Abstract: Historical advances in the care of patients with non-Hodgkin lymphoma (NHL) have been restricted largely to patients with B-cell lymphoma. The peripheral T-cell lymphomas (PTCLs), which are rare and heterogeneous in nature, have yet to experience the same degree of improvement in outcome over the past 20 to 30 years. It is estimated that there are approximately 80,000 and 14,000 cases, respectively, of NHL and Hodgkin lymphoma per year in the United States. As a subgroup of NHL, the PTCLs account for 6% to 10% of all cases of NHL, making them exceedingly rare. In addition, the World Health Organization 2017 classification describes 29 distinct subtypes of PTCL. This intrinsic diversity, coupled with its rarity, has stymied progress in the disease. In addition, most subtypes carry an inferior prognosis compared with their B-cell counterparts, an outcome largely attributed to the fact that most treatment paradigms for patients with PTCL have been derived from B-cell neoplasms, a radically different disease. In fact, the first drug ever approved for patients with PTCL was approved only a decade ago. The plethora of recent drug approvals in PTCL, coupled with a deeper understanding of the molecular pathogenesis of the disease, has stimulated the field to pursue new avenues of research that are now largely predicated on the development of novel, targeted small molecules, which include a host of epigenetic modifiers and biologics. There is an expectation these advances may begin to favorably challenge the chemotherapy paradigms that have been used in the T-cell malignancies. CA Cancer J Clin 2020;70:47-70. © 2019 American Cancer Society.

Keywords: management, novel treatment, peripheral T-cell lymphoma, standard therapy

General Overview
Historical advances in the care of patients with non-Hodgkin lymphoma (NHL) have been restricted largely to patients with B-cell lymphoma and Hodgkin lymphoma (HL). Compared with B-cell lymphomas, the peripheral T-cell lymphomas (PTCLs), which are rare and heterogeneous in nature, have yet to experience the same degree of improvement in outcome over the past 20 to 30 years. It is estimated that there are approximately 80,000 and 14,000 cases of NHL and HL, respectively, per year in the United States. As a subgroup of NHL, the PTCLs account for ony approximately 6% to 10% of all cases of NHL, making them exceedingly rare. In addition, the World Health Organization (WHO) 2017 revision describes 29 distinct subtypes of PTCL. The 2 most common forms of PTCL, PTCL-not otherwise specified (PTCL-NOS) and angioimmunoblastic T-cell lymphoma (AITL), have an incidence of only 2500 and 1800 cases per year, respectively, in the United States. This intrinsic diversity, coupled with its rarity, has stymied progress in the disease. In addition, most subtypes carry an inferior prognosis compared with their B-cell counterparts, an outcome largely attributed to the fact that few or no therapies have ever been developed exclusively for the disease. Most treatment paradigms for patients with PTCL have been derived from therapies that were developed for non-Hodgkin B-cell neoplasms, a radically different disease. In fact, the first drug ever approved for patients with PTCL was approved only a decade ago.
The plethora of recent drug approvals in PTCL, coupled with a deeper understanding of the molecular pathogenesis of the disease, has stimulated the field to pursue new avenues of research, ones that are now largely predicated on the development of novel, targeted small molecules, which include a host of epigenetic modifiers and biologics. Although it is early, there is an expectation these advances may begin to favorably challenge the chemotherapy paradigms developed in B-cell neoplasms that have been used in the T-cell malignancies.

Biological and Epidemiological Considerations
Understanding the Cell of Origin
Understanding the cell of origin is critical to appreciating the biological and clinical differences between neoplastic diseases. In the case of the PTCLs, the cell of origin is complex and poorly understood. In theory, the diversity of different types of normal T lymphocytes found in the immune system forms the basis for the intrinsic heterogeneity of diseases we categorize as PTCL. These cells, born in the bone marrow, undergo T-cell receptor (TCR) gene rearrangement in the thymus and eventually emerge as mature T lymphocytes. The diversity of PTCL can be attributed in part to the enormous repertoire of normal T cells, which can be divided into many subtypes of cells, including, but not necessarily restricted to, the following: T-helper (Th) cells, natural killer (NK) cells, suppressor T cells, cytotoxic T cells, memory T cells, regulatory T cells (Tregs), and γδ T cells. Each of these cells secretes a different spectrum of cytokines that play a role in signaling other cells in the immune system. In addition, select subsets of these cells, such as the CD4-positive Th cells, for example, can be further subdivided into discrete CD4-positive Th cells with their own unique phenotypes, including Th1, Th2, and Th17 cells, for example. Figure 1 provides a schematic representation of select types of PTCLs and their theoretical origins from their normal T-lymphocyte counterparts. Although a detailed map of these relationships has yet to be fully configured for each of the 29 PTCL subtypes, a deeper understanding of these relationships will surely evolve in the years to come.

Classification of the PTCLs
The most recent WHO 2016 Classification of Tumors of Hematopoietic and Lymphoid Tissues now recognizes 29 discrete types of PTCL (Fig. 2). Broadly speaking, these diseases typically are divided into 1 of 4 categories, including: 1) disseminated or leukemic disease; 2) nodal disease; 3) extranodal disease; and 4) cutaneous disease. Whereas the malignant disorders classified within these 4 categories have been referred to historically as the “peripheral” T-cell lymphomas (TCLs), the more modern classifications now refer to them as the “mature” T-cell neoplasms (MTCLs), a designation that reflects the fact that these cells have undergone TCR gene rearrangement in the thymus. In this report, we refer to this group of T-cell malignancies as MTCLs. This revision in nomenclature is also intended to avoid confusion with the most common subtype of PTCL, namely, PTCL-NOS. For the most part, the MTCLs are considered aggressive diseases, although several may have a more indolent course. The cutaneous TCLs (CTCLs), for example (including mycosis fungoides; primary cutaneous anaplastic large-cell
lymphoma (ALCL); primary cutaneous, acral, CD8-positive TCL; and lymphomatoid papulosis), are all considered indolent. Treatment recommendations for these entities are often tailored for the discrete entity and are not typically predicated on chemotherapy in the earliest stages. The remaining MTCLs are all considered aggressive diseases, usually require multiagent chemotherapy, and sometimes require stem cell transplantation (SCT). These aggressive MTCL entities are the major focus of the current review.

The 2016 classification of the MTCLs has created several provisional subtypes of the disease based on an improved understanding of the cell of origin. These largely revolve around the nodal MTCLs. This revised classification creates an umbrella category called nodal TCLs with T-follicular helper (TFH) phenotype.1,2 Diagnosis of these entities requires expression of at least 2 or 3 TFH-related antigens, including CD279/PD-1, CD10, Bcl6, CXCL13, ICOS, SAP, and CCR5. Under this category now fallAITLs and 2 other provisional entities, including TFH lymphoma and nodal TCL with TFH phenotype.1 These latter 2 subtypes were historically placed under PTCL-NOS, which is recognized as a wastebasket diagnosis for those subtypes that do not meet the precise criteria for other MTCL entities. AITL, the second most common form of MTCL, is widely considered aggressive and can be complicated by Epstein-Barr virus (EBV) infection and the co-development of EBV-driven diffuse large B-cell lymphoma. As discussed below, the entities under the TFH phenotypes share several recurring mutations.

The other subtype with some changes include the ALCLs, which represent a unique group of MTCLs that may carry a more favorable prognosis and are now subdivided into 4 distinct subtypes. The ALCLs are characterized by sheets of CD30-positive T lymphocytes. CD30 expression is central to the pathologic diagnosis of ALCL. Although it is not pathognomonic, it is a mandatory feature for the diagnosis. The clinical presentation and behavior of these neoplasms often are very different compared with the other MTCLs. The systemic ALCLs (sALCLs) are usually aggressive nodal diseases, which are further subdivided based on whether they carry the nucleophosmin (NPM)-ALK (anaplastic lymphoma kinase) translocation between chromosomes 2 and 5, designated as t(2;5), into ALK-positive and ALK-negative diseases. Whereas other partners with ALK have been described,3,4 some of which may be associated with a less favorable prognoses, the NPM-1–ALK t(2;5) accounts for approximately 75% of all cases. Those ALCLs that do not carry an ALK translocation are a heterogeneous group that includes systemic ALCL, ALCL with ALK+ and ALK–, and hydroa-vacciniforme-like ALCL.

### Figure 2: Classification of the Mature T-Cell Lymphomas Based on the World Health Organization 2016 Classification of Tumors of Hematopoietic and Lymphoid Tissues.

- **Nodal**
  - PTCL-NOS
  - AITL
- **Extranodal**
  - ENKTL, nasal
  - EATL
  - MEITL
  - Indolent T-cell LPD of GI tract
  - Hepatosplenic TCL
  - Breast-implant ALC
  - Chronic LPD of NK cells
- **Cutaneous**
  - MF
  - Sezary Syndrome
  - Subcutaneous panniculitis-like TCL
  - Primary cutaneous CD30+ LPD
  - Lymphomatoid papulosis
  - Primary cutaneous ALC
  - Primary cutaneous γδ TCL
  - Primary cutaneous CD8+ aggressive epidermotropic cytotoxic TCL
  - Primary cutaneous CD4+ TCL
- **Leukemic**
  - HTLV-1 Adult T-cell Leukemia/Lymphoma
  - T-Prolymphocytic Leukemia
  - T-Cell Large Granular Lymphocytes (LGL)
  - Aggressive NK cell Leukemia
referred to as ALK-negative ALCL. This entity has been recently upgraded from a provisional to a definite entity in the 2016 classification. Although the ALK-positive variants are more common in the pediatric population, both are seen in adults, accounting for approximately 1000 cases per year in the United States. The sALCLs are considered highly aggressive diseases, with the ALK-positive variant exhibiting the best prognosis of all the aggressive MTCL subtypes, being curable in nearly 80% of patients, whereas the ALK-negative variants are considered curable in <50% of patients. Although the ALK-negative ALCL variant exhibits a prognosis inferior to that of the ALK-positive variant, it is likely marginally superior to the prognosis for other types of MTCL. Many believe that the ALK-negative variant behaves more like the poor prognostic MTCL than the more favorable ALK-positive ALCL. Recently, it was reported that recurrent chromosomal rearrangements, including DUSP22-IRF4 (on chromosome 6p25.3) and TP63, occurring in 30% and 8% of ALK-negative cases respectively, have an influence on prognosis.5 These genetic lesions are not found in ALK-positive cases. Although these 2 mutations are mutually exclusive, patients carrying the DUSP22 mutation can have a highly favorable prognosis, with an estimated 5-year survival rate of 90%. The DUSP22-IRF4 entity has been classified as a provisional entity in the latest classification. Conversely, those patients who carry the TP63 mutation or rearrangement have a very poor estimated 5-year survival rate of approximately 17%.5 In addition, it has been found that the JAK/STAT pathway is constitutively activated in ALK-negative ALCL and may be emerging as a commonly dysregulated pathway across a variety of MTCL subtypes, including large granular lymphocyte leukemias of both T-cell and NK cell origin, γδ-hepatosplenic TCL, and enteropathy-associated TCL (EATL).1,6-9

The cutaneous ALK-negative ALCLs (cALCLs) are often confused with the ALK-negative sALCLs. Discriminating between the 2 is essential because the cALCLs exhibit a more indolent course with a much more favorable prognosis. These diseases are treated more like CTCLs using skin-directed therapies first. The confusion between the cALCLs and the sALCLs is attributed in part to the fact that, compared with the B-cell lymphomas, the MTCLs more commonly involve the skin. Virtually every subtype of MTCL can involve the skin. The involvement of multiple anatomic compartments (skin, lymph nodes, extranodal sites, and blood) can confound an accurate diagnosis. Patients with cALCL are more likely to have disease that involves only the skin, although systemic disease can emerge in the natural history of the disease.

Breast implant–associated ALCL, a rare entity first described in the late 1990s, is associated with particular types of textured breast implants. These diseases are typically ALK negative, are exceptionally rare, and carry a 5-year overall survival (OS) rate of essentially 100%.10,11 This subtype recently has been classified as a provisional entity in the 2016 classification. Although unusual for a lymphoma, this entity is considered a surgical disease, requiring removal of the implant and a capsulectomy, which is curative, usually with little to no role for systemic chemotherapy.12 Discriminating among these 4 types of ALCL is important for the practicing clinician because each has its own unique biology, presentation, and treatment approach, and the potential to overtreat or undertreat these diseases is high.

Molecular Pathogenesis

Deciphering the molecular pathways leading to T-cell lymphomagenesis is a complex topic because of the intrinsic diversity of the disease. Given the clinical and biological heterogeneity associated with nearly 30 subtypes, it would be beyond the scope of this article to delve into the specific biologic features of each entity. Despite this, it is possible to identify some recurring themes in T-cell lymphomagenesis, themes that may lead to some unifying concepts regarding etiology and, possibly, targeted therapeutic intervention.

The first observation regarding the molecular pathogenesis of MTCL relates to the patterns of differential gene expression profiling (GEP). Recent GEP experiences have shown that these approaches can clearly discriminate between different entities, even closely related ones (for example, ALK-positive vs ALK-negative ALCL). Practically, GEP has been shown to improve classification, as approximately 35% to 40% of MTCL cases are misclassified by hematopathologists. For example, of 152 cases of PTCL-NOS, 14 cases and 11 cases were reclassified as AITL and ALCL, respectively. Of 117 cases of AITL, 22 were reclassified as PTCL-NOS.13 At this stage, although these rates of recategorization may seem high, they may not yet be adversely affecting outcomes, because the conventional treatments used for these entities in the frontline setting are not all that different. The one exception could be for ALK-positive ALCL, for which combined cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is potentially curative therapy. Although GEP data have begun to guide treatment considerations for germinal center versus nongerminial center diffuse large B-cell lymphoma and possibly mantle cell lymphoma, these experiences have yet to give rise to actionable proposals regarding the differential treatment for the MTCLs, nor have they provided any tangible insights on precision therapy thus far.

Although histology-specific molecular pathway analyses are yet to emerge for many subtypes of MTCL, the onerecurring theme observed across some (although certainly not all) subtypes of MTCL relates to its gross epigenetic dysregulation. The first clue into this biology actually emerged empirically from the clinic. As a disease,
the spectrum of MTCL exhibits consistent and reproducible sensitivity (overall response rate [ORR], approximately 25%) to histone deacetylase (HDAC) inhibitors. It is the only disease for which HDAC inhibitors are approved as a single agent, with 4 different HDAC inhibitors being approved around the world. Although only 25% of patients can expect a response to an HDAC inhibitor, the duration of response (DOR) to these drugs across the diversity of the MTCLs is impressive, usually lasting more than a year, as discussed in detail below.

The contribution of epigenetic dysregulation to the pathogenesis of MTCL is further supported by many lines of genetic data demonstrating several recurring mutations in genes governing a host of epigenetic functions, including DNMT3A, IDH2, TET2, MLL2, KMT2A, KDM6A, CREBBP, and EP300. Collectively, the data suggest that there may be “epigenetic vulnerabilities” that can be exploited in a rational therapeutic approach. Mutations in several genes involved in DNA methylation, namely, IDH2, TET2, and DNMT3, were reported in separate publications in 2012. These mutations, which appear to be more commonly found in AITL and PTCL with TFH phenotype, conspire to produce genome-wide hypermethylation and gene silencing of likely tumor-suppressor genes. These genetic events are most common in AITL, which is the second most common form of MTCL, carries a very poor prognosis, and is considered relatively chemotherapy-resistant.

Second most common form of MTCL, carries a very poor prognosis, and is considered relatively chemotherapy-resistant. The disease is considered highly aggressive and presents a universally poor prognosis, and is considered relatively chemotherapy-resistant. Although PTCL-NOS itself is widely considered highly heterogeneous, there is a subgroup of PTCL-NOS that is derived from Th follicular cells similar to AITL, in which TET2 mutations are more common and phenotypic markers are more similar to AITL. This entity, now recognized as a new subtype by the WHO 2016 classification, is called nodal PTCL with TFH phenotype (PTCL-TFH). Dysregulation of epigenetic biology, although far from being universal across all MTCL subtypes, points toward a possible common theme across the major subtypes of the disease, suggesting that therapeutic approaches targeting the MTCL epigenome could be a viable strategy.

Perhaps the most compelling line of evidence in support of an underlying driver function of an epigenetic gene in T-cell lymphomagenesis comes from genetically manipulated murine models. In addition to the TET2 mutations, mutations in RHOA are also common in MTCL, especially AITL, in which they occur in approximately 67% of cases, and PTCL-NOS, in which they occur in approximately 18% of cases. Although RHOA is not thought to have any epigenetic influence, it does belong to the Rhofamily of small GTPases, a group of Ras-like proteins involved in intracellular signaling. Gain-of-function mutations in RHOA (p.Gly19Val; RHOA G17V) are observed in 50% to 70% of AITL cases, compared with approximately 20% in PTCL-NOS cases, and has been associated with cell proliferation and invasiveness.

By using various experimental approaches, Palomero et al., Sakata et al., and Yoo et al. have demonstrated that TET2 deletions cooperate with RHOA G17V mutations in engineered mouse models to produce spontaneous AITL. In one example, Cortes et al. conducted bone marrow transduction transplantation experiments in which hematopoietic progenitors from Tet2 wild-type and Tet2 knockout mice were transduced with retroviruses expressing either 1) GFP alone; 2) wild-type RHOA plus GFP; or 3) RHOA G17V plus GFP, followed by injection into isogenic, irradiated recipients. Interestingly, the development of lymphomas with an AITL phenotype only emerged in the Tet2−/− RHOA G17V mice. These results formally establish a unique cooperativity between epigenetic drivers and other
common recurring mutations in MTCL that can lead to T-cell lymphomagenesis.

Although the genetic landscape described above, along with its influence on T-cell lymphomagenesis, is becoming more compelling with time, it still reflects a relatively poor understanding of molecular mechanisms, especially as a function of disease diversity. Clearly, the spectrum of mutations and genetic abnormalities found across the 29 distinct subtypes is broad, complex, and will evolve as we accumulate more data on different subtypes. We refer the reader to an excellent review on the topic.\textsuperscript{30}

**Epidemiology and Risk Factors**

The distribution of different subtypes of MTCL exhibit marked geographic variability. These diseases comprise a larger fraction of all NHL cases in Asia, the Caribbean, and Latin America, in part because of exposure to viral infections such as human T-lymphotropic virus type-1 (HTLV-1) and EBV. Although there are differences between subtypes, patients who have any subtype of MTCL, except for ALK-positive ALCL (carrying the 2:5 translocation), exhibit inferior OS compared with their counterparts who have B-cell lymphoma. Several recent studies have established that the incidence and prevalence of MTCL have not changed in any substantive way over the past decade.\textsuperscript{31-34}

On the basis of the most recent Surveillance, Epidemiology, and End Results data presented by Adams et al\textsuperscript{33} based on data from 18 Surveillance, Epidemiology, and End Results registries, 20,726 TCLs were diagnosed between the years 2000 and 2012. Patients with TCL were categorized using *International Classification of Diseases for Oncology, Third Edition* codes for the following entities: PTCL-NOS; ALCCL; AITL; EBV-extranodal NK/TCL, nasal type (EBV-ENKTL); human T-lymphotropic virus-1–associated adult T-cell leukemia/TCL (ATLL); and other MTCL. Other MTCL included CTCL-NOS, EATL, hepatosplenic TCL, primary cutaneous ALCCL, subcutaneous panniculitis-like TCL, T-cell large granular lymphocytic leukemia, and T-cell prolymphocytic leukemia. Patients diagnosed with mycosis fungoides/Sezary syndrome, precursor TCL, or TCL of unknown subtype were excluded (n = 7233) from these analyses. MTCL cases in patients who had a prior TCL also were excluded (n = 150).

The annual incident rate ratio of all MTCLs was 1.3673 per 100,000 persons among all races on average. The median survival time for any given patient with MTCL was 28.5 months among all races on average. Assuming that the survival time follows exponential distribution, if, after 1995, there are 100,000 nondisease (no MTCL) individuals each year, then there will be an estimated total of 30.08 new cases (ie, per 100,000 persons). Among the new cases, 24.69 individuals (approximately 80%) are expected to die before the end of 2016, with 5.30 still alive at the end of 2016. Hence the prevalence rate is estimated to be 5.30 per 100,000 persons. It is clear that the overall prevalence of T-cell NHL is well below the orphan-disease definition of <200,000 cases.

The etiologic basis for most forms of cancer is largely unknown, and the MTCLs are no different. Despite this, it is clear that several important factors are associated with a higher incidence of MTCL. The 3 well established risk factors predisposing to a higher risk of MTCL are: 1) EBV; 2) HTLV-1; and 3) celiac disease. Another risk factor, albeit an extraordinarily rare one, would include breast implants. Although this clearly is a risk factor, we refer the reader to excellent articles on the topic\textsuperscript{35} and focus on the 3 more common forms of MTCL associated with established risk factors. In all of these cases, these factors portend a higher risk of very specific types of MTCL—lymphomas that exhibit very specific geographic distributions.

**Epstein-Barr virus**

EBV is a ubiquitous \(\gamma\)-herpes virus that infects >90% of all adults worldwide.\textsuperscript{36} Although EBV primarily targets B cells and epithelial cells, there are several T-cell malignancies characterized by ectopic infection of EBV in NK or T lymphocytes. These include EBV-ENKTL, aggressive NK-cell leukemia, and the EBV-T/NK lymphoproliferative disorders. The latter entities include EBV-associated hemophagocytic lymphohistiocytosis, hydroa vacciniforme–like lymphoproliferative disease, and severe mosquito bite allergy, all of which are described in the WHO 2016 classification.\textsuperscript{37}

Extranodal NK/TCL is an aggressive MTCL associated with clonal episomal EBV infection of NK or T cells. Although it is uncommon in the Western hemisphere, it has a substantially greater incidence in Asia, excluding Japan.\textsuperscript{34} The disease commonly involves the nasopharynx (nasal type), although it can affect other anatomic sites, albeit less frequently (extranasal). Cooperating genetic and environmental factors are thought to influence disease pathogenesis. GEP of extranodal NK/TCL has revealed overexpression of cytotoxic proteins such as granzyme H and platelet-derived growth factor receptor \(\alpha\) (PDGFR\(\alpha\)).\textsuperscript{38,39} Several articles have implicated aberrant JAK-STAT signaling because mutations in JAK3 and STAT3 result in the constitutive activation, and thus tonic signaling, of proliferation pathways.\textsuperscript{40-42} These findings suggest a role for JAK-STAT\textsuperscript{*} signaling in the pathogenesis of ENKTL and perhaps a therapeutic role for JAK-STAT inhibitors in the disease. In addition, adoptive cell therapies targeting EBV viral proteins, such as those developed using tumor antigen-associated T cells primed against the EBV viral proteins in classic HL, have proven effective and safe in EBV-infected HL and represent a
unique opportunity to tailor treatment approaches to the biology of the ENKTL.

**HTLV-1–associated adult T-cell leukemia/TCL**

HTLV-1 is a retrovirus endemic in Japan (particularly Kyushu Island), Central Africa, Iran, and the Caribbean basin. The virus infects T cells and is transmitted through infected T cells present in body fluids, including breast milk, semen, and blood, from carriers of the HTLV-1 provirus. Infection by HTLV-1 produces clonal expansion and immortalization of CD4-positive T cells. Similar to EBV, disease pathogenesis involves both viral and host factors. Viral proteins encoded by the virus, including Tax and HBZ, are known to modulate numerous signal transduction pathways, including NF-kB, JAK-STAT, mTOR-AKT, and CREB/ATF, co-opting normal cellular growth-control mechanisms. This leads to deregulated cytokine production and impairment of host immunity, which allows the survival of HTLV-1–infected lymphocytes. Clinically, HTLV-1 adult T-cell leukemia/TCL consists of 4 distinct entities, including leukemic, lymphomatous, smoldering, and chronic variants. These variants of ATLL also have widely differing clinical behavior, some more aggressive (leukemic and lymphomatous) and others more indolent (chronic and smoldering)—pathologic features that will influence treatment decisions. Genetic studies have demonstrated that these entities have unique chromosomal differences, which may account for their widely varying clinical course. GEP has revealed that the HTLV-1 virus leads to dysregulation of important oncogenic drivers such as the MYC, REL-1, and NOTCH-1 genes, all of which are known to be upregulated by the Tax protein. Interestingly, those cases exhibiting C-REL and IRF-4 overexpression have been associated with resistance to antiviral agents. Whole transcriptome analyses have shown somatic gain-of-function CCR4 mutations in 26% of ATLLs, leading to enhanced activation of the PI3K/AKT pathway. Hyperactivity of PI3K secondary to the inhibition of protein phosphatases is known to play an important role in ATLL pathogenesis and has been linked to the formation of the characteristic multilobulated, “flower-like” nuclei in tumor cells. CCR4 is a chemokine receptor predominantly expressed by Th2 and Treg cells. Its ligands, CCL17 (TARC) and CCL22 (MDC), promote T-cell migration to extranodal sites, including the skin. This biology is targeted by mogamulizumab, which depletes CCR4-expressing cells through an antibody-dependent and cell-mediated cytotoxicity. Mogamulizumab was first approved in Japan in 2012 for patients with relapsed or refractory (R/R), CCR4-positive ATLL and, in 2014, for patients with CCR4-positive MTCL and CTCL. The drug was approved in 2018 in the United States for patients with relapsed mycosis fungoides and Sezary syndrome who have failed one prior therapy. The story is a testament to understanding how biology influences disease behavior, then using that information to transform care through novel experimental drug development.

**Celiac disease and EATL**

Celiac disease is a major risk factor for EATL. The 2008 WHO Classification of Hematopoietic Malignancies recognized 2 types of EATL, referred to as EATL type I and EATL type II, in which the type I entity was associated with celiac disease. In the recent 2016 WHO classification, these entities have been revised to make each of these diseases their own entity. EATL now represents the disease related to celiac disease, and a new term, monomorphic epithelioid intestinal TCL (MEITL), represents what was formerly termed EATL type II. EATL is approximately 5 to 10 times more common than MEITL.

The cell of origin for EATL is the intraepithelial lymphocyte (IEL). These cells themselves constitute a heterogeneous group of T lymphocytes residing in the mucosal epithelium of the bronchi, reproductive organs, and gastrointestinal tract. In patients with celiac disease, the IELs modulate immunologic reactions to dietary gluten (a group of proteins found in certain grain products such as wheat, barley, and rye) by inducing inflammatory responses that can damage the mucosal epithelium, which leads to malabsorption of nutrients. In addition, gluten, like any other antigen, induces the proliferation of IELs, collectively producing an environment conducive to malignant transformation of the IELs that has more oxidative stress. Refractory celiac disease (RCD), especially RCD type II (defined by the presence of an abnormal clonal IEL phenotype, whereas RCD type I has no evidence of an abnormal or clonal lymphocyte), is considered a precursor lesion for EATL (formerly type I). On the basis of this biology, celiac disease is recognized as an autoimmune disorder that typically affects the small intestine. Although the genetic basis of the disease is too complex to share herein, the majority of patients with celiac disease are known to have a particular major histocompatibility complex class II antigen-presenting receptor, which includes 1 of 2 types of the HLA-DQ protein, namely, HLA-DQa1 and HLA-DQb1. The incidence of EATL tracks with the incidence of celiac disease and is known to vary widely, depending on the prevalence of the genetic risk factor HLA-DQ. Historically, the prevalence rate was reported to be high in Europeans, with 1% of the European population having the disease. More recent epidemiologic studies have shown that, based on strict biopsy definitions of the disease, the prevalence was 0.4% in South American, 0.5% in North American, 0.6% in Asian, and 0.8% in European populations. Countries such as Argentina, Egypt, Hungry, Finland, New Zealand, and Sweden had a pooled prevalence ranging from 0.9% to 2.4%. The worldwide prevalence is estimated to be approximately 1.4%.
These 3 examples underscore the broad and complex factors related to a higher than average risk of MTCL in select populations. Breast implant anaplastic TCL represents yet another, albeit very rare example. This entity is gradually disappearing as our understanding of the relationship of disease to the type of implant evolves. New implants do not appear to carry the same risk of ALCL.11,30 In these patients, controlling the risk factor, such as exposure to HTLV-1, the type of breast implant, and dietary gluten, represent scientifically proven approaches to lower the risk of the TCL. Clearly, from a public health perspective, understanding these associated risk factors and modulating them appropriately represents the best approach to preventing or even managing the disease.

**Clinical Management**

**Prognostic Models**

Lymphomas of the T-cell lineage have been shown to be an independent negative prognostic factor,54 because the majority of MTCLs are associated with a very poor prognosis compared with their B-cell counterparts.34 The adverse prognosis of a patient with R/R MTCL has been highlighted in a recent experience from the British Columbia Cancer Agency, as described in more detail below. These data established that the inferior outcomes of patients with R/R T-cell malignancies are only marginally improved for those who receive subsequent chemotherapy.55 This experience clearly underscores the poor performance of conventional treatment regimens in these diseases and suggests that relapse alone is a profoundly adverse prognostic feature, which is in contradistinction to the B-cell lymphomas, in which relapsed patients can still be cured. Prognostic models, including the International Prognostic Index (IPI), which is based on age, performance status, lactate dehydrogenase, stage, and extranodal involvement, that were developed for aggressive B-cell NHL are efficient as a prognostic index for many MTCL subtypes.56 However, even patients in the best risk categories (IPI 0 or 1) still exhibit a highly unfavorable outcome, and patients in the high-risk categories experience a very short survival. The curves seen for patients with TCL essentially identify 2 risk categories, those with an IPI of 0 or 1, who have a comparatively more favorable outcome, and those with an IPI ≥2, who have an unfavorable outcome. Compared with what is observed in patients with B-cell lymphoma, there is limited separation of the curves. When analyzed as a function of the histopathologic subset, the 5-year OS rates for patients with PTCL-NOS and AITL who had an IPI of 0 or 1 were only 56% and 50%, respectively, whereas, for those who had an IPI of 4 or 5, the rates were 11% and 25%, respectively. These data raise important questions about just how favorable “favorable-risk” MTCL remains. Among patients with ALCL, a subset recognized for its more favorable outcomes, the 5-year survival rates for those with an IPI of 0 or 1 are roughly 90% and 74% for ALK-positive and ALK-negative patients, respectively. Patients with an IPI ≥2 exhibit a worse outcome, with 5-year survival rates of only 33% and 13% in the ALK-positive and ALK-negative populations, respectively.

These data confirm that the IPI is an important predictor in ALK-positive ALCL. The IPI has been less useful in stratifying patients with other subtypes of MTCL, including those with ATLL, EATL, hepatosplenic TCL, and extranasal NK/TCL. Recognizing the biologic and clinical heterogeneity of MTCL, some efforts have begun to develop subtype-specific prognostic models. Although discussing the details of each prognostic model goes beyond the scope of this review,57-59 these approaches do suggest that lumping all T-cell malignancies into one prognostic model may not be a useful way to understand good-risk and poor-risk patients within any given histology. Other prognostic models have been developed specifically for patients with MTCL. The Prognostic Index for PTCL (PIT) was developed based on risk factors that include age, lactate dehydrogenase, performance status, and bone marrow involvement.60 When applied to a PTCL-NOS population, the PIT stratified patients into more distinct prognostic groups compared with the IPI. Of 322 patients studied, 20% had no adverse features, 34% had 1, and 20% had 3 or more. The 5-year OS for the most favorable subgroup with no adverse prognostic features was 62% compared with 18% for patients with 3 or 4 adverse prognostic factors. Despite improved stratification, the so-called “favorable-risk” population of patients with MTCL still had a strikingly poor outcome.

Recently, the International Peripheral Lymphoma Study (IPLS) demonstrated that the 5-year OS rate of 340 patients with PTCL-NOS was only 32% (after 3 years of follow-up), whereas the 5-year failure-free survival (FFS) rate was only 20%.61 In that analysis, each prognostic factor in the IPI was a highly significant predictor of OS and FFS (P < .001). The overall IPI was predictive of both OS and FFS, whereas the PIT was predictive only of survival. The PIT did not prove to be superior to the IPI in predicting the survival of patients with PTCL-NOS. The IPLS evaluated other potential predictive factors by univariate analysis, establishing the following factors as adverse prognostic factors for OS and FFS, respectively: B symptoms (OS, P = .004; FFS, P = .014), bulky disease ≥10 cm (OS, P = .005; FFS, P = .004), elevated serum C-reactive protein level (OS, P = .018; FFS, P = .008), circulating tumor cells (OS, P < .001; FFS, P < .001), and a platelet count <150 × 10⁹/L (OS, P < .001; FFS, P < .001).61 For unclear reasons, hyper-γ-globulinemia fell out as a favorable prognostic factor for OS (P = .04) and FFS (P = .03). When the data were analyzed in a multivariate analysis, after controlling for IPI, only bulky disease ≥10 cm was still predictive of survival, with a hazard ratio (HR) of 2.1 for OS (P = .019) and 2.5 for FFS (P = .003), whereas a
platelet count <150 \times 10^9/L was predictive of FFS (HR, 1.6; \( P = .016 \)).

Overwhelmingly, the available prognostic models in MTCL have focused on clinical factors, with very few to none evaluating biological variables. The IPLS has explored the impact of several pathologic features associated with inferior OS and FFS, including a Ki-67 index >25%, the presence of transformed tumor cells >70%, significant numbers of EBV-positive B cells (Epstein-Barr–encoded RNA), and CD56 and CD30 expression >20% on the malignant cells. EBV positivity was predictive of an adverse survival only in patients aged <60 years and was independent of a history of immunosuppressive therapy or autoimmune disorders. Factors that appeared to be favorably associated with improved OS and FFS included lymphoepithelioid (also known as Lennert disease) variant and background CD8-positive T cells constituting >10% of the cell population.

Probably the most important prognostic factor for any subtype of MTCL is the presence or absence of ALK in ALCL. The OS of patients with ALK-positive ALCL is substantially better than that of patients with ALK-negative ALCL (71% ± 6% vs 15% ± 11%, respectively). However, within the good prognostic category of ALK-positive ALCL, survival was 94% ± 5% for the low-risk/low-intermediate-risk group (age-adjusted IPI, 0-1) and 41% ± 12% for the high-risk/high-intermediate-risk group (age-adjusted IPI, ≥2). Multivariate analysis identified ALK expression and the IPI as independent variables that were able to predict survival among T/null primary, systemic ALCL. Unfortunately, as discussed below, the lack of a perceived value from risk stratification in MTCL has led to a host of clinical studies that lack this detail, making it difficult to identify the merits of limitations of different treatment strategies.

Similar to what has been demonstrated in diffuse large B-cell lymphoma, EFS at 24 months has been shown to be prognostic among a diversity of MTCL subtypes. Among 775 patients, 64% had progressed in the first 24 months, exhibiting an OS of only 4.9 months, with only 11% remaining alive at 5 years. For those patients whose EFS exceeded 24 months, the OS was not reached, with 78% remaining alive at 5 years, although relapses did occur in 23% of these patients. Although these types of descriptive natural history analyses provide insight into the further heterogeneity of these diseases, future studies will need to understand prognostic factors, including EFS at 24 months, in the context of emerging biological factors if they are to translate into therapeutic advances.

**Frontline Management: Is There a Standard of Care?**

With a near absence of randomized clinical trials to drive treatment decisions in MTCL, physicians are forced to rely on the interpretation of available clinical data, novel pathophysiologic findings, and experience. In the case of MTCL, the bulk of this information needs to be extracted from small heterogeneous studies with no comparator arm. The lack of insights into the unique biology of MTCLs, their expanding heterogeneity, and a relative shortage of agents with specific T-cell activity have left the medical community directionless. More often than not, physicians are required to extrapolate from the principles and treatment regimen experiences successfully developed for aggressive B-cell lymphoma. CHOP and CHOP-like regimens have been widely accepted as the standard of care for patients with most subtypes of MTCL. On the basis of the National High Priority study in aggressive lymphoma, a large, randomized, phase 3 clinical trial of 899 patients with advanced-stage and/or high-grade NHL (including B-cell and T-cell histology), patients were randomized to 1 of 4 regimens, including CHOP or more dose-dense regimens, including combined methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, and prednisone plus bleomycin (MACOP-B); combined prednisone, doxorubicin, cyclophosphamide, and etoposide plus cytarabine, bleomycin, vincristine, methotrexate, and leucovorin (ProMACE-CytaBOM); or methotrexate with combined bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD). The study eligibility criteria were limited to patients with aggressive lymphoma, and the overwhelming majority had some form of aggressive diffuse large B-cell lymphoma. This study famously revealed no significant differences between the treatment regimens. The OS rate at 3 years was 52% (50% in the ProMACE-CytaBOM and MACOP-B groups, 52% in the m-BACOD group, and 54% in the CHOP group; \( P = .90 \)). There was no subgroup of patients in whom survival was improved by the more drug-intensive regimen. The conclusion of the study was that CHOP remained the best treatment for patients with advanced-stage/intermediate-grade and high-grade NHL, making it the standard of care. Although the number of patients with MTCL who were enrolled on the study remains unclear, CHOP still emerged as a standard of care for MTCL. It is reasonable to suggest that, if this regimen had been conducted exclusively in patients with MTCL, the findings might have been different. Would the methotrexate-containing regimens have produced superior outcomes? Not surprisingly, the use of CHOP has led to disappointing results in patients with TCLs. Analysis of the data as a function of the primary MTCL subtypes revealed that only patients who had ALCL carrying the t(2;5) translocation (NPM-ALK fusion protein) had an equivalent or superior outcome compared with those who had diffuse large B-cell lymphoma.

Subsequently, data from a retrospective study of the German High-Grade Non-Hodgkin Lymphoma Study Group in 343 patients suggested that the addition of
etoposide to CHOP in young and fit patients could improve outcome. A total of 289 patients had 1 of the following subtypes: ALCL, including both ALK-positive (n = 78) and ALK-negative (n = 113) disease; PTCL, unspecified (n = 70); and ATCL (n = 28). Treatment consisted of 6 to 8 courses of CHOP or etoposide plus CHOP (CHOEP). The 3-year EFS and OS rates were 75.8% and 89.8%, respectively (ALK-positive ALCL); 50.0% and 67.5%, respectively (AITL); 45.7% and 62.1%, respectively (ALK-negative ALCL); and 41.1% and 53.9%, respectively (PTCL, unspecified). For patients aged ≤ 60 years with lactate dehydrogenase levels less than or equal to the upper normal value, etoposide improved 3-year EFS (75.4% vs 51.0%; P = .003) across the entire study population. In patients aged > 60 years, 6 courses of CHOP administered every 3 weeks remained the standard therapy. The true benefit of using CHOEP in this patient population is still a subject of debate. In a similar retrospective analysis conducted by the Swedish Lymphoma Registry, for patients aged ≤ 60 years, treatment with CHOP compared with CHOP was associated with superior progression-free survival (PFS) (HR, 0.49; 95% CI, 0.29-0.83), but no difference in OS, among 252 patients with MTCL (excluding ALK-positive ALCL). Other intensive chemotherapy regimens, including DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) and HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone followed by methotrexate and cytarabine), have been studied in the disease and produced promising results in terms of response rate and PFS, although these came at the cost of increased treatment toxicity. These small, nonrandomized experiences still leave the field unclear about the optimal front-line treatment.

With the development of several novel agents that have found US Food and Drug Administration (FDA) approval in the relapsed and refractory setting, several clinical trials have explored their combination with standard CHOP in the front-line setting. One example includes the recently published ECHELON-2 clinical trial (A Comparison of Brentuximab Vedotin and CHP With Standard-of-Care CHOP in the Treatment of Patients With CD30-Positive Mature T-Cell Lymphoma;临床trials.gov identifier NCT01777152). This was the first randomized phase 3 trial conducted in the front line for patients with MTCL. The study required at least 10% expression of CD30 positivity to be eligible. In addition, the trial specifically required that > 70% of the patients enrolled had to have ALCL, including ALK-positive and ALK-negative entities (ie, diseases characterized by abundant expression of CD30, the target for brentuximab vedotin [Bv]). Patients were randomly assigned to either the Bv plus cyclophosphamide, doxorubicin, and prednisone (A+CHP) (the Bv arm) group or the CHOP group. The study was positive, demonstrating superiority for patients in the Bv-containing arm. After a median follow-up of 36 months (95% CI, 35.9-41.8 months), the median PFS in the A+CHP group was longer than that in the CHOP group (48.2 months [95% CI, 35.2 months to not evaluable] vs 20.8 months [95% CI, 12.7-47.6 months]). The 3-year PFS rate was 57.1% (95% CI, 49.9%-63.7%) for the A+CHP group compared with 44.4% (95% CI, 37.6%-50.9%) for the CHOP group. Adverse events, including the incidence and severity of febrile neutropenia (n = 41 patients [18%] in the A+CHP group and 33 patients [15%] in the CHOP group) and peripheral neuropathy (n = 117 patients [52%] in the A+CHP group and 124 patients [55%] in the CHOP group), were similar between groups. This study provided the basis for the approval of Bv in combination with chemotherapy for the treatment of CD30-positive MTCL in the front line. The FDA approved the regimen in patients irrespective of the degree of their CD30 staining. Although questions persist over the extrapolation of these data to a general MTCL population, it is important to point out that the trial was not powered to perform subgroup analysis based on histology. Irrespective of the nuances around the subtype eligibility, most now accept that, for any level of CD30-positive MTCL, the ECHELON-2 treatment is a recognized standard of care for patients with ALCL, although many experts continue to debate the standard of care in other MTCL subtypes. Multiple other studies exploring the addition of novel agents to the CHOP/CHOEP backbone have been studied, although they were associated with excessive toxicity, demonstrated no clear benefit, and have been studied only in small phase 1 and 2 noncomparative trials. These CHOP-plus strategies are gradually being challenged by encouraging data on novel: novel combinations, as detailed below.

The Role of Autologous SCT
Defining the role of autologous SCT (ASCT) among patients with MTCL is wrought with controversy because of limited data and heterogeneous populations. When discussing the role of bone marrow transplantation for patients with MTCL, there are several issues that need to be kept in mind: 1) currently, there are no randomized trials comparing the role of SCT versus conventional chemotherapy; 2) the majority of the studies are retrospective; and 3) many prospective studies of ASCT include very heterogeneous patient populations with regard to histology and status of disease (first-line treatment vs R/R disease), making interpretation of the data challenging at the very least. However, because of the very poor results obtained with conventional chemotherapy in patients with MTCL, many investigators have pursued intensive treatments, including high-dose chemotherapy followed by ASCT or allogeneic SCT (alloSCT) in both the frontline and the R/R setting. Currently, for eligible patients, high-dose chemotherapy followed by ASCT...
| AUTHOR, YEAR         | NO. OF PATIENTS | SUBTYPES OF LYMPHOMA | CONDITIONING REGIMEN | RESPONSE PRE-ASCT | SURVIVAL | MEDIAN FOLLOW-UP, MO |
|---------------------|-----------------|-----------------------|----------------------|-------------------|----------|---------------------|
| Gisselbrecht 200276 (P), histology-independent | 189; 84 with PTCL | 5% ALC, 19% non-ALCL | ACVBP/CEOP-ACVBP | 63% ≥PR | PFS, 39% at 5 y; OS, 46% at 5 y | 60 |
| Mounier 200477 (R)  | 28              | 56% PTCL-NOS, 44% precuror | BEAM/CBV | 100% CR | PFS, 44% at 5 y; OS, 54% at 5 y | 78 |
| Corradini 200678 (P) | 62              | 45% PTCL-NOS, 30% ALC | Mito/Mel/BEAM | 56% CR, 16% PR | PFS, 30% at 12 y; OS, 34% at 12 y | 76 |
| Rodriguez 200779 (R) | 26              | 42% PTCL-NOS, 31% ALC, 27% AITL | BEAM | 65% CR, 8% PR | PFS, 53% at 3 y; OS, 73% at 3 y | 35 |
| Mercadal 200880 (P) | 41              | 49% PTCL-NOS, 29% AITL, 5% HSTL, 5% NK/T | BEAM/BEAC | 49% CR, 10% PR | PFS, 30% at 4 y; OS, 39% at 4 y | 38 |
| Reim 200972 (P)    | 83              | 39% PTCL-NOS, 33%, AITL, 16% ALC | TBI-C | 47% CR, 24% PR | PFS, 36% at 3 y; OS, 48% at 3 y | 33 |
| Nickelsen 200981 (P) | 33              | 39% ALC, 33% PTCL-NOS, 12% AITL | Mega-CHOEP | 49% CR, 6% PR | PFS, 26% at 3 y; OS, 45% at 3 y | 53 |
| D’Amore 201271 (P) | 115             | 39% PTCL-NOS, 19% ALC, 19% AITL, 13% EATL, 4% panniculitis-like, 3% T/NK nasal type, 3% HSCT | BEAM/BEAC | 83% CR, 31% PR | PFS, 44% at 5 y; OS, 51% at 5 y | 60 |
| Park 201973 (P)    | 119 (36)        | 47% PTCL-NOS, 22% AITL, 31% ALK-negative ALC | BEAM | CR | OS at 2.8 y not reached |  |
| Shmitz 201985 (P)  | 103; 54 to ASCT |                       | BEAM | CR/PR/SD | EFS, 38% at 3 y; OS, 70% at 3 y | 42 |

Abbreviations: (P), prospective study; (R), retrospective study; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; AITL, angioimmunoblastic T-cell lymphoma; ALC, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ASCT, autologous stem cell transplantation; BEAC, carmustine, etoposide, cytarabine, and cyclophosphamide; BEAM, carmustine, etoposide, cytarabine, and melphalan; CBV, cyclophosphamide, carmustine, and etoposide; CEOP, cyclophosphamide, etoposide, vincristine, and prednisone; CR, complete response; EATL, enteropathy-associated T-cell lymphoma; EFS, event-free survival; HSCT, hematopoietic stem cell transplantation; HSTL, hepatosplenic T-cell lymphoma; Mega-CHOEP, high-dose cyclophosphamide, doxorubicin, vincristine, and prednisone plus etoposide; Mel, melphalan; Mito, mitoxantrone; NK/T, natural killer/T-cell lymphoma; NOs, not otherwise specified; OS, overall survival; PFS, progression-free survival; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease; TBI-C, total body irradiation plus cyclophosphamide.

*This was a prospective cohort study of the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment [COMPLETE] registry. Of the 119 patients reported, only 36 underwent transplantation in first remission.
represents the treatment of choice for those with relapsed, aggressive B-cell lymphomas, resulting in 40% to 50% long-term disease-free survival, as demonstrated by the pivotal PARMA study. The role of ASCT in MTCL remains far more controversial, although the practice of performing ASCT in first “remission” has been commonly accepted by many clinicians, despite conflicting data sets. Data in support of ASCT in first remission have been based on older, small, single-arm, phase 2 studies and some more recent, larger, randomized studies. D’Amore et al published one of the largest prospective studies of upfront ASCT, enrolling 160 patients with MTCL, excluding those with ALK-positive ALC. Approximately 63% of patients in that study achieved complete remission (CR), 37% achieved partial remission (PR), and both populations moved on to undergo ASCT. The 5-year OS and PFS rates for the intent-to-treat population were 51% and 44%, respectively. The subgroup analysis showed superior OS and PFS for patients who had ALK-negative ALC compared with those who had other subtypes. A second, large, prospective study published a few years before enrolled 83 patients who had MTCL, with the exclusion of those who had primary CTCL and ALK-positive ALC. In total, 59 patients (71%) completed mobilization after obtaining a complete response (66%) or a partial response (34%) to induction therapy, and 55 underwent ASCT. The 3-year OS rate was 48% for the intent-to-treat population. Collectively, these data have led some to suggest that consolidating CRs with an ASCT in first remission, usually complete, may be associated with superior outcomes. Failure to achieve a CR was associated with markedly inferior outcomes.

More recently, the COMPLETE registry (Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment) reported on a large, multi-institutional, prospective cohort directly comparing the survival outcomes of patients who had nodal MTCL with or without consolidative ASCT in first remission. All histologies of MTCL were included, with the exclusion of large granular lymphocyte leukemias of T-cell origin, precursor T/NK neoplasms, mycosis fungoides, Sézary syndrome, and primary cutaneous CD30-positive disorders. A total of 213 patients were identified as having achieved CR after frontline therapy, 119 of whom had a nodal MTCL, including PTCL-NOS, ALK-negative ALC, and AITL. Eighty-three of these patients did not undergo ASCT, whereas 36 underwent a consolidative ASCT in first remission. At 2.8 years of median follow-up, the median OS was 57.6 months (4.8 years) for the group without transplantation and was not reached for the transplantation group. The data suggested that ASCT was associated with superior survival in patients with advanced-stage disease or with intermediate-high IPI MTCL. These data revealed that ASCT produced a statistically significant improvement in survival only for patients with AITL, but not for patients with other MTCL subtypes.

The data seemed to be reminiscent of the findings published by the European Group for Blood and Marrow Transplantation, which demonstrated that, among 146 patients with AITL, those who underwent ASCT experienced a longer PFS (56% at 4 years) compared with those who had primary refractory disease (PFS, 23% at 4 years).

The first randomized prospective trial to explore the merits of front-line ASCT versus alloSCT in patients with MTCL was addressed by the AATT Study (Autologous or Allogeneic Transplantation in T-Cell Lymphoma). Patients were treated with CHO(E)P for 4 cycles and dexamethasone, high-dose cytarabine, and cisplatin (DHAP) for 1 cycle. A total of 103 patients were randomized to receive either upfront to ASCT or alloSCT. Thirty-six patients (35%) could not proceed to transplantation, mostly because of early disease progression. The 3-year EFS and OS rates did not differ significantly between alloSCT (EFS, 43%; OS, 57%) and ASCT (EFS, 38%; OS, 70%). Patterns of relapse were notably different. Among those who received alloSCT, 8 patients (31%) died of treatment-related mortality, although there were no relapses. In contrast, 13 patients relapsed (36%) after ASCT. The data suggested that, for younger patients with MTCL, ASCT remains the preferred consolidation, in particular because patients who relapse after ASCT have some probability of being successfully salvaged with alloSCT. Table 1 shares the published results of ASCT trials in MTCL both in first CR (CR1) and beyond CR1. In conclusion, it appears that ASCT has a role for patients with MTCL in CR1; patients with ALK-positive ALC also have a favorable outcome with conventional chemotherapy, allowing for the possibility of delaying this strategy until it can be delivered in a salvage setting. ASCT remains fundamentally relevant to improve the results of induction therapy in this disease and seems to be the main determinant of outcome in these patients.

All of these data regarding the role of ASCT in first remission need to be considered in light of an interesting study published by Abramson et al. In that retrospective study, patients who achieved CR after induction therapy were compared with those who attained CR with induction therapy followed by ASCT. Proactively, the curves demonstrated no advantage for those patients who underwent ASCT and suggested that achieving CR with induction therapy may be a favorable prognostic factor for patients with MTCL treated in the front line.

The Role of AlloSCT

The role of alloSCT has been investigated mostly through retrospective studies in patients with R/R MTCL. Most of the data on the role of alloSCT for MTCL are based on limited subtypes, including PTCL-NOS, AITL, and ALK-negative ALC. Prospective studies are available only for patients who underwent ASCT as part of first-line therapy.
and in whom the results of ASCT were compared with the results of alloSCT. In one such study,83 17 patients with R/R MTCL, including 8 who underwent prior ASCT, received salvage therapy with 4 to 6 cycles of DHAP followed by reduced-intensity alloSCT. After a median follow-up of 28 months, the estimated 3-year OS and PFS rates were 81% and 64%, respectively, and the transplantation-related mortality rate was 12%. Donor lymphocyte infusion induced a response in 2 patients with progressive disease, suggesting the existence of a graft-versus-lymphoma effect.83 Feyler et al84 reported on the experience of the British Society of Bone Marrow Transplantation and the Australian Recipient Registry and described the outcome of 82 patients with R/R MTCL who received ASCT (n = 64) or alloSCT (n = 18). After a median follow-up of 57 months, of the 18 patients who received a full-intensity alloSCT, 5 patients were alive, 5 died of progressive disease, and 8 died of nonrelapse mortality. The estimated 3-year OS, PFS, and relapse rates were 39%, 33%, and 28%, respectively. The use of full-intensity allogeneic transplantation was limited by high transplantation-related mortality.84

By using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, Smith et al85 reported on the outcome of 241 patients with ALCL, PTCL-NOS, and AITL who underwent ASCT (n = 115) or alloSCT (n = 126). ASCT was more likely to be performed in CR1 (35% vs 14%; \( P = .001 \)), in patients with chemosensitive disease (86% vs 60%; \( P < .04 \)), and in those who had received \( \leq 2 \) lines of prior therapy (65% vs 44%; \( P < .001 \)) compared with patients who underwent alloSCT. The 3-year PFS and OS rates of ASCT recipients beyond CR1 were 42% and 53%, respectively. Among allo-SCT recipients who received transplantation beyond CR1, 31% remained progression free at 3 years, despite being more heavily pretreated and having more refractory disease. Nonrelapse mortality was 3.5-fold higher (95% CI, 1.80-fold to 6.99-fold higher; \( P < .001 \)) for patients who underwent alloSCT. In a multivariate analysis, chemotherapy sensitivity and receipt of \( \leq 2 \) lines of pretransplantation therapy were prognostic of better survival. Zain et al86 reported a case series of 37 patients with peripheral T-cell NHL who underwent alloSCT from related and unrelated donors between the years 2000 and 2007. All patients were pretreated; the majority had either relapsed or progressive disease (n = 25; 68%), 13 had cutaneous histologies (CTCL), and all were ineligible for autologous transplantation. Fully ablative conditioning regimens were used in 13 patients, whereas 24 patients underwent reduced-intensity conditioning. At 5 years, the OS and PFS probabilities were 52.2% and 46.5%, respectively. At the time of analysis, 9 patients (24.3%) had either relapsed (n = 6) or progressed (n = 3) after alloSCT. The cumulative incidences of relapse/progression and nonrelapse mortality at 5 years were 24.3% and 28.9%, respectively.
No statistically significant variables for survival or relapse were discovered by univariate Cox regression analysis of disease and patient characteristics; differences between CTCL and other histologies were not significant. The median follow-up of 64.0 months (range, 16.4-100.4 months) indicates a mature data set with a probable cure in the survivors. The relapse/progression curves reached and maintained plateaus 1 year after transplantation, demonstrating that long-term disease control is possible after allogeneic hematopoietic cell transplantation in patients with PTCL who have advanced disease. Table 2 presents a brief summary of alloSCT studies in MTCL.

AlloSCT remains a therapeutic option for patients with R/R MTCL. The identification of the most appropriate timing, conditioning regimen, and donor type continues to be the object of research. Furthermore, the identification of specific patients with high-risk disease who could benefit from alloSCT in first remission needs to be further elucidated.

Managing the Relapsed or Refractory Patient
Management of the patient with R/R disease represents a substantial challenge, even for physicians with abundant experience. In general, the 2 strategies involve either: 1) conventional chemotherapy, in combination or as single agents; or 2) single-agent use of recently approved agents.

Patients with R/R disease carry a very poor prognosis. Mak et al provided one of the most comprehensive data sets on the subject. Through the British Columbia Cancer Agency registry, they sought to define the natural history of the disease in patients at first relapse. They identified 153 patients, most of whom had PTCL-NOS, but they also included patients with AITL and ALCL. The median time from initial diagnosis to relapse or progression of disease after primary therapy was 6.7 months. The median OS and PFS were 5.5 months and 3.1 months, respectively. These outcomes were only marginally better for patients who received chemotherapy. The median OS and PFS for these patients \((n = 89)\) were 6.5 months and 3.7 months, respectively. Although there may be a host of factors that influence any individual patient’s outcome, these data are a testament to the marginal benefit provided by traditional chemotherapy in this challenging setting. This raises important questions about the decision-making process and how to choose the best approach for any given patient. Traditional combination chemotherapy regimens will carry substantially more toxicity, will be time-limited in their administration (ie, for a fixed number of cycles), and will rarely produce meaningful durations of benefit. Single-agent therapy, conversely, can be administered safely for protracted periods of time, can allow patients to recover from the cumulative effects of sequential combination chemotherapy, and can produce protracted durations of benefit in some fraction of patients.

FDA-Approved Drugs Without an Indication in MTCL
The first question when deciding on an appropriate therapy is to determine whether the patients are candidates for some form of SCT, whether it is autologous or allogeneic. Although we discussed the available data on these approaches above, it is important to recognize the intrinsic and acquired drug-resistance features of these diseases when weighing the options.

First, it is essential to recognize that there is no standard of care for patients with R/R MTCL. Therefore, patients should be strongly encouraged to participate in clinical trials when appropriate. Currently, no single chemotherapy regimen has been shown to be clearly superior to any other, and the selection of treatment should be based on the goals of care, anticipated toxicities, patient comorbidities, and convenience. For most patients with R/R MTCL who are not candidates for SCT, palliative chemotherapy (single agent, lower toxicity, protracted duration of exposure) is usually the preference. Aside from the newer agents approved for patients with R/R MTCL mentioned below, there are several conventional chemotherapy agents that have produced some activity in the disease, although most of these data are based on very small numbers of patients.

The antimitabolite gemcitabine is one of the traditional chemotherapy drugs widely used in the treatment of MTCL both in the R/R settings. It has been shown that gemcitabine as a single agent is active in several small clinical trials, with an ORR of 51% \((20 \text{ of } 39 \text{ patients})\) and with complete partial response rates of 23% (9 of 39 patients) and 28% (11 of 39 patients), respectively. The proteasome inhibitor bortezomib has also shown activity in patients with MTCL. A small experience using bortezomib as a single agent showed that it was well tolerated and had activity in patients with MTCL and CTCL. Specifically, 15 patients were accrued, of whom 12 (10 with CTCL, all with mycosis fungoides, and 2 who had PTCL-NOS with isolated skin involvement) were assessable. The ORR was 67%, with 2 (17%) complete responses and 6 (50%) partial responses. The remaining 4 patients experienced disease progression. All responses were durable, lasting from 7 to ≥14 months. Overall, the drug was well tolerated, with no grade 4 toxicity. Several other agents have demonstrated activity with an acceptable toxicity profile when used in the R/R setting, including bendamustine, lenalidomide, and single-agent etoposide. Most of these experiences, however, are associated with limited data, are largely anecdotal, and generally have limited duration of benefit in the majority of patients. In our estimation, we recommend use of the FDA-approved agents because these studies have the most robust data in this setting, all are based on at least 100 patients, can be administered for extended periods of time safely, and have been shown to attain CR, enabling bridging approaches to SCT.
FDA-Approved Drugs With an Indication in MTCL

There is little question that one of the most promising new areas in MTCL research resides in the pace of new drug development. Over the past several years, 4 new drugs, all with relatively unique mechanisms of action, have been approved for the treatment of patients with R/R disease. These drugs, which now have substantial data demonstrating their marked single-agent activity, have created a unique opportunity to build non–CHOP-based platforms, as discussed below, where we review the merits and limitations of these new agents and how they are beginning to change the treatment paradigms for MTCL.

Pralatrexate

Pralatrexate was the first drug approved for patients with R/R MTCL in 2009. Pralatrexate is a novel antifolate that has been rationally designed to have increased affinity for the reduced folate carrier (RFC-1), allowing for better internalization of the drug into the cell.93 Pralatrexate is also a better substrate for polyglutamation by FPGS (folylpolyglutamyl synthetase), allowing for better cellular retention compared with other antifols, which collectively leads to more potent inhibition of the target enzyme dihydrofolate reductase (DHFR).94 Although much discussion around the activity of pralatrexate has focused on its pharmacology, it is clear that the drug exhibits several unique effects based on gene expression array analysis and the fact that leucovorin does not compromise its effect in preclinical or clinical experiences. This observation alone suggests that the lethal effect of the drug is not mediated by the inhibition of DHFR.

The early phase 1 and 2 results of pralatrexate reported by O’Connor et al demonstrated a striking predilection for activity in TCLs over B-cell and HLs. The ORR in the entire patient population was 31%, with 8 patients attaining a complete response. However, when broken down by lineage in B-cell lymphomas and TCLs, the ORR was 5% and 54%, respectively, and all 8 complete responses occurred among the patients with MTCL. In addition, these results produced highly durable DORs in excess of a year. These data gave rise to the pivotal PROPEL study (Pralatrexate in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma).

PROPEL was an international, single-arm, phase 2 study conducted in patients with aggressive MTCL subtypes and included patients with blastic NK/TCL, HTLV-1 ATLL, and transformed mycosis fungoides, which are particularly aggressive subtypes of MTCL. These aggressive entities were excluded from the registration-directed studies for romidepsin or belinostat. In addition, the PROPEL population remains the most heavily treated population ever studied in this setting, with a median of 3 prior therapies, and 20% of patients received >5 lines of prior treatment. As discussed below, the number of lines of prior therapy has an impact on outcome, with more heavily treated patients doing more poorly than those who are less heavily treated. PROPEL demonstrated an ORR of 29% with a CR/unconfirmed CR rate of 11%, with an updated PFS and DOR of 3.5 and 12.4 months, respectively. The PROPEL study led to accelerated FDA approval of pralatrexate for patients with R/R MTCL in 2009. The most frequent adverse events, regardless of causality, included fatigue (n = 86; 47%), nausea (n = 74; 41%), mucosal inflammation (n = 67; 37%), stomatitis (n = 66; 36%), and constipation (n = 65; 36%).97,98

To gain a better understanding of the drug’s performance in this setting, O’Connor et al conducted several analyses on the PROPEL data set. The first observation relates to an analysis of primary and secondary endpoints as a function of the line of therapy. These data demonstrated that, for patients who received ≥3 lines of prior therapy (N = 57), the ORR, complete response rate, PFS, and DOR were 29.8%, 7%, 1.7 months, and 8.2 months, respectively. For patients who received 2 lines of prior therapy, those same metrics were 24.1%, 10%, 3.2 months, and 10 months, respectively, whereas for patients who received only 1 line of prior therapy, the same metrics were 35%, 17%, 8 months, and not reached at 2 years, respectively. These data suggest that using pralatrexate earlier in the natural history of the disease may produce greater clinical benefit. Although randomized studies are the gold standard for determining OS benefit, single-arm studies, more often than not, are the only data regulatory agencies have to assess clinical benefit in orphan diseases. Given the paucity of patients, the time required to conduct these studies, and the cost, sponsors are often left trying to make decisions regarding the merits of randomized studies in orphan diseases, for which the commercial return on investment is substantially less that it is for other diseases. In an effort to understand the OS impact in PROPEL, a case–matched control analysis of the PROPEL data set was performed.99 An international database of 859 patients with MTCL was assembled from 4 institutions (Seoul, New York, Omaha, and Paris) that maintained well annotated registries of their respective patient populations. Approximately 386 of the original 850 patients were considered eligible for matching against the PROPEL criteria. By using a propensity score-matching algorithm and a 1:1 case match, 88 patients from PROPEL were matched against the historical control population. The analysis demonstrated an OS benefit for the PROPEL population, with a median OS of 4.07 versus 15.24 months (HR, 0.432). Highly statistically significant improvements in survival were noted for the PROPEL population with regard to all variables explored, including the subtype of MTCL (except ALCL, for which the curves were superimposable, suggesting equivalency) and age, in which age >65 years exhibited one of the most significant benefits.99 Although this was not a prospective randomized study, the analysis does provide another layer
of information about how to assess drug benefit in a more rigorous statistical setting, and it helps to inform critical decision making regarding clinical studies in MTCL.

Another path to learning more about drugs in rare diseases is to follow studies conducted by investigators in other countries as they seek to satisfy their own parochial regulatory requirements leading to approval. Maruyama et al\(^ {100} \) from Japan reported on 20 patients with R/R MTCL treated with pralatrexate, demonstrating an ORR, DOR, and PFS of 45%, 9.83 months, and 4.93 months, respectively. The median number of prior therapies was 2, which was lower than that reported in PROPEL. A similar study conducted by Chinese investigators in patients (n = 71) who also received 2 prior therapies reported an ORR, DOR, and PFS of 52%, 8.7 months, and 48 months, respectively. Most recently, a Taiwanese group reported on a study of patients (n = 21) with R/R MTCL after receiving only a single line of prior therapy and demonstrated an ORR, DOR, and PFS of 71%, 3.9 months, and 3.3 months, respectively, although that study had a short follow-up and is still ongoing. Collectively, these data seem to suggest that earlier use of pralatrexate may be associated with greater clinical benefit. Some of these studies have also been favorably affected by recent data suggesting that the use of leucovorin can substantially reduce one of the untoward toxicities of pralatrexate, namely, mucositis.

Although the dose of leucovorin and its schedule have varied between studies, doses of 15 mg orally twice daily on days 3 through 6 can substantially reduce the risk of mucositis.

The HDAC inhibitors: Romidepsin and belinostat

For reasons that are not entirely clear, the HDAC inhibitors exhibit a class effect in MTCL. It is the only disease for which these drugs are approved as single agents, now with 4 different HDAC inhibitors being approved for patients who have R/R TCL, including: vorinostat, which was approved in 2006 for R/R CTCL; romidepsin was approved in 2009 for R/R CTCL and in 2011 for R/R MTCL; belinostat was approved in 2015 for R/R MTCL; and chidamide, which was approved only in China in 2015 for R/R MTCL.

HDACs are enzymes that catalyze the removal of acetyl groups from the lysine residues of various proteins, including histones and transcription factors. Original thoughts regarding the mechanisms of action of these drugs evolved around effects on chromatin remodeling. Accumulation of acetylated histone H3 and H4 leads to an “open” chromatin structure, and thus transcriptional activation, whereas deacetylation of H3/H4 results in a “condensed” chromatin, leading to transcriptional repression. Although it is still believed that this mechanism is important, more recent evidence has focused on posttranslational modification of nonhistone proteins as an equally or more important impact of these drugs. At the biochemical and cellular levels, HDAC inhibitors are known to be pleiotropic drugs that work through a myriad of different mechanisms, including: 1) alteration in the expression of genes that regulate the cell cycle, including the upregulation of p21/p27 and the downregulation of cyclin D; 2) acetylation of nonhistone proteins, including STAT-3, RelA/p65/p53, HIF-1-α, and Hsp 90, in a way that may impair their function and influence cell growth and survival; and 3) direct activation of apoptotic pathways by affecting the balance between the antiapoptotic proteins such as BCL-2 and the proapoptotic proteins such as BAX and BAK.\(^ {103} \)

Although it has been difficult to assign any one or more of the above-listed mechanisms as the mechanism of action of HDAC inhibitors in TCL, many lines of evidence suggest they could be an important cornerstone in future MTCL treatment programs.

Romidepsin is a potent macrolide HDAC inhibitor isolated from Chromobacterium violaceum. In the original phase 2 study of romidepsin in patients with R/R PTCL conducted by the National Cancer Institute, the ORR was 38%, and the median DOR was 8.9 months.\(^ {104} \) In the pivotal registration-directed phase 2 study, the ORR was 25% (33 of 130 patients), with a median PFS of 4 months.\(^ {105} \) These data led to accelerated FDA approval of romidepsin in patients with R/R MTCL in 2011. The most common drug-related adverse events were similar to what have been seen with other agents in the class, including gastrointestinal symptoms (diarrhea, nausea, anorexia, weight decrease, vomiting, and constipation), constitutional symptoms (fatigue, chills), hematologic abnormalities (thrombocytopenia, anemia), and taste disorders (dysgeusia, dry mouth). These data gave rise to an international, open-label, pivotal, phase 2 study of romidepsin in patients with R/R MTCL who had received at least a single line of prior therapy. The median number of prior therapies was 2, with a range from 1 to 8. The ORR was 25%, which included CR in 15% (n = 19) of patients and a median DOR of 17 months. These data led to a conditional approval of romidepsin in patients with R/R MTCL by the FDA in June 2011.\(^ {105} \)

In 2014, belinostat became the third HDAC inhibitor approved for the treatment of patients with R/R MTCL. Belinostat is another hydroxamic-based pan-class I and II HDAC inhibitor similar to vorinostat and chidamide.\(^ {106} \) It is currently approved for patients with R/R MTCL who have received at least one line of prior therapy. The original phase 2 trial (study CLN-6) included patients with various subtypes of TCLs (n = 24) and reported an ORR of 25%.\(^ {107} \) This activity led to the BELIEF study (A Multicenter, Open Label Trial of Belinostat in Patients With Relapsed or Refractory T-Cell Lymphoma), in which 129 patients with R/R disease received belinostat. The median number of prior therapies was 2, and the study reported an ORR of 26% (complete
response rate, 11%; partial response rate, 15%), with a PFS, DOR, and OS of 1.6 months, 13.6 months, and 7.9 months, respectively. Overall, it was believed that this drug was less toxic than romidepsin although likely equally as active.

These data demonstrate remarkably similar benefits in patients with MTCL, raising the questions regarding whether it is the same 25% of patients who experience benefit and whether there is a predictive biomarker of HDAC inhibitor activity. In addition, it appears that this response rate does not change as a function of the patient’s prior therapy, further suggesting some predisposed vulnerability that does not share the same mechanisms of cross-resistance with conventional chemotherapy. These and other data suggest that the HDAC inhibitors do potently synergize with a host of drugs active in MTCL and may play a more significant role in combination.

**Brentuximab vedotin**

Monoclonal antibodies have emerged as potentially important new therapeutic agents in the treatment of many subtypes of NHL. Monoclonal antibodies are now being developed against a host of other cell surface proteins, including the chemokine receptor CCR4, and other surface proteins such as CD37, CD70, PD-1/PDL-1, and CD30. Bv is the best known and most successful of the biologic drugs developed in MTCL, targeting CD30. CD30 (also known as TNFRSF8) is a 120-kD transmembrane protein of the tumor necrosis factor family and a known tumor marker found on many kinds of lymphoma. The receptor is found on the surface of only activated T cells and some B cells. CD30 is found in virtually all patients with ALCL and in the majority of patients with HL, in which it is observed on the surface of the Reed-Sternberg cell. It is also expressed by several nonlymphoid malignancies, including embryonal carcinoma and some cases of non–small-cell lung cancer. Clinical trials with the naked chimeric anti-CD30 monoclonal antibody were uniformly disappointing in patients with ALCL and HL. For example, among 38 patients with HL and 41 patients with ALCL who were treated with SGN-30 (an anti-CD30 monoclonal antibody), no responses were seen in patients with HL, whereas 2 patients with ALCL achieved a complete response. Similar results have been reported with other anti-CD30 monoclonal antibodies. Conjugation with a linker and “warhead” markedly changed the efficacy of the antibody.

The conjugation of small molecules to highly targeted monoclonal antibodies to create an antibody drug conjugate offers a promising way to deliver highly toxic drugs to select populations of cells. The conjugation of a highly potent antimitotubule agent, monomethyl auristatin E, to the anti-CD30 monoclonal antibody creates a novel antibody drug conjugate now referred to as Bv. Clinical trials of this drug in patients with HL and ALCL have demonstrated remarkable activity in these CD30-expressing diseases. A pivotal trial of Bv in patients with R/R ALCL produced an ORR of 86%, with a complete response rate of 57%. These remissions were found to be very durable, with a median DOR of 12.6 months and a median DOR among patients in CR of 13.2 months. The majority of patients enrolled in the ALCL study exhibited poor prognostic features: 72% had ALK-negative ALCL, 63% were refractory to front-line therapy, and 22% had never responded to any prior therapy. These results led to an accelerated regulatory approval of Bv in patients with ALCL. A subsequent experience in non-ALCL MTCL (n = 35 patients), essentially restricted to patients with PTCL-NOS andAITL who had not received much prior therapy, revealed an ORR of 41% (24% had a complete response), with a median PFS and DOR of 2.6 months and 7.6 months, respectively. Although these results are less compelling than those reported in ALCL, it is important to note that the spectrum of CD30 positivity in MTCL is less than that in ALCL, because approximately 50% of all patients with MTCL have between 0% and 5% CD30 staining. Although Bv is only approved in patients with ALCL, it has found wide use in patients with other forms of MTCL, in which the benefit is less well established. Whereas CD30 expression is obligatorily required for Bv, it is unclear whether there is a threshold or CD30 level that correlates with the efficacy of Bv. Many ongoing studies are now exploring the benefits of Bv in combination with a host of drugs and drug platforms emerging in MTCL.

The Future of MTCL

The notion of adding potentially “good” drugs (such as those approved for patients with MTCL) or any other MTCL active drug to a CHOP backbone represents one approach to improve outcomes. However, the odds that a single good drug added to 4 suboptimal drugs will change an unfavorable natural history seem long at best. Over the past few years, a few groups have adopted the strategy of trying to configure novel backbones predicated on drugs with exclusive and potent activity in TCL or leveraging drugs that target discrete molecular features of the disease (ie, epigenetic dysregulation). Although this represents a more arduous approach to the development of improved treatment platforms, it may well represent a viable and provocative alternative to the CHOP-plus philosophy.

Development of Novel:Novel Backbones

The starting point for novel:novel drugs is to identify the agents and rationale for their combination. It is important to point out that the single-agent data for these agents, as shared in Figure 3, are not the same. There is a substantial difference in the quality of data obtained between registration studies performed in a multicenter
fashion with central pathology and response review, and smaller, single-center studies without central review. Nonetheless, these smaller studies can reveal clues that can lead to new opportunities. To date, there are 4 relatively new drugs approved in MTCL, including pralatrexate; 2 HDAC inhibitors; and Bv, an anti-CD30 antibody drug conjugate. In addition to these agents, there are drugs in development with some evidence of activity in MTCL, including PI3K inhibitors (duvalisib); proteasome inhibitors (bortezomib and carfilzomib); a host of biologics targeting CD37, CD70, and CD47; and bispecific NK engagers. Figure 4 shares some data regarding these combinations, recognizing that much of this information has not yet been published in peer-reviewed journals and is available only in abstract form.

Romidepsin plus pralatrexate
One of the first combinations published in a T-cell population was of the 2 drugs that attained accelerated approval for patients with R/R MTCL. In preclinical models, Jain et al found that the 2 drugs were highly synergistic in in vitro and in vivo models of MTCL. This led to a phase 1 study, which identified a maximum tolerated dose (MTD) for the 2 drugs of pralatrexate at 25 mg/m^2 administered concurrently with romidepsin at 12 mg/m^2 on days 1 and 15 of a 28-day schedule. Administration of the drugs on weekly schedules produced thrombocytopenia, which preempted maintenance of the weekly dosing. The ORR across all patients was 57% (13 of 23 patients), whereas the response rates in patients with B-cell lymphoma and TCL were 33% (3 of 9 patients) and 71% (10 of 14 patients), respectively. The phase 2 part of the study is now near completion in patients with MTCL.

Romidepsin plus 5-azacytidine
The combination of romidepsin and 5-azacytidine theoretically targets the biology of the disease, namely, gross epigenetic dysregulation, by combining an HDAC inhibitor plus a hypomethylating agent (HMA). In theory, only HMAs represent the pharmacologic counterbalance to the mutations in TET2 and IDH2 described above. Preclinical studies published by Marchi et al demonstrated profound synergy between these drugs in vivo and in vitro models of MTCL. In addition, it has been demonstrated that the combination induces marked changes in gene expression favoring an activated immune state for the malignant T cells. In a recent abstract presented at the International Conference for Malignant Lymphoma in Lugano, Falchi et al reported on results from the phase 1 study of oral 5-azacytidine and romidepsin in patients with advanced lymphoid malignancies, with an emphasis on the MTCL population. Following a 3 + 3 design, patients were assigned to 1 of 7 cohorts, with a total of 31 patients being treated. The MTD was azacytidine at 300 mg on days 1 through 14 and romidepsin at 14 mg/m^2 on days 8, 15, and 22 of a 35-day cycle. The major dose-limiting toxicities were primarily hematologic, and were managed with cytokine support when necessary. Interestingly, the combination was substantially more active in patients with MTCL than in those with B-cell lymphoma. The ORRs in all patients, in those with B-cell lymphoma, and in those with TCL were 32%, 10%, and 73%, respectively, whereas the complete response rates were 23%, 5%, and 55%, respectively. Although the follow-up duration is short, the data also suggest a marked prolongation in PFS of approximately 9 months. The phase 2 trial has completed recent accrual. These data have laid the groundwork to explore the addition of newer targeted biologics to the backbone (ClinicalTrials.gov identifier NCT01998035).
Panobinostat and bortezomib

On the basis of the sensitivity of MTCL to HDAC inhibitors and published experiences demonstrating the activity of proteasome inhibitors in MTCL, Tan et al\textsuperscript{120} studied the combination of panobinostat and bortezomib in patients with MTCL and NK/TCL. In addition, numerous preclinical studies have consistently confirmed synergy between these 2 classes of drugs. On the basis of 25 patients treated on study representing various different histologies, the ORR and complete response rate were 43% (10 of 23 patients) and 22% (5 of 23 patients), respectively. Unfortunately, the time to response was somewhat slow (ie, approximately 6 weeks), which may have contributed to the poor reported PFS in this highly aggressive disease.

Romidepsin and duvalisib

On the basis of reports of the single-agent activity of PI3K inhibitors in MTCL, a combination study exploring the activity of the combination has been reported in abstract form.\textsuperscript{116} The MTD for the combination was romidepsin at 10 mg/m\textsuperscript{2} (on days 1, 8, and 15) and continuous duvalisib at 75 mg twice daily on a 28-day cycle. The major toxicities appeared to be those largely seen with the PI3K inhibitors, including elevated transaminases and diarrhea, at the MTD in 23% and 19% of patients, respectively. Although it has been published only in abstract form at this time, among 27 patients with R/R MTCL, the ORR and complete response rates were 59% and 33%, respectively. The PFS was estimated to be approximately 6 months. Although it is early, these few studies suggest that combinations of drugs, without conventional cytotoxic chemotherapy, can produce meaningful ORR and complete response rates in patients with heavily treated MTCL. In addition, these preliminary studies suggest that they may be able to improve the time-to-event metrics that historically have been some of the harder endpoints to change in MTCL studies. Moving forward, the goal is to explore additions to these backbones, many of which are now ongoing, exploring the merits of adding immune checkpoint inhibitors, for example. Marchi et al have begun 2 studies (ClinicalTrials.gov identifiers NCT03240211 and NCT03161223) that are systematically evaluating the addition of the PD-1 antibody pembrolizumab to pralatrexate, decitabine, or pralatrexate plus decitabine. In a second study, efforts are focused on exploring the merits of adding duvalumab (PDL-1) to romidepsin, oral 5-azacytidine, romidepsin plus 5-azacytidine, and pralatrexate plus romidepsin. These types of strategies, which identify promising new backbones that are not necessarily predicated on chemotherapy as the basis for exploring the addition of complementary third agents, represent a viable approach to the development of innovative and novel regimens specifically developed for the disease.

Possible New Drugs in Development

Currently, there are large numbers of drugs in development that could have an impact as single agents and could be complementary to the backbones now emerging. Clearly, one of the major categories of new agents for which there is a great need, and a strong rationale, would include biologic agents. One obvious biologic that has been studied in patients with R/R MTCL is the PD-1 inhibitor pembrolizumab. In a phase 2 study, patients were treated with pembrolizumab at
200 mg every 21 days. Of 18 patients enrolled, 13 were eval-
uable for the primary endpoint.127 The trial was halted early
after a preplanned interim futility analysis. The ORR was
33%, and 4 patients achieved a complete response. The PFS
was short at only 3.2 months. Although 2 of the 4 patients
who achieved CR remained in remission for >15 months, it
was believed overall that the drug had modest activity as a
single agent. It is likely that, as with many drugs that exhibit
a primary immunologic effect, these agents will be substi-
tually more active with other rational combinations, such as
HDAC inhibitors and HMAs. Other biologics of interest
include the anti-CD47 drugs, which target the “do not eat”
signaling pathways on macrophages. Although the experi-
ence is still one in evolution, recently published abstracts have
demonstrated some activity in heavily treated patients with
tumor mycosis fungoides and R/R MTCL.128,129 Likewise,
novel bispecific NK engagers targeting CD16a and CD30
have also demonstrated activity in CTCL and MTCL. One
such drug, AFM-13, is now entering a registration directed-
study in patients with R/R CTCL.130

Finally, although the development of chimeric anti-
gen receptor (CAR)–modified T cells for the treatment of
T-lineage leukemia and lymphoma has potential, just as in
other forms of B-cell lymphoma, it has encountered several
unique challenges. The most widely expressed tumor antigen
targets for malignant T cells often also are expressed on non-
malignant T cells. Transducing T cells with CARs targeted
to these shared antigens thus can promote overactivation or
fratricide of CAR T cells, reducing their therapeutic potency.
If fratricide is resolved, then clinical CAR T-cell activity
may eliminate normal T-cell subsets and cause temporary
immunosuppression.

Although this was not intended to be a comprehen-
sive review of all drugs now in development for MTCL, it
is clear that there are several new agents that appear to be
highly lineage-specific and to have a strong biologic ratio-
ne in MTCL, one that may lend itself to greater benefit in
logical combinations.

Conclusions

It is evident that times are changing rapidly in the care of
patients with MTCL. Developments in the disease are pro-
ducing unprecedented efficacy in a disease long neglected by
the medical and scientific community. Although there are no
perfect drugs for any disease, using the imperfect ones bet-
ter is clearly beginning to light a new direction forward, one
predicated on leveraging the unique effects of single agents
in a combinatorial fashion. Major advances moving forward
will depend on our ability to identify complementary bio-
logical drugs that can be added to the existing backbones
in a way that will not magnify overlapping toxicities. Given
the paucity of patients with MTCL and the ever-expanding
diversity of diseases, our most significant challenge will be
to define those disease (ie, histology, prior treatment) and
molecular features (mutations in driver genes such as TET2)
that influence responsiveness to the emerging platforms,
which is obviously best done within the context of clini-
cal trials. Nonetheless, we have turned a corner in thinking
about and developing T-cell–centric regimens for the dis-
eease, one we need to continue collaboratively.

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