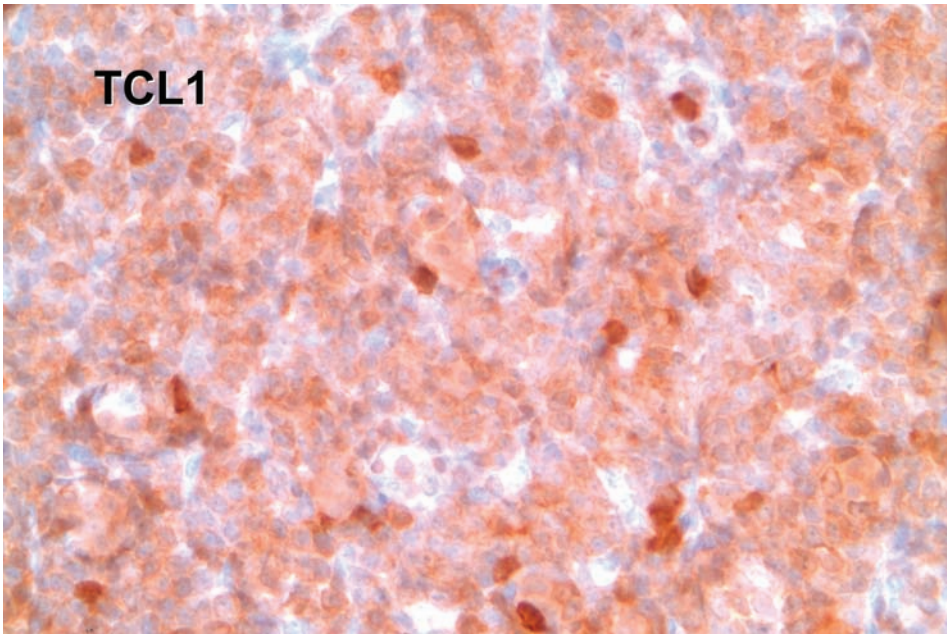

Figure 4. Case 3: T-cell prolymphocytic leukemia with secondary skin involvement. Initial staining results indicated possible peripheral T-cell lymphoma not otherwise specified, but the correct diagnosis was determined on the basis of positive immunostaining for T-cell leukemia-1 (TCL-1) and clinical findings of a very high white blood cell count with 95% lymphocytes.

recognized variant translocation partner genes for ALK. The important thing for a pathologist to be aware of is that the variant translocations may have different patterns of ALK immunostaining. For example, the clathrin heavy-chain translocation with ALK will show a cytoplasmic and granular staining pattern and not a nuclear staining pattern such as that seen in t(2;5)+ cases. The typical hallmark cells of ALCL are comma-shaped cells with strong CD30-positive staining and are seen in all cases.

Case 3: T-Cell Prolymphocytic Leukemia with Secondary Skin Involvement

This case highlights the importance of clinical information in enabling a pathologist to correctly interpret diagnostic findings. In this patient, a 67-year-old man with axillary lymphadenopathy, lymph node biopsy revealed diffuse effacement in the architecture, most likely attributable to a lymphoma. Other findings included a possible residual germinal center and a sea of other small lymphocytes in the T-cell zone of the lymph node. The cells were somewhat atypical, with some notching and mitotic figures. Immunostaining revealed CD3- and CD4-positive cells but almost no CD8-positive cells. More studies demonstrated positivity for other pan–T-cell antigens such as CD5 and CD7 and negativity for CD10, CXCL13, EBER, and CD30. Analysis for T-cell–receptor γ gene rearrangement was positive, confirming the presence of a monoclonal population. These findings suggested a diagnosis of PTCL NOS.

Another immunostain, however, showed that these cells were all positive for T-cell leukemia 1 (TCL-1) (Figure 4), a marker that is overexpressed in prolymphocytic leukemia owing to translocations or genetic abnormalities for that gene. We consulted the clinician regarding the results of analysis of the patient's blood and learned that he had a very high white blood cell count of 80×10^9/L with 95% lymphocytes, and so the more appropriate diagnosis was lymph node involvement by T-cell prolymphocytic leukemia (T-PLL).

This disease is a leukemic process occurring in older individuals with lymphadenopathy and organomegaly. Skin infiltration occurs in 20% of cases. This feature is a diagnostic pitfall, particularly for dermatopathologists who may not be familiar with this disease. On the basis of a skin biopsy suggesting T-cell lymphoma, dermatopathologists may diagnose cutaneous T-cell lymphoma, not knowing that what they are dealing with is secondary skin involvement by T-PLL. The blood data showing high white blood cell counts and cytopenias are a very important finding along with small lymphocytes with round or irregular nuclei. The phenotype is usually a CD4-positive T-cell, but there could be other variations of CD4 and CD8. CD52 is expressed in almost all cases, and TCL-1 is involved in many of these translocations. Because TCL-1 is an activator of AKT it is thought to have a pathogenic role in development of T-PLL.

This leukemia has a poor prognosis, with a median survival of less than 1 year. Some cases have been recognized that start off with an indolent phase and then go into a more aggressive phase with poor survival.

CONCLUSIONS

The classification of T-cell lymphomas is a process that is evolving along with techniques that allow more detailed tissue analysis and with the discovery of new diagnostically useful markers. Amidst this technological progress, however, clinical features remain an important factor enabling pathologists to arrive at the correct diagnosis when interpreting tissue biopsy results. Thus, ongoing communication between pathologists and clinicians and mutual understanding of modern classification paradigms are essential for optimal patient care.

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Therapeutic Options for Patients with Peripheral T-Cell Lymphoma

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Peripheral T-cell lymphoma is a disease that in many cases lacks effective treatment options, and thus the search for new approaches is ongoing. Anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma has a relatively good prognosis and frequently responds well to standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. Unfortunately, other peripheral T-cell lymphomas have a very poor prognosis and poor outcome with conventional treatment, even in patients who present with early-stage disease. For the small number of patients who present with limited localized disease the outcome seems to be better than with those with more widespread disease.

CONVENTIONAL TREATMENT

Conventional treatment for peripheral T-cell lymphoma is most effective in patients with early-stage disease. At the University of Nebraska, patients with limited stage I/II-A non-bulky peripheral T-cell lymphomas were treated with various therapies. Most of the patients received chemotherapy with or without radiation therapy, about half underwent combined modality treatment with chemotherapy and radiation therapy, and a small number received radiation therapy alone. With a median follow-up of approximately 9 years, the results were fairly good, with progression-free survival of 60% and overall survival of 50% [1].

Unfortunately, patients with peripheral T-cell lymphoma more commonly present with widely disseminated disease. In such cases the results are poor for treatment with conventional chemotherapy such as CHOP, with about 20% long-term disease-free survival; so, an approach that has been used at Memorial Sloan-Kettering in New York and other institutions is front-line intensive treatment with high-dose chemotherapy and autologous stem cell transplantation.

Results of a retrospective review of patients who underwent autologous stem cell transplantation for peripheral T-cell lymphoma at Stanford from 1989 to 2006 [2] indicated that transplantation results were not very good for patients with refractory or relapsed disease but were very promising for patients in either complete or partial first remission, with an actuarial 5-year progression-free survival rate of 76% and an overall survival rate of 51%. In an intent-to-treat analysis of newly-diagnosed patients for whom autologous stem cell transplantation was planned, 66% actually made it to transplantation with an overall survival rate of 48%, which is better than the 20% percent overall survival rate expected with CHOP therapy (Figure 1) [3].

NEW TREATMENT APPROACHES

Because of poor results with conventional therapies, new treatments for peripheral T-cell lymphoma are under investigation.

Pralatrexate

Pralatrexate(10-propargyl-10-deazaaminopterin) is a folate analog inhibitor that has demonstrated dramatic activity in patients with relapsed/refractory peripheral T-cell lymphoma [4]. Pralatrexate is a novel targeted antifolate that is designed to accumulate preferentially in cancer cells. High affinity for the reduced folate carrier protein-1 enables the drug to enter cells. It also has a high affinity for the folate polyglutamate synthetase, and the resulting polyglutamylation is important in its effectiveness. These features were noted in preclinical work and were then investigated in cell lines and xenographs and showed much higher activity than many other classical antifolate drugs such as methotrexate.

In a large phase I/II trial that included patients with a broad variety of lymphomas, a particularly promising and high response rate to pralatrexate was observed in the patients with peripheral T-cell lymphomas compared to those with B-cell lymphomas. It was also noted that a dose-limiting side effect, in common with other antifolates, was stomatitis, but this toxicity was reduced with administration of supplements of vitamin B12 and folate [5]. Other major toxicities were hematologic: febrile neutropenia, neutropenia, anemia, thrombocytopenia, leukopenia, and lymphopenia as well as, in a small percentage of patients, alanine aminotransferase and aspartate aminotransferase elevations. The Pralatrexate in Patients with Peripheral

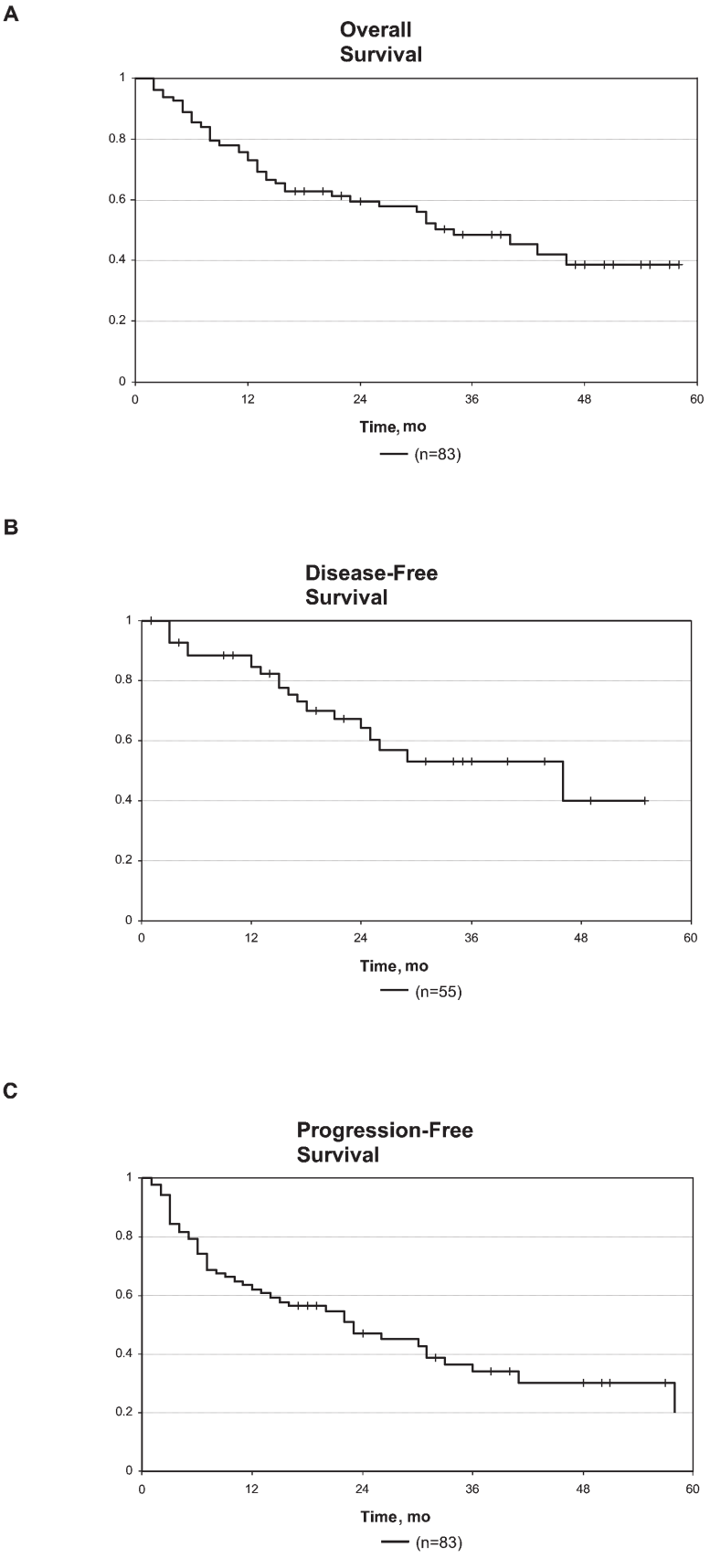

Figure 1. Pralatrexate (PDX) has high affinity for the reduced folate carrier protein-1 (RFC-1), which enables the drug to enter cells. It also has a high affinity for the folate polyglutamate synthetase (FPGS), resulting in PDX polyglutimation [PDX$(G)_n$].

T-cell Lymphoma (PROPEL) trial, a phase II, multicenter study of pralatrexate with vitamin supplementation with vitamin B12 and folic acid in relapsed and refractory peripheral T-cell lymphoma, has demonstrated an overall response rate of 29%, including 11% complete responses, in patients with heavily pretreated disease [6].

Romidepsin

Histone deacetylase inhibitors are another class of drugs under investigation for the treatment of a number of lymphomas. For one of these, romidepsin (depsipeptide), a trial has been performed to investigate its use in the treatment of relapsed peripheral T-cell lymphoma [7]. The overall response rate in this study was 39%. Grade 3 and 4 toxicities were rare, but mild toxicities were seen, including nausea, fatigue, decreased platelets, and a decreased neutrophil count. These drugs have been associated with cardiac arrhythmias and prolongation of QT intervals, and in this trial 1 death attributable to cardiovascular causes may have been drug related, although it occurred in a patient who had prior cardiovascular disease.

Zanolimumab

The immunologic agent zanolimumab, a fully human monoclonal cytotoxic IgG1 antibody that targets the CD4 molecule on T-cells, is a novel agent that has been tested in CD4-positive relapsed/refractory peripheral T-cell lymphoma [8]. In this small trial of 21 patients an overall 24% response rate was observed, and the drug was well tolerated in heavily pretreated patients. Zanolimumab in combination with CHOP is now being investigated in previously untreated patients with nodal T-cell lymphoma.

Denileukin Diftitox

Denileukin diftitox is a drug that recently received full FDA approval for the treatment of cutaneous T-cell lymphoma. An immunotoxin with diphtheria toxin and a

portion of the interleukin-2 molecule containing the ligand for the high-affinity and intermediate-affinity interleukin-2 receptor, denileukin diftitox also has activity in peripheral T-cell lymphoma. The recent CONCEPT trial [9] investigated the use of combined CHOP and denileukin diftitox to treat peripheral T-cell lymphoma. Although this study looked primarily at safety and treatment results were not the primary endpoint, there was quite an impressive overall response rate of 85%, with a 75% to 76% complete response rate. The durations of response and the overall survival were also quite impressive, somewhat comparable with those for autologous stem cell transplantation. Because this was not an intent-to-treat analysis, however, this treatment cannot be recommended outside of the setting of a clinical trial until it is better established.

CONCLUSIONS

The therapeutic options for peripheral T-cell lymphoma are as follows: ALK-positive anaplastic large-cell lymphoma has a relatively good prognosis when treated with standard CHOP chemotherapy. Peripheral T-cell lymphoma and ALK-negative anaplastic large-cell lymphoma have a relatively poor prognosis. The results with upfront autologous stem cell transplantation are promising, as are those of the CONCEPT trial of denileukin diftitox. Several other promising new agents offer hope in cases for which few effective treatment options have been available.

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Clinical Vignettes in Cutaneous T-Cell Lymphoma: Practical Applications for Emerging Data on Mycosis Fungoides/Sézary Syndrome

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INTRODUCTION

Non-Hodgkin's lymphomas may manifest as cutaneous lesions with no evidence of disease in other parts of the body at the time of diagnosis, although systemic involvement does occur. In the United States, cutaneous T-cell lymphomas (CTCLs) make up approximately 80% of cutaneous lymphomas, and B-cell lymphomas make up approximately 20%. Because most cases of CTCL are not fatal and patients often live with CTCL for 10 or more years, it has been estimated that between 16,000 and 20,000 Americans currently have and are under treatment for CTCL. This review focuses mainly on the CTCLs mycosis fungoides and the systemic aggressive leukemic variant of mycosis fungoides, Sézary syndrome. Mycosis fungoides/Sézary syndrome lymphomas are the most common CTCLs. They are characterized by the proliferation of helper-type T-lymphocytes. Five-year survival rates for indolent mycosis fungoides are as high as 100%, whereas those for Sézary syndrome are only about 24%. Characteristic disease manifestations, often occurring with orderly progression, include patches, plaques, and tumor lesions that may lead to ulceration, breakdown, infection, and death. Cosmetic concerns and discomfort such as extreme pruritis contribute to decreased quality of life in CTCL patients. Palliative treatments may be very effective, but allogeneic transplantation may be the only curative therapy for patients with advanced disease.

MYCOSIS FUNGOIDES/SÉZARY SYNDROME EPIDEMIOLOGY

Mycosis fungoides/Sézary syndrome lymphomas are the most common CTLCs, with an incidence of 0.36 cases per 100,000 people and a prevalence of 16,000 to 20,000 cases in the United States from 1973 through 1992. From 1972 to 1999 incidence rates stabilized, and mortality rates declined. The disease is more common in men than women (2:1 ratio); mean patient age is 50 years. African Americans are more frequently affected than whites, with Asians least likely to be affected [1].

The most common forms of mycosis fungoides have an indolent disease course. Most cases are diagnosed early in the patient's disease and have an excellent 5-year survival rate that may be as high as 100%, whereas Sézary syndrome, the systemic aggressive leukemic variant of mycosis fungoides, has a 5-year survival rate of only about 24% [2].

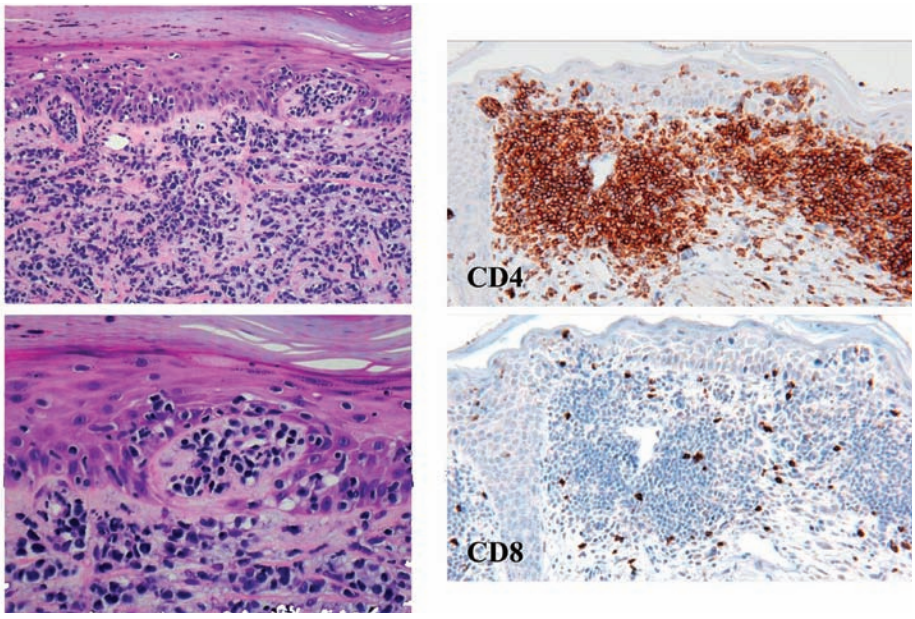

Figure 1. Histopathological analysis of mycosis fungoides cutaneous lymphoma reveals infiltration of malignant cells in the dermis extending into the epidermis and CD4-positive and CD8-negative cells in the Pautrier abscess.

DISEASE CHARACTERISTICS

Mycosis fungoides exemplifies characteristics shared by many CTCLs. It is a low-grade lymphoma that originates as a postthymic T-cell malignancy. The characteristic immunophenotype is CD4-positive and CD45RO-positive. Mycosis fungoides lymphomas are typically associated with proliferation of helper-type T-lymphocytes and have a T-helper 2 cytokine profile, which is associated with the secretion of a number of interleukin molecules. The classic presentation is a patch, plaque, or tumor lesions. Examination of affected tissue reveals characteristic histology with infiltration of the malignant cells in the upper dermis and then epidermal tropism. Malignant cells enter the epidermis in groups termed Pautrier microabscesses. Histopathological analysis (Figure 1) reveals infiltration of malignant cells in the dermis extending into the epidermis and CD4-positive and CD8-negative cells in the Pautrier abscess.

The characteristic presenting manifestations of mycosis fungoides often show orderly progression from patches to plaques to tumor lesions to ultimate ulceration, breakdown, infection, and death. Thus this disease carries significant cosmetic consequences and effects on quality of life in addition to the risk of fatality.

Sézary patients typically exhibit exfoliative erythroderma, palmoplantar keratoderma, ectropium that sometimes leads to extremely uncomfortable tearing, and alopecia due to damage to the hair follicles, Severe, disabling pruritis is associated with this entity.

In Sézary syndrome atypical malignant T-cells, termed Sézary cells, circulate in the peripheral blood. These cells have a hyperconvoluted nucleus and a very cerebriform nature that is visible by electron microscopy (Figure 2). A characteristic immunophenotype ($CD3^+$, $CD4^+$, $CD5^+$, $CD7^{+/-}$, $CD8^-$, $CD25^{+/-}$, $CD26^-$, $CD30^-$, $CD45RO^+$, $CD52^+$, $CD158^+$) is an important feature of these cells because it indicates the presence of critical targets that have therapeutic applications. In a study performed at our institution to assess genetic susceptibility as determined by the major histocompatibility complex in white patients who were typed for human leukocyte antigen (HLA)-A, -B, and -C, we observed an association with an atypical HLA profile in patients with Sézary syndrome but not in those with mycosis fungoides [3].

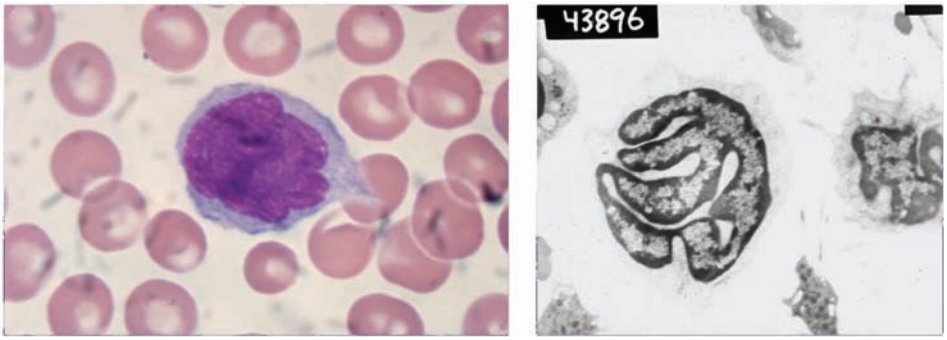

Figure 2. Circulating atypical malignant T-cells in Sézary syndrome have a very cerebriform nature (left) and a hyperconvoluted nucleus (right).

One of the most fascinating aspects of mycosis fungoides is that even though patch skin lesions from various locations are known to arise from the same clone, it may be decades before clonal cells can be found in the circulation or in internal organs. What we do know is that malignant cells have skin-homing ligands and receptors that recognize venules, keratinocytes, and dendritic cells. Molecules known to be associated with skin-homing T-cells, cutaneous lymphocyte antigen and the chemokine receptor CCR4, were found in high levels in CTCL lesions and were increased in the peripheral blood of patients with systemic CTCL [4].

Chromosome aberrations are a universal feature in CTLC patients. Chromosomes 1 and 10 are most commonly involved, but there is no signature chromosome abnormality and no characteristic profile. The same is true of the diminished expression and activation of tumor suppressor genes and enhanced expression and activation of a variety of signaling and antiapoptotic molecules associated with proliferation, such as JUNB, which may be important in primary CTLC pathogenesis [5]. Analyis of gene expression data from Sézary patients has shown consistent overexpression of 2 genes, the tyrosine kinase receptor EphA4 and the transcription factor TWIST [6].

At the time of disease presentation most patients (42%) have patches or plaques covering <10% of the body surface (the palm of the hand and fingers represent 1% of the body surface); approximately 30% have more extensive patches; 15% have tumors; and 12% have erythroderma [7]. Disease-specific survival of patients with mycosis fungoides and Sézary syndrome is associated with clinical stage at the time of diagnosis. Patients whose disease is confined to skin patches do reasonably well, whereas patients with tumor or nodal involvement or systemic involvement do quite poorly [8].

In some cases of mycosis fungoides/Sézary syndrome the disease undergoes a transformation to large-cell lymphoma. Typically these patients are CD30-negative, have increased lactic acid dehydrogenase (LDH), systemic symptoms, and a poor prognosis.

TREATMENT

An important National Cancer Institute trial that was initiated in the late 1970s and culminated in the early 1990s [9] had a profound impact on how we treat mycosis fungoides/Sézary syndrome patients. In this randomized trial patients received either very aggressive chemotherapy and total skin electron beam radiation therapy or sequential

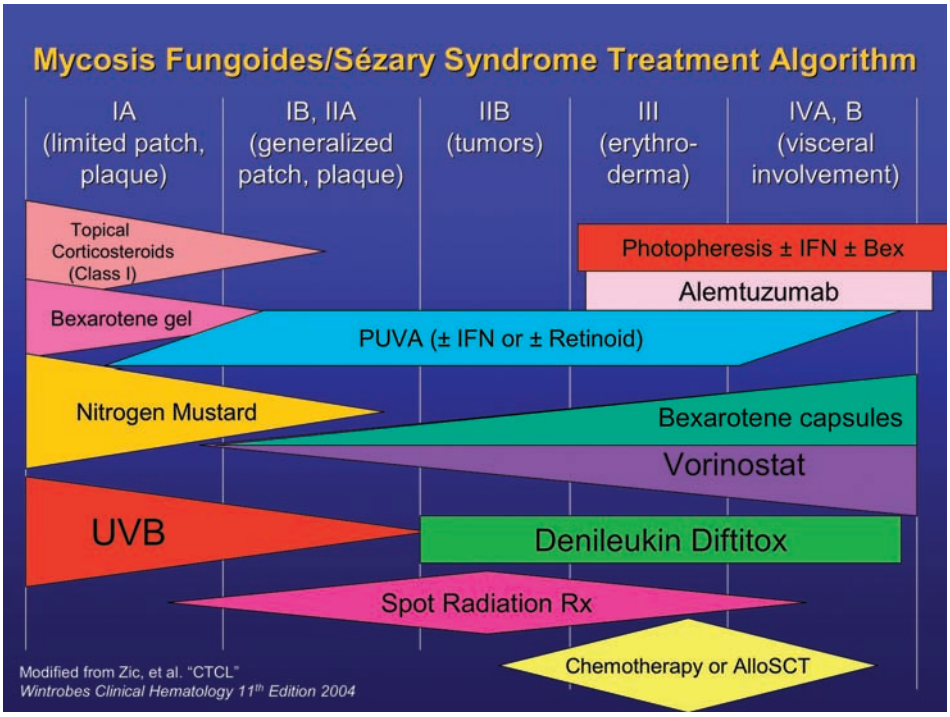

Figure 3. Treatment options according to disease stage for mycosis fungoides/Sézary syndrome. IFN indicates interferon; Bex, bexarotene; PUVA, psoralen plus UVA; AlloSCT, allogeneic stem cell transplantation.

topical chemotherapy. Because outcomes were similar for both groups, most clinicians tend to take a less aggressive approach in the initial phases of treatment, trying to control the disease and provide palliation without delivering significant toxicity. Information about available treatments has been compiled by the National Cancer Institute and is available on the internet [10].

Skin-directed therapies include topical corticosteroids and topical chemotherapy. The most common topical therapeutic agent is nitrogen mustard. Carmustine has also been used, but some clinicians avoid it because of its association with telangiectasia. The use of topical retinoids is usually confined to localized lesions because they can cause inflammation before healing and are quite expensive.

Phototherapy is used to treat patches and narrow-band UVB for deeper lesions. Psoralen with UVA (PUVA) and radiation therapy are also used. Site-directed radiation is commonly used for isolated lesions. Some institutions use total-body skin electron-beam radiation because electrons, as charged particles, have limited depth of penetration.

In regard to systemic therapies, mycosis fungoides/Sézary syndrome has been the paradigm for the development of a number of biologic agents and targeted therapies. These include steroids and biologic therapies such as interferon alpha, which in our hands has been the most potent agent although it can take months to induce a meaningful response; bexarotene, which is a resinoid; vorinostat, which is a histone deacetylase inhibitor; and bortezomib. Targeted therapies include Denileukin diftitox, which targets the interleukin-2 receptor; alemtuzumab, which is an anti-CD52 antibody; and zanolimumab. Toxicity concerns with these agents include fatigue, malaise, and diarrhea associated with vorinostat and infection associated with alemtuzumab.

In addition, extracorporeal photochemotherapy can be used for patients who have low levels of circulating malignant cells, and single-agent chemotherapy can be quite palliative. Single agents that can be effective include alkylating agents, antifols such as methotrexate and pralatrexate, nucleoside analogs such as gemcitabine, and pegylated anthracyclines. At our treatment center we usually reserve combination chemotherapy for patients with advanced aggressive disease, and we have had some success with allogeneic transplantation, possibly the only curative therapy for patients with advanced disease.

An algorithm of treatment options according to disease stage for mycosis fungoides/Sézary syndrome, shown in Figure 3, represents the strategy we use at the Robert H. Lurie Comprehensive Cancer Center. For patients with limited patches/plaques, we use topical corticosteroids, bexarotene gel, nitrogen mustard, or UVB. As the disease progresses we start with PUVA with or without interferon or with or without a retinoid or resinoid. Single-agent bexarotene or vorinostat can also be used at this stage. We use Denileukin diftitox mainly for patients with more advanced disease; the response can be dramatic, but unfortunately it is often short-lived. Spot radiation can be very effective for a single disturbing lesion, and we use chemotherapy and allotransplantation for patients who have progressive disease and for whom other reasonable alternatives have not been effective. Photopheresis with or without interferon or bexarotene can often be used for erythrodermic patients, and we have found that alemtuzumab is very effective for erythrodermic patients.

Recently there have been major advances with the use of new agents in the treatment of mycosis fungoides/Sézary syndrome and other CTCLs. The histone deacetylase inhibitor panobinostat (LBH589) has thus far shown promising results in an ongoing open-label, multicenter, phase 2 study of patients with relapsed/refractory mycosis fungoides or Sézary syndrome [11]. Final clinical results of a National Cancer Institute phase 2 multicenter study of the histone deacetylase inhibitor romidepsin for treatment of recurrent CTCL showed significant responses at all stages of disease.

In addition, molecular analyses confirmed that romidepsin inhibited target deacetylases [12]. Another promising treatment approach has been demonstrated in preliminary results for a multicenter dose-finding trial of pralatrexate, a novel targeted antifolate that is designed to accumulate preferentially in cancer cells. According to a recent report, pralatrexate has shown marked clinical activity in the treatment of CTCL at much lower doses than used for aggressive lymphomas. CTCL patients showing a favorable response had received up to 8 prior treatment regimens [13].

CONCLUSIONS

Patients with mycosis fungoides/Sézary syndrome and other CTCLs may suffer significant physical discomfort as well as cosmetic concerns throughout what may be a long disease course. Fortunately effective palliative treatments are available, but the only curative option is allotransplantation. Ongoing investigation is essential, and recent promising results in clinical trials of new treatment agents offer hope for better future.

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What's New in Gastric MALT Lymphoma?

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INTRODUCTION

This review presents new information on mucosa-associated lymphoid tissue (MALT) lymphoma. This lymphoma occurs most commonly in the gastrointestinal tract, but it can arise from a wide variety of extranodal tissues even if mucosa-associated lymphoid tissue is physiologically absent in the normal tissue (acquired MALT). MALT lymphoma is associated with other diseases such as Sjogren and Hashimoto syndromes and *Helicobacter pylori* (Hp) gastritis. The discovery of the association with Hp infection has led to exciting advances in treatment of MALT lymphoma with antibiotics targeted against Hp infection, a strategy that produces complete response (CR) rates of 60% to 100% in patients with stage 1 Hp-positive gastric MALT lymphoma. Unfortunately, 10% of patients whose therapy is successful suffer relapse. In such cases, treatment options include surgical excision, radiation treatment, chemotherapy, and a new agent, rituximab.

DISEASE PATHOGENESIS

MALT lymphoma, first described in the stomach by Isaacson and Wright [1], is included in the Revised European and American Lymphoma/World Health Organization classification as a separate B-cell entity, the extranodal marginal zone lymphoma of MALT. This disease may occur at extranodal sites where MALT is normally present (native MALT), but it usually occurs where lymphoid tissue is not a natural component (acquired MALT), such as in Sjogren and Hashimoto syndromes and Hp gastritis.

A pathogenesis model (Figure 1) of tumor progression [2] postulates that mucosal T-cell proliferation occurs as a result of genetic damage from chronic Hp-associated gastritis, leading to Hp-dependent MALT lymphoma. Some MALT lymphomas translocations result in HP-independent growth, while other forms of genetic damage may result in histological transformation to diffuse large B-cell lymphoma.

CHROMOSOMAL TRANSLOCATIONS IN MALT LYMPHOMA

In the last few years new data have become available regarding the importance of chromosomal translocation in MALT lymphoma (Figure 2). MALT lymphoma is unique among B-cell lymphomas in having been associated with apparently unrelated chromosomal translocations that involve various anatomic oncogenes and mechanisms of oncogene activation.

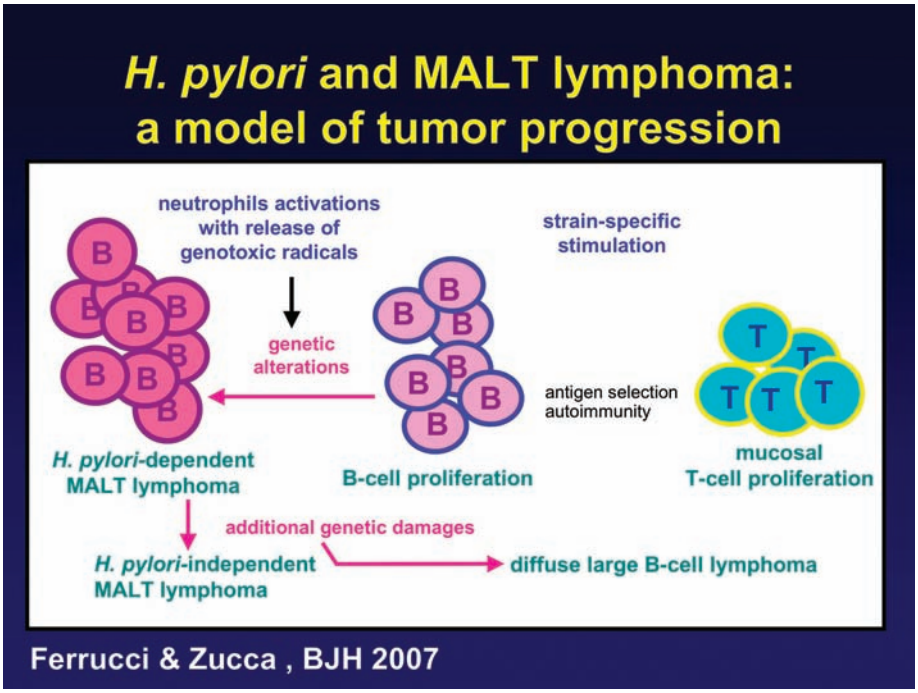

Figure 1. This image summarizes the pathways of mucosa-associated lymphoid tissue (MALT) lymphoma development and progression. In the background of chronic gastritis the expansion of some B-cell clones is continuously stimulated by the presence of *Helicobacter pylori* infection. Free radicals released by neutrophils can damage the B-cell genome, thus resulting in tumor development and progression [1].

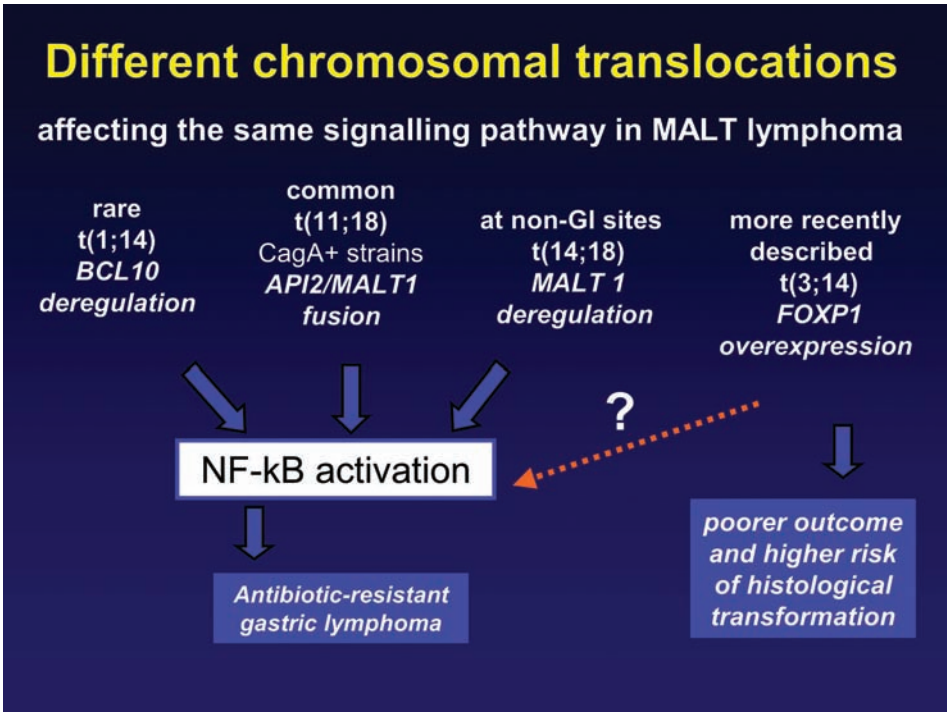

Figure 2. Chromosomal translocation in mucosa-associated lymphoid tissue (MALT) lymphoma. MALT lymphoma is unique among B-cell lymphomas in having been associated with apparently unrelated chromosomal translocations that appear to impact on the same signal transduction pathway, with activation of nuclear factor kappa-light-chain-enhancer of actived B-cells (NF-κB), a transcription factor with a central role in the activation of genes involved in the control of cell proliferation. The resultant increase in NF-κB activity may be critical to lymphoma progression.

These differing translocations are found at markedly variable frequencies in MALT lymphomas arising from various sites, suggesting the presence of site-specific pathways for the lymphoma development. All of these distinct translocations appear to impact the same signal-transduction pathway, with activation of nuclear factor kappa-light-chain-enhancer of actived B-cells (NF-κB), a transcription factor with a central role in the activation of genes involved in the control of cell proliferation, apoptosis, and inflamation. Under physiological conditions, BCL10 is the ligand of MALT1; they form a tight bond and synergize to activate NF-κB. The common gastrointestinal chromosomal translocation t(11;18) generates *API2-MALT1* fusion, which enables NF-κB activation independent of BCL10. The resultant increase in NF-κB activity may be critical to lymphoma progression. This pathway is the therapeutic target of bortezomib, a drug under investigation that may become an important therapeutic agent.

Other chromosomal translocations associated with MALT lymphoma are t(1;14), a rare translocation that leads to BCL10 deregulation; nongastrointestinal t(14;18), which is associated with *MALT1* deregulation; and t(3;14), which is associated with *FOXP1* overexpression. In the subset of patients with the t(3;14) translocation there is a poor outcome and high risk of histological transformation. Additional new translocations in MALT lymphoma have recently been described [3].

In addition to their role in disease initiation and progression, chromosomal translocations have been implicated in the development of antibiotic resistance, a characteristic that impacts therapeutic options for Hp-positve MALT lymphoma, for which antibiotic treatment is currently the front-line treatment.

TREATMENT OF MALT LYMPHOMA

Because gastric MALT lymphoma is a rare disease, no randomized clinical trial data are available. According to other recent data, treatment options include antibiotic treatment, surgical excision, radiation treatment, chemotherapy, and the chimeric monoclonal antibody rituximab for early disease (stages 1 and 2) and chemotherapy and anti-CD20 monoclonal antibody for advanced disease (stages 3 and 4).

Antibiotic Treatment

In the last 15 years the most important development in the treatment of stage 1 Hp-positive gastric MALT lymphoma is the use of antibiotics to eradicate the Hp infection [4]. This treatment has a CR rate of 60% to 100%. The treatment duration required to achieve CR ranges from a few months to close to 2 years. Thus it is important to wait and to observe patients carefully to determine whether their response is complete to avoid discontinuing treatment when only a partial response has occurred. The relapse rate is less than 10% in patients who achieve CR in response to antibiotic therapy.

Treatment of Recurrent Disease

The success of eradication treatment has made it the front-line treatment in patients with Hp-positive disease, and this treatment is effective in 90% of patients. Histological CR occurs in 50% to 100% of patients. Endoscopic and histological remission following antibiotics does not mean "cure," however. Polymerase chain reaction assay for the detection of monoclonal B-cells remained positive in approximately 50% of histological CR [5]. Most patients with minimal residual histological gastric lymphoma remain stable and can be managed safely by a "watch and wait" strategy [6], but disease relapse occurs in 10% of patients. The treatment of persistent recurrent lymphoma after eradication treatment with antibiotics presents a major challenge.

Surgical treatment is a primary option, with reported 5-year overall survival ranging from 80% to 95% [7]. Total gastrectomy should be considered because MALT lymphoma is often multifocal, but this

procedure entails risks of acute surgical complications as well as long-term complications affecting patient quality of life.

In our institution we have investigated a second treatment option, surgical resection with or without additional treatment with local radiotherapy in patients with low-grade gastric MALT lymphoma after Hp eradication and relapse. The treatment strategy was determined according to each patient's situation after the surgical treatment. Patients underwent local radiotherapy if there was a positive surgical margin with or without regional lymph-node involvement and with or without internodal invasion. Of 67 patients treated with this option, the relapse-free survival was more than 80% after 15 years [8].

Data also support the role of radiotherapy as a single agent in a gastric MALT lymphoma, with failure-free progression after 2, 4, or 5 years ranging from 80% to 100% [9-11]. The number of study patients is small, but the preliminary data are very interesting in terms of disease-free survival. Questions remain regarding this approach, however. Reported radiation doses range from 28 to 34 Gy, and it is difficult to determine the optimal radiotherapy volume, dose, and method of delivery. Another concern with radiotherapy is long-term toxicity, which may lead to a second malignancy and gastric and renal toxicity. Such risks may not be acceptable, particularly in patients with indolent disease.

Several studies have addressed the use of chemotherapy in patients with disease relapse. In 24 patients who had relapsed after Hp-antibiotic treatment and splenectomy and/or adjunct therapy, Hammel and coworkers [12] investigated the use of continuous oral administration of the single alkylating agents cyclophosphamide (100 mg/d; n = 21) or chlorambucil (6 mg/d; n = 3) for 8 to 24 months as single-agent chemotherapy. The overall response rate was 100%, and the CR rate was 75%, but the event-free survival after 5 years was only 50%, with relapses at the initiation site occurring in 5 patients and disease transformation into large-cell lymphoma occuring in 1 patient.

The nucleoside analog cladribine (2-chlorodeoxyadenosine [2-CDA]) is a very interesting drug for this subset of patients. To treat 25 patients with histologically verified MALT-type lymphoma, most with primary gastric lymphoma, Jäger and coworkers [13] administered 2-CDA at a dose of 0.12 mg/kg body weight on 5 consecutive days, as a 2-hour infusion. Cycles were repeated every 4 weeks for a maximum of 6 cycles. At least a partial response occurred in 21 patients, and 84% of these had a CR. Progression-free survival was approximately 80% after 3 years. A long-term concern with this treatment, however, is the risk of myelodysplastic syndrome.

At our institution we began a trial of fludarabine-containing chemotherapy as frontline treatment of nongastrointestinal MALT lymphoma, and we have started investigating the use of this treatment in gastric MALT lymphoma as well [14]. We have also added the chimeric monoclonal antibody rituximab to the regimen for both gastric and nongastric MALT lymphoma. In a series of 31 patients with nongastric intestinal MALT lymphoma the CR rate was 100%, and disease-free survival at 5 years was 85%. We are now investigating the role of fludarabine plus rituximab in more than 40 patients with previously treated gastric MALT lymphoma. Salar et al [15] also reported results with the use of a fludarabine plus rituximab regimen for MALT lymphoma. The CR rate was 94% percent, and the 1-year progression-free survival was more than 90%.

Additional data on the role of rituximab in MALT lymphoma have been reported. Conconi and coworkers [16] treated 35 patients with gastric and nongastric MALT lymphoma. The overall response rate was more than 70%, and in patients who had received prior chemotherapy, the CR rate was approximately 40%. Martinelli and coworkers [17] treated 26 patients with gastric MALT lymphoma resistant or refractory to antibiotic treatment or with no clinical evidence of Hp infection. The CR rate was roughly 50%, and the overall response rate was 77%. Thus data are very encouraging with regard to the use of rituximab in this subset of patients.

CONCLUSIONS

Antibiotic therapy in Hp-positive patients is an exciting new treatment option for MALT lymphoma. The optimal strategy for good sequential treatment after antibiotic therapy remains to be determined, however. Although CR rates with antibiotic therapy are as high as 100%, preliminary data suggest that only 20% to 30% of these patients have a real molecular response. Thus it is important to optimize front-line treatment with a sequential combination. Fortunately, however, the prognosis seems excellent regardless of treatment. General guidelines are to use initial antibiotic therapy in localized Hp-positive disease. Radiotherapy, chemotherapy, and rituximab can be used in patients who do not respond to antibiotics or who relapse. The optimal role of surgery remains to be defined, and the role of rituximab requires further evaluation. Based on what we have learned about pathogenesis and the role of chromosomal alterations in NF-κB activation, bortezomib may become a very important drug for the next phase of the treatment of these entities.

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Primary Central Nervous System Lymphoma

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INTRODUCTION

Primary central nervous system (CNS) lymphoma is an aggressive B-cell non-Hodgkin's lymphoma confined to the CNS. Typically CNS lymphoma involves the brain, but it may also affect the cerebrospinal fluid (CSF) and the globe of the eye including the vitreous fluid and the retina. CNS lymphoma is both a radiosensitive and a chemosensitive disease. Some young patients may be cured with a combination of methotrexate and whole-brain radiation, but the vast majority of patients are at high risk for relapse. Although high-dose chemotherapy and whole-brain radiotherapy may prolong survival, the neurotoxicity of these regimens frequently leads to severe cognitive deficits. Recently promising results have been obtained with new chemotherapeutic agents combined with standard chemotherapy and reduced-dose radiotherapy, but further investigation is needed.

CNS LYMPHOMA DIAGNOSIS

CNS lymphoma occurs most commonly in the brain (85% of cases) and is typically diagnosed on the basis of brain biopsy results. CSF involvement is seen in 30% to 40% of cases, and ocular involvement is seen in 15% to 20%. Because of the possibility of systemic involvement (<5% of cases), systemic staging is recommended for all patients. For all patients who can safely undergo a lumbar puncture, cytological analysis of a CSF sample should be performed. At Memorial Sloan-Kettering Cancer Center we typically recommend a computed tomographic (CT) scan of the chest, abdomen, and pelvis for systemic staging. All of our patients also undergo bone marrow biopsies.

The role of body or brain positron-emission tomography (PET) has not been clearly defined for CNS lymphoma, but our findings suggest that (18)F-fluorodeoxyglucose body PET might be more sensitive than conventional body-staging methods in CNS lymphoma patients [1].

To address CNS lymphoma affecting the eye, an ophthalmologist should perform a detailed ophthalmologic examination that includes a dilated fundus exam with a slit lamp. Other techniques that ophthalmologists use include fluorescein angiography and color photography of the posterior pole, but the slit-lamp exam is the most important procedure.

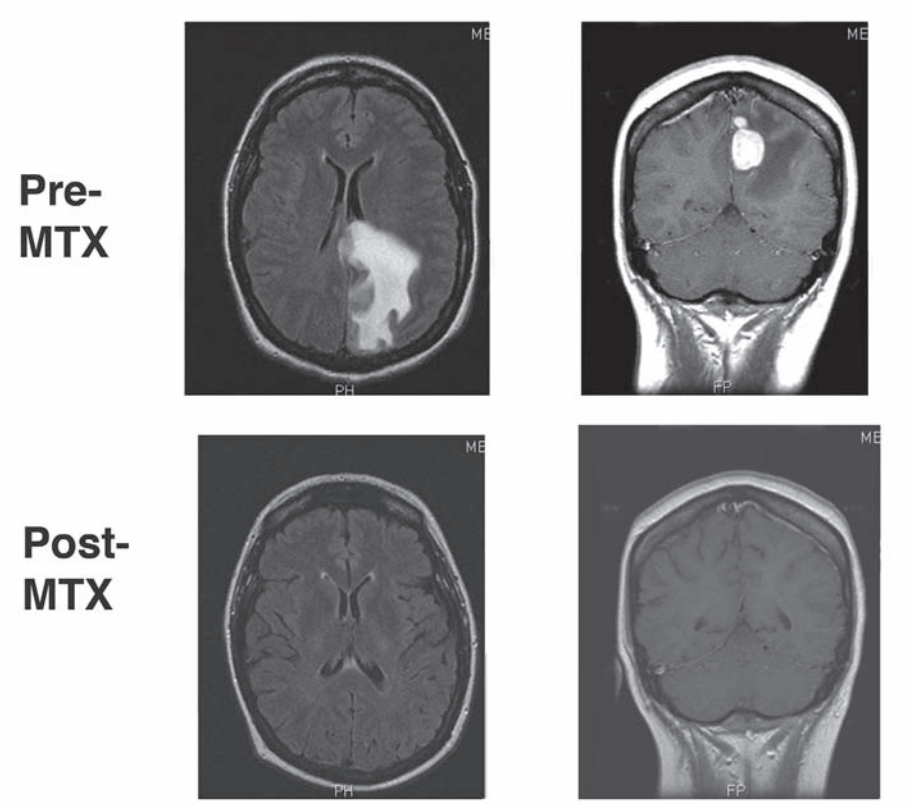

Figure 1. Magnetic resonance imaging of a patient with primary central nervous system (CNS) lymphoma before (above) and after (below) treatment with methotrexate (MTX). After treatment the lymphoma is no longer visible, but the risk for relapse remains high.

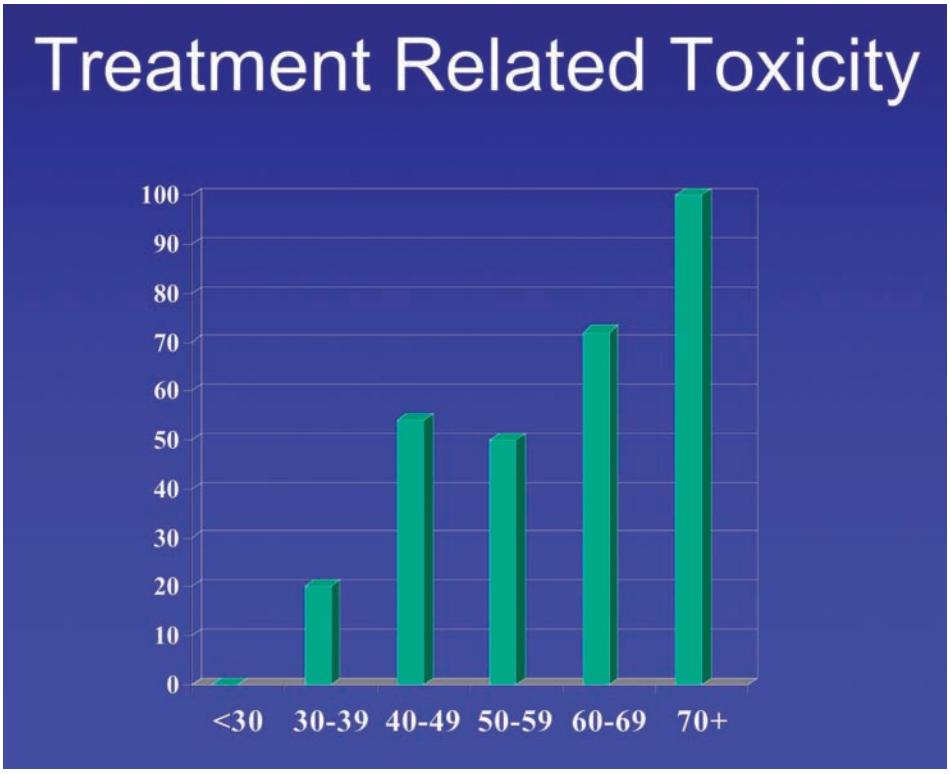

Figure 2. Rates of neurotoxicity in long-term survivors of central nerous system (CNS) lymphoma treated with methotrexate and whole-brain radiation. Although such treatment decreases the risk of relapse, neurotoxicity may lead to severe disability and poor quality of life.

TREATMENT OF CNS LYMPHOMA

Standard Treatment

CNS lymphoma is sensitive to both radiotherapy and chemotherapy. With radiotherapy alone results are not particularly good, with median survival of approximately 12 months with an optimal dose of 40 to 50 Gy. Methotrexate is the most effective chemotherapeutic drug, with median survival of 30 to 60 months with high-dose systemic administration. Standard treatment approaches are similar to those used for other aggressive B-cell lymphomas, but the regimens that are typically used for systemic lymphoma are not particularly effective for treating CNS lymphoma. For CNS lymphoma these regimens often work for 1 or 2 treatment cycles, but then relapse occurs, probably because the blood-brain barrier heals just as the systemic lymphoma therapies start to enter the CNS. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) lymphoma regimens are not effective for CNS lymphoma because these agents are blocked by the blood-brain barrier.

The effectiveness of early treatment with methotrexate can be seen in magnetic resonance imaging scans (Figure 1). The problem, however, is that although many patients achieve remission, at least half suffer relapse. Relapse usually occurs within 2 years of diagnosis. Relapse location is the CNS in 90% of cases and systemic in 10%, and the risk of relapse is increased with primary ocular and CSF tumors. Unfortunately, although we can successfully combat relapse by using the most aggressive therapies, combinations of methotrexate with whole-brain radiation, patients pay a significant price. The rates of neurotoxicity in long-term survivors are quite high (Figure 2), with a 100% rate of neurotoxicity in 70-year-old patients treated with methotrexate and radiation. Most of these patients eventually require 24-hour care similar to that of Alzheimers disease patients. Although aggressive therapy may cure the lymphoma, death secondary to neurotoxicity occurs in 38% of patients. In long-term survivors (≥5 years), 51% suffer dementia, and complications of neurotoxicity are the primary cause of death. In younger patients the effects of neurotoxicity may develop at delayed intervals. For example, a 54-year-old man who was treated at our institution in 1998 did well for a number of years but then began to have progressive cognitive decline in 2002. This patient obtained some benefit from treatment with a ventriculoperitoneal shunt but remained completely bed-bound, requiring total care at home.

TREATMENT AGENTS AND STRATEGIES

Exploration of new treatments for CNS lymphoma must address both the need for more effective treatment because of the high risk of relapse and the need for less toxic therapies to minimize CNS damage.

With existing agents many questions remain as to which treatment approaches are the best. Large amounts of data address various methotrexate treatment strategies, such as whether it is most effective when used alone or when combined with other agents and whether its effectiveness may be enhanced by intrathecal administration directly into the CSF. The extreme neurotoxicity of radiation therapy calls into question its appropriateness for use in CNS lymphoma. If radiation continues to be a treatment option, the optimal dose remains to be determined. If the risks of radiation are determined to outweigh the benefits, compensatory intensification of chemotherapy is an option to be explored. Further complications arise when treatment must target CNS lymphomas occurring in the eye and leptomeningeal disease invading the CSF.

Methotrexate Strategies

Data are scarce regarding variations in methotrexate dose amounts. Typically patients are given high doses, and when methotrexate was used as a single agent before other therapy, similar response rates were observed for

doses of 1, 3.5, or 8 g/m^2. The association of methotrexate dose with survival cannot be determined because these patients received many other treatments, but these results suggest that doses as high as 8 g/m^2 are not more effective than lower doses. Pharmacology data indicate that achieving an effective cytocidal concentration of methotrexate in the CSF requires a dose of at least 3 g/m^2 given rapidly over a period of 1 to 3 hours. If this amount is administered over a longer period, such as 24 hours, a cytocidal concentration in the CSF will not be achieved, so if less than 3 g/m^2 is administered intravenously then additional intrathecal administration is recommended.

Comparative data are not available regarding the use of methotrexate by itself versus its use in combination with other agents, but results of a series of studies with single-agent methotrexate or methotrexate in combination with other agents suggest that response rates are similar but generally tend to be a little bit better with methotrexate in combination therapy. Progression-free survival is also slightly better, but overall survival is similar. I am a believer in multiagent therapy, however, and few other aggressive B-cell lymphomas are treated with single-agent chemotherapy regimens.

Although intrathecal methotrexate is certainly necessary for patients with high-risk systemic lymphomas, it has not been found to increase the effectiveness of methotrexate treatment in primary CNS lymphoma. In a matched case-controlled retrospective study of patients at Memorial Sloan-Kettering, we did not find any difference in overall survival, progression-free survival, risk of treatment failure in the CSF, or neurotoxicity with use of intrathecal methotrexate in patients who were matched for their treatment, their age, and whether or not their CSF was involved at diagnosis [2]. Similarly, a large study of European data [3] showed that intrathecal chemotherapy did not improve survival.

The large European study mentioned above [3] also showed that the addition of whole-brain radiation did not improve survival in patients treated with methotrexate. Similarly, when we looked at our patient population at Memorial Sloan-Kettering, particularly at patients older than 60 years and patients treated with chemotherapy alone versus a combination of chemotherapy and radiation, we found that median survival rates were identical. Rates of relapse were much higher in patients treated with chemotherapy alone, but patients treated with chemotherapy and radiation had a significant risk of neurotoxicity (83% in patients ≥60 years old), which can be just as lethal as a recurrent tumor if the result is a bed-bound patient needing total care [4].

A number of studies have investigated ways to make radiation safer. The Radiation Therapy Oncology Group found that disease control and neurotoxicity rates were identical with a hyperfractionated lower-dose schedule of radiation compared with a standard dose [5]. The use of techniques such as focal or gamma knife radiation to focus on the visible tumor have not been effective and have actually resulted in higher relapse rates within as well as outside the radiated portion [6].

The Barcelona-Nottingham group looked at decreasing the dose of radiation in patients who obtained complete remission with their chemotherapy regimen and found that the disease control and survival was actually inferior, particularly in younger patients who are hoped to have a much better prognosis and potential outcome in this disease [7]. Thus far, results for attempts to reduce radiation toxicity without compromising the effectiveness of treatment have been sobering, and as yet there is no good answer to this dilemma.

In patients with isolated ocular lymphoma, extensive local treatment does not seem to improve disease control or overall survival, so it may be preferable to defer more extensive therapy to minimize treatment-related complications. In brain lymphoma with ocular dissemination, directed ocular therapy with radiation and chemotherapy seems to improve disease control [8].

New Therapeutic Agents

The standard chemotherapy regimen at the Memorial Sloan-Kettering Cancer Center has been a combination of methotrexate, procarbazine, and vincristine for 5 cycles. In an ongoing study that has been conducted since 2001, we changed the regimen by

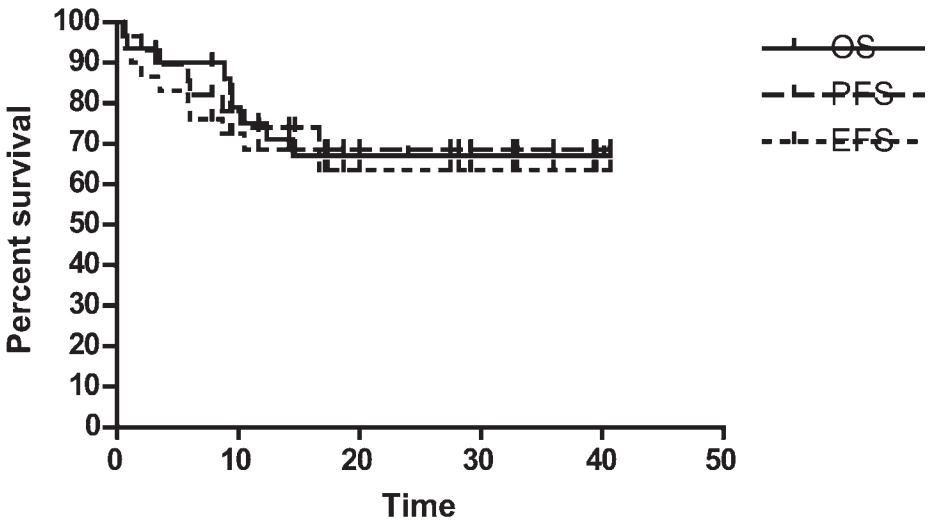

Figure 3. Patient survival time (months) in response to treatment with combined methotrexate-based chemotherapy with rituximab and reduced-dose whole-brain radiotherapy for newly diagnosed primary central nervous system lymphoma at Memorial Sloan-Kettering Cancer Center [9]. OS indicates overall survival; PFS, progression-free survival; EFS, event-free survival. Reprinted with permission.

giving rituximab on day 1 and methotrexate on day 2. In addition, patients who achieved only a partial response after 5 cycles are given extra cycles, going up to 7 cycles to try to get patients into complete remission. For patients who go into complete remission, the radiation dose is cut in half. At the time of our first report of this study [9], 30 patients were enrolled, with an average age of 57 years and average follow-up time of 22 months. The response rate was 92%, which is very encouraging. We also performed detailed prospective neurocognitive testing [10] and have not seen any cognitive decline. Survival curves are shown in Figure 3. One 81-year-old patient continues to do well after 3 years of follow-up, but clearly more follow-up is needed.

Summary of Current Treatment Recommendations

On the basis of current data, some specific treatment recommendations can be suggested. In administering methotrexate, a high dose of 8 g/m^2 has not been shown to be more effective, so patients who cannot tolerate such an increased dose are not at a disadvantage. Trends seem to indicate that combination therapy is slightly better than single-agent methotrexate, and the data indicate that intrathecal therapy is not necessary, particularly in patients without cytologic involvement of their CSF at diagnosis.

In administering radiotherapy, it is probably reasonable to defer whole-brain radiation, particularly in older patients. The data are much less clear in younger patients, who may in some cases be cured with a combination of methotrexate and whole-brain radiation. A difficult question is where to draw the cutoff point at which patients are considered too old for the most aggressive therapies. If that age is determined to be 60 years, what do you do with your 58-year-old patients or your really healthy 65-year-old patient with no comorbidities who may have a very healthy brain? It's hard to say. Focal radiation does not seem to be the answer in any of these patients. Despite our encouraging results at Memorial Sloan-Kettering, half-dose radiation cannot be considered safe because of worrisome data from the Barcelona-Nottingham group indicating that some of their patients were relapsing early. In our ongoing study at Memorial Sloan-Kettering we have doubled our sample size and will be reanalyzing our data in the near future.

CONCLUSIONS

A number of recent reports suggest that we have made real progress with CNS lymphoma, but overall in the last 15 years we have not achieved a clear improvement in patient survival. The optimal approach to treating primary CNS lymphoma is not well defined, and many questions remain unanswered. Thus it is vitally important that clinicians enroll their patients in clinical trials, and we investigators must keep working hard to come up with new treatment strategies for these patients.

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6.	A	B	C			
7.	A	B	C	D		
8.	A	B	C	D		
9.	A	B	C	D		
10.	A	B	C			
11.	A	B	C			
12.	A	B	C			
13.	A	B	C	D	E	F
14.	A	B				
15.	A	B	C			

POST-TEST FOR CME

Thank you for participating in this CME activity. There are no fees for participating and receiving CME credit for this activity. During the period April 2009 through April 2010 participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test by recording the best answer to each question in the answer key on the back of the evaluation form; 4) complete the evaluation form; and 5) mail or fax the evaluation form with answer key to Global Eduction Group.

1. Which of the following markers would distinguish peripheral T-cell lymphoma from a precursor (thymic) lymphoblastic lymphoma?
   A. CD3
   B. CD2
   C. TdT
   D. CD20
   E. ALK

2. In general, which of the following is the best prognosis?
   A. Primary cutaneous $CD30^+$ lymphoma
   B. Anaplastic large cell lymphoma, ALK positive
   C. Peripheral T-cell lymphoma, not otherwise specified
   D. Anaplastic large cell lymphoma, ALK negative
   E. $CD30^+$ transformed mycosis fungoides

3. Which of the following pathologic features is not associated with angioimmunoblastic T-cell lymphoma?
   A. Arborizing vasuclarity
   B. CD30 expression
   C. Expanded $CD21^+$ follicular dendritic cells
   D. CD10 expression
   E. CXCL13 expression

4. A 42-year-old man sees you with stage III peripheral T-cell lymphoma, unspecified. Your treatment choice would be:
   A. CHOP
   B. CHOP + denileukin diftitox
   C. CHOP followed by an autologous stem cell transplantation program
   D. Pralatrexate

5. A 42-year-old man sees you with stage III peripheral ALK+ anaplastic large cell lymphoma. Your treatment choice would be:
   A. CHOP
   B. CHOP + denileukin diftitox
   C. CHOP and then an autologous stem cell transplantation program
   D. Pralatrexate

6. The high activity of pralatrexate is thought to be due to:
   A. High affinity for the reduced folate carrier protein-1
   B. High affinity for folate polyglutamate synthetase
   C. A and B

7. Which of the following is NOT true regarding cutaneous T-cell lymphomas (CTCLs)?
   A. Mycosis fungoides/Sézary syndrome lymphomas are the most common CTCLs
   B. Most cases of CTCL have a grim prognosis with 5-year survival rates of only 24%
   C. Palliative treatments may be very effective, but allogeneic transplantation may be the only curative therapy for patients with advanced disease
   D. None of the above (all are true)

8. Which of the following statements are true regarding disease presentation and manifestations in mycosis fungoides/Sézary syndrome?
   A. At the time of disease presentation most patients (42%) have patches or plaques covering >40% of the body surface
   B. Affected tissues show no characteristic histology
   C. These diseases carry significant cosmetic consequences and effects on quality of life in addition to the risk of fatality
   D. All of the above

9. Which of the following statements are true regarding treatment of mycosis fungoides/Sézary syndrome?
   A. An important National Cancer Institute trial showed similar outcomes for very aggressive chemotherapy and total skin electron beam radiation therapy or sequential topical chemotherapy, thus supporting a treatment strategy that controls the disease and provide palliation without delivering significant toxicity
   B. Response to Denileukin diftitox, used mainly for patients with more advanced disease can be dramatic, but unfortunately it is often short-lived
   C. Promising new treatment agents include the histone deacetylase inhibitors panobinostat (LBH589) and romidepsin and the novel targeted antifolate pralatrexate
   D. All of the above

10. Is there a real survival difference among the different therapeutic approaches in patients with stage IE gastric MALT lymphoma?
    A. No
    B. Yes
    C. Only in particular subsets of therapeutical approaches

11. Are endoscopic and histological remission following antibiotics sufficient to consider the patient “cured”?
    A. Yes
    B. No
    C. Yes, if you use PCR assay

12. Is there a role for maintenance treatment after antibiotics therapy?
    A. Yes, rituximab
    B. Yes, interferon
    C. No

13. Which of the following tests should be done to evaluate the extent of disease in a patient diagnosed with brain lymphoma?
    A. MRI brain with gadolinium
    B. CSF cytology
    C. Detailed ophthalmologic examination
    D. Bone marrow biopsy
    E. Body CT scan
    F. All of the above

14. True or false: Methotrexate administered at a dose of 8 g/m^2 is associated with a higher radiographic response rate than lower doses (1-3.5 g/m^2).
    A. True
    B. False

15. Which of the following statements about the use of intrathecal methotrexate in patients with primary CNS lymphoma is true?
    A. All patients with PCNSL should receive intrathecal methotrexate
    B. Intrathecal methotrexate does not contribute to improved survival in PCNSL
    C. Intrathecal methotrexate may contribute to treatment-related neurotoxicity in PCNSL survivors

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