This chapter describes the various ways in which the non-Hodgkin’s lymphomas can involve the skin, how these diseases should be assessed, standard treatments available in 2002, and new directions in research. The goal of the session is to succinctly review recent developments in lymphoma classification and treatment as they apply to the unique aspects of lymphoma when manifest in the skin.

In Section I, Dr. Eric Hsi reviews the special characteristics of the lymphomas seen when they proliferate in the skin and the application of the new World Health Organization classification system to the cutaneous lymphomas, emphasizing the unique challenges of recognizing and correctly classifying these diseases. He summarizes the evidence in favor of including the skin lymphomas in the overall lymphoma classification scheme and concludes with a practical description of the specific skin lymphoma entities.

In Section II, Dr. Joseph Connors describes the current optimal treatment of the B-cell lymphomas when they present in or metastasize to the skin. Building on the classification scheme described by Dr. Hsi, Dr. Connors outlines a treatment approach based on current understanding of pathophysiology of these diseases and application of each of the effective modalities available for cutaneous lymphoma including radiation, chemotherapy, and immunotherapy.

In Section III, Dr. Francine Foss concludes the session with a discussion of the different T-cell lymphomas that start in or spread to the skin concentrating on mycosis fungoides, cutaneous anaplastic large cell lymphoma and peripheral T-cell lymphoma. She includes comments on the newer anti-T-cell chemo- and immuno-therapeutics focusing on agents and techniques specific for cutaneous T-cell lymphomas.
tities to show that they are quite similar in both systems. Then I will present the conceptual evolution of thinking about PCBCLs; the features of PCBCLs; a review of the major classifications of these lymphomas; and an assessment of the merits of the WHO classification and EORTC proposal, particularly related to PCBCLs. Finally, some areas of controversy will be addressed that serve to outline future areas of investigation.

Primary Cutaneous T-Cell Lymphomas

There is little disagreement in the T-cell entities that are described in the EORTC proposal and the WHO classification, although the organization is somewhat different (Table 1). The indolent clinical entities of the EORTC are recognized in the WHO classification. In particular, the variants of MF, such as MF-associated follicular mucinosis and pagetoid reticulosis, are present in both systems. Likewise, granulomatous slack skin, a putative variant of MF, is described as such in the WHO classification and is considered a provisional entity in the EORTC proposal.

The CD30+ large cell lymphoproliferative disorders vary in their nomenclature. Termed cutaneous T-cell lymphoma, CD30+ in the EORTC proposal, these lymphomas are equivalent to primary cutaneous anaplastic large cell lymphoma (ALCL) in the WHO system. Both systems recognize the clinical and histopathologic features of these lymphoproliferative disorders (sheets of atypical large cells, sometimes but not always resembling nodal anaplastic large cell lymphoma; T-cell phenotype with strong uniform CD30 expression; favorable prognosis). The EORTC cutaneous T-cell lymphoma, CD30+ may also include non-anaplastic large cell type of peripheral T-cell lymphoma, unspecified (WHO) that express CD30. Lymphomatoid papulosis (LyP) is listed as a variant of primary cutaneous CD30+ T-cell lymphoproliferative disorders in the WHO and EORTC systems and is not considered a malignancy. Clinical features (such as multiple waxing and waning papules less than 2.5 cm in size) are important in the diagnosis of LyP. LyP usually follows an indolent clinical course. Initially, other lymphomas, such as systemic anaplastic large cell lymphoma or MF, may have a similar appearance; however, the typical clinical course eventually reveals the correct diagnosis. The above described clinical features of LyP and the histopathologic findings of a non-epidermotropic, wedge-shaped infiltrate with scattered very large, atypical and multilobated cells set in an inflammatory cell background help distinguish LyP from cutaneous ALCL and MF. LyP can also have a different histopathologic picture (so-called type B) in which a predominance of intermediate-size atypical cerebriform cells is seen.

The main difference between the EORTC and WHO classifications of PCTCL is with the EORTC entities of large cell CD30-negative cutaneous T-cell lymphoma.

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Table 1. Comparison of EORTC and WHO classifications of primary cutaneous lymphomas.

<table>
<thead>
<tr>
<th>EORTC</th>
<th>WHO</th>
</tr>
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<tbody>
<tr>
<td>B-cell lymphomas</td>
<td></td>
</tr>
<tr>
<td>Indolent</td>
<td></td>
</tr>
<tr>
<td>Follicle center cell</td>
<td>Follicular lymphoma and diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Immunocytoma (marginal zone B-cell lymphoma)</td>
<td>Extranodal marginal zone B-cell lymphoma</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Large B-cell lymphoma</td>
<td>Diffuse large B-cell lymphoma and follicular lymphoma</td>
</tr>
<tr>
<td>of the leg</td>
<td></td>
</tr>
<tr>
<td>Provisional</td>
<td></td>
</tr>
<tr>
<td>Intravascular large B-cell lymphoma</td>
<td>Intravascular large B-cell lymphoma</td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td>Plasmacytoma</td>
</tr>
<tr>
<td>T-cell lymphomas</td>
<td></td>
</tr>
<tr>
<td>Indolent</td>
<td></td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>Mycosis fungoides-associated follicular mucinosis</td>
<td>Mycosis fungoides-associated follicular mucinosis</td>
</tr>
<tr>
<td>Pagetoid reticulosis</td>
<td>Pagetoid reticulosis</td>
</tr>
<tr>
<td>CTCL, large cell, CD30+</td>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>Lymphomatoid papulosis</td>
</tr>
<tr>
<td>Aggressive</td>
<td></td>
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<tr>
<td>Sezary syndrome</td>
<td>Sezary syndrome</td>
</tr>
<tr>
<td>CTCL, large-cell, CD30-</td>
<td>Peripheral T-cell lymphoma, unspecified</td>
</tr>
<tr>
<td>Provisional</td>
<td></td>
</tr>
<tr>
<td>Granulomatous slack skin</td>
<td>Granulomatous slack skin</td>
</tr>
<tr>
<td>Pleomorphic small/medium-sized CTCL</td>
<td>Peripheral T-cell lymphoma, unspecified</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
</tbody>
</table>

Abbreviations: CTCL, cutaneous T-cell lymphoma; EORTC, European Organization for Research and Treatment of Cancer; WHO, World Health Organization.
(CTCL) and CTCL, pleomorphic small/medium cell type. Both present with plaques or tumors without patches typical of MF. The former lymphoma is recognized as an aggressive T-cell lymphoma by the EORTC, highlighting its poor survival. The latter EORTC type of lymphoma also appears to be a relatively aggressive lymphoma. Although the number of cases is small, the Dutch Cutaneous Lymphoma Working Group reports a 62% 5-year survival.² Both of these lymphomas would be considered as peripheral T-cell lymphoma, unspecified in the WHO.

A few other rare entities require brief mention. Subcutaneous panniculitis-like T-cell lymphoma is a provisional entity in the EORTC and a distinct well-characterized entity in the WHO. The provisional status in the EORTC proposal appears to be due to a lack of experience with this lymphoma by that group. Finally, other uncommon entities such as nasal-type T-NK-cell lymphomas (WHO), blastic NK-cell lymphomas (now thought to be possibly related to dendritic cells), and gamma-delta T-cell lymphomas can occur primarily in skin and are not specifically mentioned in the EORTC classification.³⁵

Regarding terminology, the use of “cutaneous T-cell lymphoma” as a diagnostic term in the EORTC proposal should, in my opinion, not be formalized since this is a nonspecific term and literally encompasses numerous disparate types of lymphomas. Some have even used it as a synonym for MF. Therefore, other than a purely descriptive term (a T-cell lymphoma in the skin), it has little meaning and should be abandoned as a term to designate a diagnostic category. Eliminating this term would avoid potential confusion of the non-MF lymphomas with MF.

Primary Cutaneous B-Cell Lymphomas

Historical perspective of PCBCLs

PCBCLs comprise approximately 20% of cutaneous lymphomas.⁶ Our understanding of the clinical, morphologic, and molecular genetic features of PCBCLs has been impeded by the relative rarity of these lymphomas, lack of precise definitions, and confusion with nonneoplastic entities. Through recent studies with relatively rigorous clinical and histopathologic criteria, we have begun to make headway in characterizing PCBCLs.

As with nodal lymphomas, our understanding of the nature of cutaneous lymphomas evolved slowly over the first part of the last century and then accelerated over the past 20 years. Bolstered by advances in immunology and molecular genetics, we are now able to diagnose and classify lymphoid neoplasms more accurately than ever before. This rapid advance has caused some confusion. Because of our lack of understanding of the immune system and lack of knowledge of basic molecular genetic events important in lymphomagenesis, numerous morphologic classifications of nodal-based lymphomas were in use prior to the development of the Revised European and American Classification of Lymphoid Neoplasms (REAL classification).⁷ These systems included the Rappaport, Lukes-Collins, International Working Formulation, and Kiel classifications. Thus, many studies of cutaneous lymphomas were not directly comparable due to variations in nomenclature. Furthermore, these systems did a poor job of recognizing features that might be specific to extranodal lymphomas. Difficulties in cutaneous lymphoma diagnosis and classification were compounded by the addition of nomenclature specific to the dermatology dermatopathology literature and by differences in biology that may be peculiar to cutaneous B-cell lymphomas.

Delving deep into the past, one might credit Kaposi, Spiegler, and Fendt with early descriptions of cutaneous lymphoproliferative disorders that were probably B-cell lymphomas.⁸¹³ They described single and multiple sarcoma-like skin lesions (“sarcoids”) with varied clinical outcome—some regressing and others causing significant morbidity and mortality. Darier coined the term Speigler-Fendt sarcoïd to encompass these lymphoid lesions.⁸ Subsequent descriptions often focused on the more indolent, rather than fatal, cases and a bewildering array of names proliferated, such as lymphocytoma, lymphadenosis benigna cutis, cutaneous lymphoplasia, cutaneous lymphoid hyperplasia, large cell lymphocytoma, and reactive pseudolymphoma. These entities probably encompassed both neoplastic and reactive lesions and hence caused as much diagnostic confusion as clarity. Even more troubling were the reports of things such as malignant transformation of pseudolymphoma, evolutions of lymphoma from pseudolymphoma, and “pseudolymphomas with monoclonal plasma cells.” Today, appreciating how difficult the diagnosis and classification of PCBCLs is even with modern ancillary studies, such as immunophenotyping and molecular genetic analysis, we can understand the confusion that resulted from the use of such terminology.

To emphasize the attention that these cutaneous lesions attracted, we note that the concept of the pseudolymphoma was refined to a rather detailed discipline of its own by Burg et al.¹³ They divided pseudolymphoma into two major categories based on whether one knew the presumed etiology or not (“strict sense” versus “loose sense”). A category of conditions termed “pseudolymphoma-like conditions” or “pseudopseudolymphomas” was even suggested, consisting of inflammatory conditions (such as ruptured follicular in-
At the core of the matter is the fact that the clinical and morphologic overlap between benign and malignant lymphoid lesions in the skin is significant. Many PCBCLs follow an indolent clinical course (waxing and waning over many years). The histology may evolve over time. Furthermore, biopsies are often very small punch biopsies, making diagnosis a challenge. For example, a major series in the late 1970s, before the availability of detailed immunophenotyping and molecular genetic studies for demonstrating monoclonality, noted that clinical features were not very helpful to distinguish benign from malignant cutaneous lymphoid infiltrates. The authors reported that the most helpful histologic features for recognizing lymphoid hyperplasia (which were not present in non-MF lymphomas) were the presence of germinal centers, marked paucity of medium-sized lymphocytes, and sharp margination between adjacent groups of small and large lymphocytes. They recognized the limitations of even these criteria since some cases that they felt were benign (based in part on clinical follow-up) lacked any of these features. They further reluctantly admitted, as others had already published at the time, that lesions composed predominantly of small lymphocytes could not be reliably diagnosed as lymphoma by biopsy alone.

Of course, we now know that germinal centers are characteristically seen in some PCBCLs (marginal zone lymphoma [MZL]) and that many PCBCLs, including follicular lymphomas, are of low cytologic grade (small cells). Distinguishing between benign and malignant cutaneous lymphoid lesions is also made difficult by the fact that the prognosis of PCBCL is often excellent. Thus, if one used clinical outcome, such as death from disease, as a criterion to build experience in cutaneous lymphoma, one could easily be led astray. For example, a report of cases of “large cell lymphocytoma” shows histologic and clinical features of cutaneous follicular lymphoma. However, because of the indolent behavior of such cases (which included multiple relapses), a benign interpretation resulted.

A major advance in our understanding of cutaneous B-cell lymphomas came from studies that began to separate primary from secondary forms. Since most series tended to group all cutaneous lymphomas and since PCBCL is a rare disorder, this seemingly basic difference tended to be overlooked. Burke et al were among the first to describe entities that are now considered characteristic of PCBCL. In their 1981 series of non-MF lymphomas, the authors were able to show that those lymphomas limited to the skin at diagnosis had a much better relapse-free and overall survival compared with those with secondary involvement. These data are similar to more recent series of well-defined PCBCL.

Although criteria for confirming the primary nature of a cutaneous lymphoma have varied, a current working definition would be a lymphoma which is determined to be confined to the skin after physical examination, chest/abdomen/pelvis imaging studies, blood smear review, and bone marrow staging biopsies.

In the mid to late 1980s much was learned regarding lymphoma diagnosis. Importantly, immunophenotyping became readily available and thus B-cell lymphomas could be identified and large cell lymphomas in particular could be accurately divided into B- and T-cell types. Another major advance was the recognition of mucosa-associated lymphoid tissue (MALT) type lymphomas. The extension of this concept to the skin in the form of skin-associated lymphoid tissue and so-called immunocytomas of the skin helped define a new type of PCBCL that had been often mistaken for a benign lesion. Recognition of this type of lymphoma set the stage for modern classifications and definitions of PCBCL.

**The major types of PCBCL**

A review of the major types of PCBCL will now be presented, as defined by the WHO classification. Then the recently described EORTC classification will be discussed. The major WHO types include lymphoblastic lymphoma, MZL (immunocytoma), follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), and intravascular lymphoma. Of note, there are some types of B-cell lymphoma that virtually never occur as primary disease in the skin, such as small lymphocytic lymphoma and mantle cell lymphoma.

B precursor lymphoblastic lymphoma (LBL) accounts for less than 10% of LBL. In a recent series of B precursor LBL, cutaneous locations were present in 36% of cases. Unlike noncutaneous LBL, which is predominantly T-cell phenotype, primary cutaneous LBL is most often of B-cell lineage. These lymphomas most often present in the head and neck region as large solitary lesions. Histologically, they appear similar to LBL at other noncutaneous sites. The cells diffusely infiltrate the dermis and are intermediate in size with fine chromatin. Mitotic figures are common and a “starry sky” pattern may be seen. The nuclear contours may be round or convoluted, and this feature cannot be reliably used to predict phenotype. The cells express the early B-cell marker CD79a and may be negative for CD20 due to their immature B-cell phenotype. Other antigens characteristi-
cally expressed include CD10, CD34, and TdT. Surface immunoglobulin may be variably expressed in rare cases. Since other small round cell tumors are considered in the differential diagnosis, including Ewing’s sarcoma, it should be remembered that CD99 is often positive in LBL.

Perhaps no other advance in the characterization of extranodal low-grade B-cell lymphomas has been as significant in the past 20 years as the concept of extranodal marginal-zone B-cell MALT lymphomas, first introduced in 1983. The prototype of the MZL is gastric MALT lymphoma. These lymphomas arise in the background of an inflammatory precursor—Helicobacter pylori gastritis. Hence, their histologic features often overlap. In particular, reactive follicles are seen in both entities and can cause differential diagnostic problems. Prior to the MALT lymphoma concept’s introduction, many of these lesions were erroneously termed pseudolymphomas. A similar situation occurred in the skin, with some cases previously reported as pseudolymphomas likely representing MZLs. Analogous to H. pylori in gastric MALT lymphomas, it has been suggested that Borrelia burgdorferi is involved in the development of MALT-type lymphomas in the skin, at least in some cases.

Clinically, primary cutaneous MZLs occur most commonly on the head/neck/trunk at a median age of 55 years; they predominate in females. These MZLs account for approximately 25% of PCBCL. Histologically, they may have a heterogeneous appearance. Well-developed lesions are characterized by a dense lymphoid infiltrate. The infiltrate may be either “bottom” heavy or “top” heavy, and the distinction between these 2 patterns is not a useful diagnostic feature. Hyperplastic germinal centers may be observed with or without mantle zones. External to the germinal centers are small lymphocytes with slight nuclear irregularity and moderate amounts of cytoplasm. Occasional larger cells are present with visible nucleoli. Plasmacytic differentiation may occur in these lymphomas, and plasmacytic cells can often be shown to be monocytic. Although lymphoepithelial lesions (LELs) are characteristic of MALT-type lymphomas in other sites such as stomach, salivary gland, and thyroid gland, LELs are not commonly seen in cutaneous MZLs. The typical immunophenotype is CD20+, CD5–, CD10– with immunoglobulin (Ig) light chain restriction. Monoclonal Ig gene rearrangement can be demonstrated by molecular genetic methods such as Southern blot or polymerase chain reaction (PCR). Like their counterparts in other extranodal sites, the behavior of these lymphomas is indolent. Cutaneous recurrence is common, but systemic dissemination and death from disease are uncommon.

Primary cutaneous follicular lymphoma (PCFL) is another major type of PCBCL, representing 39% of cases as defined by the REAL/WHO classification. These lymphomas typically present on the head/neck of adults with a median age of 60 years and a slight male predominance (M:F, 1.5:1). Characterization of this type of lymphoma has been made difficult by varying definitions. The main issue is the use of the term “follicle center cell lymphoma” in the EORTC classification, which appears to be a heterogeneous entity, encompassing follicular lymphoma, DLBCL, and perhaps some cases of MZL.

When defined as set forth in the WHO classification, PCFL must have at least a partial follicular growth pattern. Histologically the lymphocytes within the follicles are similar to those seen in nodal follicular lymphoma FL. A varying mixture of centrocytes and centroblasts are seen. Similar to nodal FL, mantle zones are attenuated or absent and tingible body macrophages are not present. Early lesions may show a periadnexal pattern. Most cases are composed predominantly of small centrocytes, although grade 3 PCFL can be seen in approximately 25% of cases.

Immunophenotypically, these lymphomas are similar to nodal FL in that they are CD20+, CD10+, and bcl-6+ in over 90% of cases. These markers are helpful in distinguishing PCFL from cutaneous MZL. The latter lacks CD10 and bcl-6 expression. However, in contrast to nodal FL, the majority of cases of PCFL lack both bcl-2 expression and the t(14;18). In a recent series of PCFL from the United States and Canada, bcl-2 expression was seen in 41% of cases, and the t(14;18)(q32;q21) was found in 32% of cases by PCR for the major breakpoint region. It should be noted that there are discrepancies in the proportions of cases of PCFL that are found to express bcl-2 protein and harbor the t(14;18), with one group finding no cases positive and other groups finding a proportion of cases positive for these markers. In general, however, it appears that bcl-2 expression and presence of the t(14;18)(q32;q21) are found less frequently than in primary nodal FL.

Clinically, these lymphomas appear to have an indolent course. Local therapy is effective, and death from disease is distinctly uncommon (less than 5%). However, cutaneous recurrence is fairly common.

Primary cutaneous DLBCL is the other major type of PCBCL. These lymphomas, as defined by the REAL classification, appear to comprise 33–46% of PCBCL in recent series. Clinically, patients present with lesions on the head/neck/trunk or, less commonly, on the extremities with a median age of approximately 64 years. Histologically, the lymphoid infiltrate is composed of large, transformed cells with vesicular chromatin and multiple small nucleoli resembling centroblasts. Rare
cases have an immunoblastic cytology. The infiltrate is, by definition, diffuse and involves the entire dermis. Epidermotropism is not a feature. Less well-developed lesions can show a tendency to cluster around adnexal structures. Immunohistochemical stains confirm the B-cell phenotype with uniform CD20 expression. In our series, two thirds of cases expressed bcl-2. Bcl-6, also seen in a substantial number of nodal DLBCLs, was seen in approximately half the cases. In contrast, CD10 was seen in only 1 of 15 cases. We were unable to demonstrate the t(14;18) in any case by PCR. Primary cutaneous large cell lymphoma of the leg, as defined by the EORTC, may have a distinct immunophenotype, with almost all cases expressing bcl-2 protein. This is discussed further below.

Despite the nonuniformity in diagnostic criteria, it appears that many cases of DLBCL of the skin (WHO nomenclature) and large B-cell lymphoma (EORTC nomenclature) follow an indolent clinical course, and conservative therapy is appropriate. Cutaneous relapse can occur in a subset of cases (20% in our experience), but extracutaneous spread and death from disease are uncommon. The relapse-free 4-year survival is 74%, and the 5-year overall survival is over 90%. The EORTC reports that large B-cell lymphoma of the leg is a more aggressive lymphoma than those arising at other cutaneous sites, with a 5-year survival of only 58%, and that multiagent chemotherapy may be required. However, this less favorable behavior may also be the case in PCBCL of large cells in other sites when multiple lesions are present. These authors suggest that it is the fact that multiple sites are involved that confers a worse survival, rather than the fact that it occurs on the leg.

A recent retrospective study examining prognostic factors in primary cutaneous large B-cell lymphomas found that multiple skin lesions, round cell morphology (lymphomas of centroblasts or immunoblasts), and location on the leg were poor prognostic factors. Direct application of these findings to cases of DLBCL (as defined by the WHO criteria) is difficult since all large B-cell lymphomas (EORTC defined primary cutaneous follicle center cell lymphoma [PCFCCL] and large B-cell lymphoma of the leg) were likely included.

A peculiar variant of DLBCL, intravascular large B-cell lymphoma, deserves to be mentioned because of its propensity to involve skin. However, it is debatable whether this lymphoma is truly a primary cutaneous lymphoma. These lymphomas are a subtype of extranodal DLBCL in the WHO classification and a provisional entity in the EORTC classification. This is a rare lymphoma that affects older adults (median age 71 years); it has a slight female predominance. The most commonly biopsied site in the largest series to date was the skin. Central nervous system and renal involvement are also common. These lymphomas may present as plaques on the trunk or lower leg. Atypical large lymphoid cells with vesicular chromatin and variably prominent nucleoli are seen, usually exclusively within capillaries, venules, and arterioles. Extravascular lymphoma with only a minor component of intravascular lymphoma should not be included in this type of lymphoma. Immunophenotypically, the lymphomas express CD20. Three major subtypes can be discerned based on CD10 and CD5 expression. The most common type is CD20+/CD5−/CD10− (61%), followed by CD20+/CD5+/CD10− and CD20−/CD5−/CD10− (17% each). These lymphomas are aggressive, and patients have a very poor prognosis. Multiagent chemotherapy is the treatment of choice.

The EORTC proposal for PCBCL and the WHO classification

It is apparent that PCBCLs have some specific clinical and pathologic characteristics that may distinguish them from their nodal counterparts. This fact, along with similar concerns for some cutaneous T-cell lymphomas, prompted the EORTC to propose a separate classification for cutaneous lymphomas. Since this proposal was made, many articles have appeared in the literature arguing for the EORTC classification, supporting use of the REAL/WHO system, and also disparaging all current classifications. With regard to T-cell lymphomas, most of the shortcomings in the REAL classification have been addressed in the WHO classification. I will confine my discussion to the major differences between the two systems and to the relative merits of a unified system for lymphoma classification versus an organ-specific classification for cutaneous lymphomas, with an emphasis on the issues pertaining to PCBCL.

Within the context of the EORTC and the WHO classifications, there are several areas of disagreement about the features of specific PCBCL entities and over whether certain entities are distinct. These areas are immunocytoma and MZL, cutaneous follicular lymphoma, and large B-cell lymphoma of the leg. Understanding some of the details of the controversy will aid in understanding some of the arguments to be made for a separate versus a unified lymphoma classification.

Regarding MZL, there is general agreement between the two systems in the pathologic and clinical characteristics of this lymphoma. However, the EORTC proposed the term immunocytoma, a term that has lost favor among hematopathologists since the REAL classification. Immunocytoma, as it was used in the Kiel classification, is more akin to lymphoplasmacytoid lymphoma in the REAL/WHO classifications. This lymphoma is composed of small lymphocytes, plasma cells, and
lymphoplasmacytic lymphocytes and is often associated with an IgM paraprotein; lymph node, spleen, and bone marrow involvement, and clinical Waldenström’s macroglobulinemia. With the acceptance of MZLs of MALT type and the recognition of their morphologic spectrum, it was suggested in the early 1990s that perhaps most cases of PCBCL might be best considered as cutaneous MALT-type lymphomas or skin-associated lymphoid tissue lymphomas.⁴⁷ This position has been tempered by others so that only cases that truly fit the characteristic morphologic features are accepted as MZL. With further analysis, most authors came to believe that cutaneous immunocytomas should be considered extranodal MZLs.²,³,⁷,⁴³,⁵⁹,⁶⁰ Hence, later authors using the EORTC system have used “immunocytoma” and “MZL” synonymously.⁴³

As alluded to earlier, primary cutaneous follicle center cell lymphoma (PCFCCL) as defined by the EORTC can be a diffuse or a follicular (architecturally speaking) lymphoma. It is composed of either small or, more commonly, large cells that resemble follicle center cells (centroblasts and centrocytes).²,³⁷,⁴³,⁶¹ Thus, EORTC PCFCCL could include DLBCL, FL, and even some cases of MZL as defined by the WHO.Occurring on the head/neck, PCFCCLs have an excellent prognosis and lack the t(14;18) and bcl-2 expression.⁴⁰,⁶²,⁶³ However, other studies specifically looking at PCFL (as defined by a follicular architecture) show that some cases do in fact harbor the t(14;18) and express bcl-2.³⁸,³⁹,⁴¹,⁴² The largest of these series (32 patients) showed the t(14;18) in 34% and bcl-2 expression in 41%.³⁸ The most directly comparable European study by Cerroni et al, which looked at 15 follicular PCFCCLs (presumably equivalent to PCFL), failed to find the translocation or bcl-2 protein in any of the cases.⁴⁰ The reasons for this discrepancy are uncertain and may include case definitions/inclusion criteria and regional differences, since most series finding t(14;18) and bcl-2 protein expression are from North America, while the other series are from Europe. Regardless, all authors find the same excellent survival curves with local therapy.

Large B-cell lymphoma of the leg, as defined by the EORTC, has been specifically identified as a distinct clinical entity because of its perceived poor outcome compared with PCBCL (particularly PCFCCL) at other sites. The malignant cells of these lymphomas resemble follicle center cells cytotologically and are felt to be of follicle center origin.⁴⁵ Based on an original report of 18 cases (many of which had multiple lesions),⁴⁷ subsequent reports from some of the same authors suggested that these lymphomas did indeed have a poor prognosis. Furthermore, bcl-2 expression was most common in the cutaneous lymphomas of the leg.⁴⁵,⁴⁹ Focusing on DLBCL (WHO classification) at all cutaneous sites, lymphomas of the leg are uncommon. A recent small series did not have enough statistical power to confirm that they have a worse prognosis than cutaneous DLBCL at other sites.⁴⁴ Whether large B-cell lymphoma of the leg should remain a separate entity is debatable. It may not represent a single histology. Furthermore, it may be that known poor prognostic features in DLBCL, such as bcl-2 expression⁴⁴ or multifocal lesions, rather than location itself, dictate the poor prognosis.⁴⁴,⁵³

An Assessment of the EORTC and WHO Classifications for PCBCL

Given this background, the advantages and disadvantages of these systems will now be examined. We begin by listing qualities that make a classification system useful and desirable: (1) definitions of distinct pathologic entities with characteristic morphologic, phenotypic, and molecular genetic features; (2) reproducibility; (3) comprehensiveness; (4) clinical relevance; and (5) broad acceptance from practitioners. How does each system address these desired qualities?

The EORTC system clearly has clinical relevance and has served to draw attention to the clinical features particular to primary cutaneous lymphomas. Driven by the desire to produce a system that merges pathologic, phenotypic, molecular genetic, and clinical features, the EORTC system relies heavily on the experience of the Dutch Cutaneous Lymphoma Working Group.²,⁵² In doing so, however, the EORTC system appears to combine multiple histologic entities into a single category. As mentioned, PCFCCL appears to be a histopathologically heterogeneous entity. True follicular lymphomas, of the type seen in lymph nodes, appear not to be included. Despite this, the name PCFCCL implies that all lymphomas within this category are of follicular derivation. However, data for this unified theory of histogenesis are lacking. Large B-cell lymphoma of the leg is separated from PCFCCL and appears to be defined as much by clinical presentation on the leg as by pathologic features. Immunocytoma has been expanded from its traditional meaning to include both what may be lymphoplasmacytic lymphoma (immunocytoma) and MZL.⁵⁵,⁵² Primary cutaneous immunocytoma (lymphoplasmacytic lymphoma) only rarely, if at all, occurs and use of this term may falsely imply a high risk of systemic disease. Reproducibility has not been addressed for this system. The EORTC system, while accounting for most primary cutaneous lymphomas, does not account for secondary lymphomas involving the skin, which, while uncommon, do indeed occur. Clinicians and pathologists should be aware of the clinical and pathologic features of both primary and secondary lymphomas. A system limited to only pri-
mary cutaneous lymphomas does not promote this comprehensive view of lymphoid malignancies in skin and may mislead those not aware of these differences. Furthermore, some lymphomas may not be readily classifiable, and any classification system should have an “unclassifiable” category. This category is absent from the EORTC proposal. Regarding acceptance from practitioners, it remains to be seen whether such a system will gain wide use.

The WHO classification is an extension of the REAL classification and, like the EORTC, attempts to define distinct entities with characteristic pathologic, phenotypic, and genetic features. With respect to primary cutaneous lymphomas, the REAL system was shown to be applicable to PCBCL. The reproducibility and clinical relevance of the REAL/WHO system has been shown. Although the general clinical features have been described, direct application of the WHO system to a uniformly treated patient population with primary cutaneous lymphomas is lacking. A valid criticism is that clinical features specific to cutaneous lymphomas were not originally recognized in the REAL system. However, as these features were recognized, some modifications were made in the WHO classification, such as including PCFL as a variant of follicular lymphoma.

Regarding comprehensiveness, the WHO classification is a relatively complete description of lymphoid, myeloid, and histiocytic/dendritic neoplasms, and its continued evolution should improve this feature. Finally, this system is currently widely accepted by oncologists and pathologists alike in North America, Europe, and Asia.

With the above discussion in mind, it is my opinion that while the EORTC system has done much to encourage better definition and characterization of PCBCLs, it is not in the best interest of pathologists, oncologists, and dermatologists to use different lymphoma classification systems. This would pave the way for continued confusion and possible misinterpretation regarding a patient’s diagnosis. Pathologists may have difficulty in translating between two systems in formulating diagnoses, particularly given the confusion relating to EORTC nomenclature for immunocytoma, PCFCCCL, and large B-cell lymphoma. Oncologists—who, by and large, have adopted the WHO classification—will likewise be loath to adopt separate classifications of lymphomas based on individual organ systems. Dermatologists dependent on a system that addresses only primary cutaneous lymphomas will lack a global view of lymphoma and be at a loss for guidance in management of other cutaneous lymphomas. To be sure, the WHO classification has room for improvement by more specifically recognizing some of the differences between nodal lymphoma and PCBCL. However, this goal can be achieved through expanding descriptions and recognizing specific clinical variants. All parties involved in the diagnosis and management of these patients should be aware of the clinical and pathologic characteristics of these lymphomas. When common nomenclature is used, future studies can be more easily done and compared, to help resolve some of the controversies in PCBCL. Three areas should be addressed:

1. PCFL. While PCFCCCL, as defined by the EORTC, has been determined to generally lack bcl-2 protein expression and the t(14;18) characteristic of nodal lymphoma, I and others in North America find these features in a significant minority of PCFL. Although this discrepancy may be due to different diagnostic criteria, it may be that European cases of PCFL also lack bcl-2 protein and t(14;18). Is there truly a difference in molecular pathogenesis between PCFL in North America and Europe?

2. Primary cutaneous DLBCL. Cases arising on the leg are suggested to be clinically different from those in other cutaneous sites, in the experience of the Dutch Cutaneous Lymphoma Working Group. Morphology (round cell morphology) and location on the leg appear to be poor prognostic indicators and may be related to bcl-2 expression. Some have called into question whether location on the leg confers an aggressive clinical behavior and suggest that it may be due to a propensity for multifocal disease. Of note, it is not clear what is accepted as “leg” (below the knee only or perhaps below the hip?). Since defining a lymphoma subtype with distinct biologic and prognostic characteristics based primarily on location seems scientifically unsound, further studies of DLBCL are needed to resolve these questions.

3. MZL. Is Borrelia infection the common inciting event in cutaneous MZL, similar to H. pylori in gastric MALT lymphomas? Borrelia infection has been known to cause several cutaneous lesions, such as erythema chronica migrans, acrodermatitis chronica atrophicans, and “lymphocytoma.” Studies from European investigators have also shown the presence of the organism in tissues of PCBCL. Further support for a causative role is shown by the regression of some cases of PCBCL infected with B. burgdorferi after antibiotic treatment. Despite this mounting evidence, a causative role has not been as precisely established as it has been for H. pylori and gastric MALT lymphoma. Direct response of T cells or B cells from lymphomas to the organism has not been shown. Further, the percentage of cases of PCBCL and MZL with detectable B. burgdorferi is
much lower than that of *H. pylori* in gastric MALT lymphoma. A recent study from North America failed to detect *Borrelia* in PCBCL.\(^6\) Thus, other antigens must be involved. This finding suggests that other as-yet undefined genetic and environmental factors must be important in the pathogenesis of cutaneous MZL.

Clearly, more research is needed to answer these questions. A uniform and relevant classification system is needed so that studies can be fairly compared with one another. Furthermore, a common system is required for multicenter clinical trials. While the EORTC proposal serves to emphasize the clinical features particular to cutaneous lymphomas, I have outlined above the reasons for making the WHO classification the system of choice. Its use should allow clearer communication between dermatologists, pathologists, and oncologists. It accounts for the full spectrum of primary and secondary lymphoid malignancies in skin. Finally, through the continuing efforts of classification committees, the WHO classification can be modified, taking into account new information as it becomes available.

**II. B-CELL LYMPHOMA OF THE SKIN**

*Joseph M. Connors, MD*

By weight and size the skin is arguably the largest single organ in the human body. In addition, it is 1 of the 3 major epithelial surfaces exposed to organisms and material from the external world, along with the bronchoalveolar structures of the lung and the absorptive and secretory surface of the gastrointestinal tract. Given its role as a barrier to potentially invasive organisms, it is not surprising that the skin has an intimate relation with the immune system and that it is richly endowed with a full repertoire of lymphoid and other cells essential for recognition of and reaction to foreign antigens. Likewise, given this rich numerical endowment of lymphocytes and the need for these cutaneous lymphocytes to proliferate, diversify, and undergo apoptosis, we should also not be surprised to find that the skin is among the most common sites of extranodal lymphoma. Several consequences of the wide variety of lymphoid cells in the skin complicate our ability to categorize the cutaneous lymphomas: (1) lymphoma of the skin may be of B-, T-, or NK-cell origin predicting clinical heterogeneity; (2) lymphomas may arise in or metastasize to the skin with very different resultant natural histories; (3) cutaneous lymphoma, even when exclusive to the skin, may be unifocal, regionally localized, or widespread; (4) all of the biological characteristics that govern lymphoma behavior in general, such as oncogene overexpression, cell membrane antigen expression, alteration in apoptotic pathways, and changes in factors regulating cell proliferation, can also vary widely in the cutaneous lymphomas. Thus, reflecting these influences toward heterogeneity, a confusing literature concerning the natural history of lymphomas, especially of the B-cell lymphomas, of the skin has accumulated.\(^1\)\(^-\)\(^10\) Fortunately, as discussed in Section I, a much more coherent picture of the pathologic classification of the cutaneous lymphomas is emerging, reflecting the recent remarkable progress in molecular biology. In Sections II and III Dr. Francine Foss and I will try to bring equally useful coherence to the clinical management of these diverse entities.

In Europe and North America approximately 90% of the 150,000 new lymphomas that are diagnosed each year are of B-cell origin. Of these, approximately 25% are follicular lymphomas, 30% to 40% are DLBCL, and the remaining 35% to 40% are one of the less common B-cell types, with none individually exceeding about 5% of the entire group. Virtually any B-cell lymphoma can involve the skin primarily or by metastasis; however, most cutaneous B-cell lymphomas are derived from the small subset composed of follicular lymphoma, DLBCL, and MZL of the MALT type. In distinct contrast with the overall relative proportions of B- and T-cell lymphomas, only one fourth to one half of all cutaneous lymphomas are of B-cell origin, and these frequencies are skewed even more toward T cell if one considers cases presenting initially in only the skin. Fortunately, we can draw on the wide experience in managing B-cell lymphomas in general when we approach the B-cell lymphomas found in the skin.

When follicular lymphoma or DLBCL involves the skin in addition to other systemic nodal or extranodal sites, management should be dictated by standard clinical indicators, including histologic subtype, stage, age at diagnosis, and presence of symptoms, with appropriate additional attention to other prognostic factors of potential utility in treatment planning, such as performance status, lactate dehydrogenase level, and biomarkers such as BCL-2, BCL-6, and CD10 expression. Other than counting as an extranodal site for purposes of assessing tumor burden and prognosis or perhaps requiring irradiation to control local disease, cutaneous involvement with systemic B-cell lymphoma does not have any distinct therapeutic implications. Thus, an asymptomatic elderly patient with follicular lymphoma of lymph nodes, bone marrow, and skin would be best served initially by watchful waiting or, if necessary to

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elimate cosmetically unacceptable lesions, small fields of local irradiation. On the other hand, a 65-year-old man with DLBCL with widespread cutaneous nodules and nodal involvement should receive an extended course of cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (CHOP-R) or an equivalent. Little controversy surrounds these choices. The challenge arises in choosing a best approach to B-cell lymphoma confined to the skin, so-called primary cutaneous B-cell lymphoma. To approach this subject I will need to identify past and present sources of confusion.

**Primary Cutaneous B-Cell Lymphoma**

PCBCL is rare, constituting no more than 20% to 30% of cases in series reporting experience with lymphoma of the skin of all types and only 1% to 3% of lymphomas in general. It is seen about twice as often in women as in men and is diagnosed at a median age similar to non-Hodgkin’s lymphoma in general, that is, 60 to 65 years. Cases before the age of 25 years are anecdotal. The etiology of PCBCL is unknown. A proposed association between infection with *B. burgdorferi* and MALT-type PCBCL has not been verified, and antibiotic treatment has proven unrewarding, in striking contrast to its effectiveness for gastric MALT lymphoma, which responds excellently to antibiotic eradication of *H. pylori*. Expected chromosomal abnormalities and oncogene overexpression have been found in subtypes of PCBCL such as t(14;18) and BCL-2 overexpression in follicular PCBCL but usually at lower frequencies than those encountered with the systemic form of the same disease. By definition, PCBCL presents largely in the skin, but most reports focusing on this entity have not provided adequate data to separate patients with stage I disease (presentation confined to a single or small number of locally clustered lesions) from those with stage IV disease (widely separated cutaneous lesions), a point I will return to.

Only three types of B-cell non-Hodgkin’s lymphoma commonly present as PCBCL: follicular lymphoma, DLBCL, and MALT-type lymphoma. Although any B-cell neoplasm, even including Hodgkin’s lymphoma or plasmacytoma, can present confined to the skin, such cases are anecdotal or, at most, very rare. As stated above, when systemic lymphoma, usually follicular or DLBCL and rarely MALT-type lymphoma, presents with cutaneous involvement in addition to other widespread sites, no special addition to standard treatment is necessary. The question of whether special measures are needed for PCBCL of follicular, diffuse large B, or MALT types has been controversial. However, using common sense and resorting to standard principles of lymphoma treatment can provide clear guidance for almost all cases. For treatment planning purposes we need to keep in mind a pragmatic staging system and the goal of curing or controlling disease with the least toxic approach. Practically, it is reasonable to divide PCBCL cases into 2 stages, I and IV, using the Ann Arbor system borrowed from Hodgkin’s lymphoma. Thus, stage I should be reserved for disease of no more than quite limited extent, such that all of it could be encompassed in a modest radiotherapy field. Stage IV should refer to widely separated or extensive lesions. The stage of most PCBCL cases can be easily assigned using these definitions. With knowledge of type, stage, age, and symptoms in hand, treatment planning is usually straightforward.

Although biologically distinct, for treatment planning purposes we can group follicular and MALT-type PCBCLs together. Stage I disease of either of these types should be treated with local irradiation unless nearby important structures, such as the eyes, might be threatened. Although long remissions have been reported after local resection without radiotherapy, local recurrence is common. In addition, the morbidity of the radiation is minimal, the cosmetic and psychological benefits of complete remission obvious, and the theoretical potential to prevent dissemination attractive. On the other hand, stage IV follicular or MALT-type PCBCL, even when evident only in the skin, is equivalent to stage IV presentation of these diseases at other sites and should be approached similarly. Measures ranging from watchful waiting to systemic chemotherapy are appropriate, and the choice should depend on standard indications, including symptoms, cosmetic acceptability, and patient desire. In this situation it is important to remember that cure is quite unlikely but long-term control with intermittent courses of chemotherapy with alkylating agents, purine analogues, or rituximab may be straightforwardly achieved. This simple approach to follicular and MALT-type PCBCLs has been associated with excellent long-term survival.

Diffuse large B-cell PCBCL, as would be expected from the behavior of this lymphoma at other sites, can progress much more aggressively than the other 2 common types of PCBCL. The penalty for not discovering more widespread disease at diagnosis is much greater with this type of PCBCL, mandating complete standard staging, including computed tomography scanning of at least the abdomen and pelvis and bone marrow biopsy. Stage I diffuse large B-cell PCBCL should be treated with brief chemotherapy with CHOP or an equivalent for 3 cycles, followed by involved field irradiation. Although some authors have argued that this may be overtreatment, several have found clearly inferior outcomes when chemotherapy was omitted or compromised by leaving out the anthracycline. The combined

American Society of Hematology
modality approach optimizes systemic and local control with the least toxicity. Stage IV diffuse large B-cell PCBCL, although confined to the skin, should be treated the same as widespread DLBCL of any presenting site using an extended course of multiagent chemotherapy.

Formulation of a desirable treatment approach to PCBCL, thus, turns out not to be very difficult once the questions of correct diagnosis and sensible stage assignment have been addressed. Following the recommendations above will lead to excellent long-term overall and disease-specific survivals with little or at most modest toxicity. Whence, then, the claim for controversy? This claim has arisen for several reasons. First of all, as clinicians we need a classification scheme that is reproducible, biologically sensible, and clinically relevant. Fortunately, as shown by Dr. Hsi, this is achievable by applying the WHO classification system. Although the EORTC Cutaneous Lymphoma Study Group, the French Study Group on Cutaneous Lymphomas, and the Dutch Cutaneous Lymphoma Working Group have drawn attention to PCBCL through their excellent work, their proposals that a separate classification scheme be used just for cutaneous lymphoma are not compelling. On the one hand, their large category of primary cutaneous follicle center cell lymphoma is an overly inclusive lumping of follicular and many of the diffuse large B-cell lymphomas together; on the other hand, their small category of large B-cell lymphoma of the leg lacks justification and reflects an unnecessary subdivision by region of the body. It is much more likely that the purported difference in prognosis for this latter entity reflects other factors such as multiple lesions, frailty of the elderly population in which it has been described, and known prognostic factors, such as presence of BCL-2, or absence of BCL-6 oncogene expression. Patients and clinicians are best served by a reproducible, simple, and clinically relevant classification scheme that identifies biologically distinct lymphomas. This scheme should be familiar to clinicians, researchers, and general, hemato-, and dermatopathologists. The now widely accepted WHO classification scheme for all lymphomas, although not perfect, serves this purpose well. Use of that scheme, sensible application of standard staging assignments, and employment of currently standard treatment approaches for the individual lymphomas within the spectrum of PCBCL will serve all of us—patients, pathologists, and clinicians—quite well.

III. CUTANEOUS T-CELL LYMPHOMA

Francine M. Foss, MD *

Primary cutaneous T-cell lymphomas (CTCLs) comprise a constellation of heterogeneous lymphoproliferative disorders characterized by clonal accumulation of neoplastic T lymphocytes in the skin. T-cell lymphomas consist of approximately 80% of all primary cutaneous lymphomas. The most common of these are MF, which takes its name from the mushroom-shaped tumor nodules that result from the vertical proliferation of infiltrating cells, and Sézary syndrome (SS). ALCL (CD30+) comprises 25% and CD30- peripheral T-cell lymphomas 10%, respectively. The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program reports an increase in the overall incidence of CTCL in the United States from 1973 to 1984, with a rise from approximately 0.2 cases per 100,000 population in 1973 to 0.4 cases per 100,000 population in 1984. However, there was no evidence of increasing incidence rate during the period of 1983 through 1992. This data included follow-up through 1994. Overall, the incidence rate from 1973 through 1992 was 0.36 per 10^5 person years.

The WHO lymphoma classification system identifies MF and the SS as a distinct clinical entity under the category of mature T-cell neoplasms. Other less common types of cutaneous T-cell lymphomas or lymphoproliferative disorders include the CD30+ lymphoproliferative disorders (lymphomatoid papulosis, primary anaplastic large cell lymphoma of the skin), pagetoid reticulosis (Woringer-Kolopp disease), granulomatous slack skin, lymphomatoid granulomatosis, large plaque parapsoriasis, and T-gamma lymphoproliferative disorder. T-cell lymphomas with more aggressive clinical features include HTLV-1-associated adult T-cell leukemia/lymphoma, peripheral T-cell lymphoma, and CD8+ epidermotropic cytotoxic T-cell lymphoma.

Clinical Manifestations

MF is characterized by infiltration of the skin by neoplastic T lymphocytes with hyperconvoluted cerebriform nuclei (mycosis cells) that usually express a mature peripheral T-cell (CD4+) phenotype. A suppressor phenotype (CD8+) may be seen infrequently. Partial loss of pan-T-cell antigens such as CD7 and CD3 may be a feature of MF but is not pathognomonic for the disease. Acti-
Skin involvement can be manifest as patches, plaques, or tumors, but patients may have more than one type of lesion simultaneously. The patch stage consists of erythematous macular lesions which occur most frequently over the trunk and extremities and are often associated with scaling or pruritis. In the plaque stage, lesions are oval or circular and well demarcated, with raised borders. Patches may coalesce into larger plaques or even give the appearance of patchy erythroderma. Dermal thickening of the skin by T-cell infiltration may lead to an infrequent but classical appearance on the face known as “leonine facies.” The differential diagnosis of plaque stage disease includes nonmalignant conditions such as eczema, psoriasis, and parapsoriasis.

Tumor stage disease represents a vertical growth phase that presents clinically as expanding nodules, which may ulcerate. The differential diagnosis for tumor stage cutaneous lymphoma includes lymphomatoid papulosis, anaplastic T-cell lymphoma of the skin, peripheral T-cell lymphoma, angioimmunoblastic T-cell lymphoma, and other rare entities.

At the time of diagnosis, 42% of MF patients have limited plaques involving 10% or less of total body surface; 30% have extensive plaques; 16% have cutaneous tumors; and 12% have generalized erythroderma. Palpable lymphadenopathy is infrequent in patients with limited plaque but occurs in approximately 50% of patients with extensive plaques, tumors, or erythroderma. SS, the leukemic variant of MF, is characterized by the triad of diffuse erythroderma, generalized lymphadenopathy, and the presence of a predominance of Sézary leukemia cells in the peripheral blood. Clinical manifestations include scaling or fissuring of the palms and soles, alopecia, pruritis, and frequent infections related to poor skin integument. The differential diagnosis includes HTLV-1 associated T-cell leukemia/lymphoma (ATL), which is distinguished by detection of antibodies directed against HTLV-1. Clinical features distinguishing ATL from SS include hypercalcemia and lytic bony lesions. Immune abnormalities noted in MF/SS include decreased cell-mediated cytotoxicity, decreased natural-killer cell and lymphokine-activated killer-cell activity, eosinophilia, increased levels of immunoglobulin E and A, and decreased cutaneous hypersensitivity.

**Prognosis and Staging**

The staging system for MF/SS is based on the type and extent of skin involvement in the form of plaques, tumors, or erythroderma, the presence of palpable lymph node involvement, and visceral disease. Lymphadenopathy is present in approximately 47% of all patients with the highest frequency occurring in tumor-stage MF, and in 80% to 90% of patients with erythroderma. Visceral involvement is most frequently found in the liver and bone marrow. At autopsy, pulmonary involvement and bone involvement are found in 60% and 40% of cases, respectively.

Skin stage is the most important prognostic factor. A recent analysis of published epidemiological data on MF concluded that 90% of patients with patch or plaque stage disease involving 10% or less of the skin surface survive for 15 years or more. In a study of 122 patients with limited cutaneous involvement, only 2% of patients had died after 32 years and 9% showed disease progression. A multivariate analysis of data from 309 Dutch patients with MF found that the 5-year disease-specific survival rates for individuals with limited skin involvement and skin tumors were 100% and 80%, respectively, but that the rate for individuals with lymph node involvement dropped to 40%. Older data indicate that median survival for patients with visceral involvement is 24 to 30 months.

Overall, patients with SS have an inferior survival compared to patients with patch or plaque stage MF. In a multivariate analysis of 51 patients with SS, the overall 5-year survival was 33.5%. When patients were stratified for risk based on 3 variables found to be adverse independent prognostic indicators—periodic acid-Schiff (PAS)-positive cytoplasmic inclusions in circulating Sézary cells, CD7+ phenotype, and evidence of histopathologic transformation of circulating Sézary cells to a large cell variant—those with zero or 1 of the indicators had a 5-year survival rate of 58%, while those with 2 or 3 had a 5-year survival rate of 5%.

Recently, the International Society for Cutaneous Lymphomas (ISCL) consensus conference defined 3 subsets of erythrodermic CTCL based on prognosis: SS (“leukemic phase” E-CTCL), erythrodermic MF (secondary E-CTCL that develops in patients with MF), and E-CTCL not otherwise defined. The hematologic criteria recommended for SS are intended to identify patients with a worse prognosis compared with the other E-CTCL subsets and consist of 1 or more of the following: (1) an absolute Sézary cell count of 1000 cells/mm³ or more, (2) a CD4/CD8 ratio of 10 or higher caused by an increase in circulating T cells and/or an aberrant loss or expression of pan-T-cell markers by flow cytometry, (3) increased lymphocyte counts with evidence of a T-cell clone in the blood by the Southern blot or polymerase chain reaction technique, or (4) a chromosomally abnormal T-cell clone.

In addition to the risk for disease progression in MF/SS patients, there is a well-established risk for cytologic transformation to CD30+ large-cell lymphoma.
diagnosis of which is established by the presence of at least 25% large cells on biopsy. In one series of 150 CTCL patients, the risk of transformation was 12%, with a median time from diagnosis to transformation of 21.5 months and median survival following transformation of 2 months. In another study of 115 MF/SS patients, 23% underwent transformation with a median time from diagnosis to transformation of 12 months, and median survival subsequent to transformation of 19 months. Analysis by the French Study Group on Cutaneous Lymphomas determined that the median time from diagnosis to transformation was 6.5 years, and the mean survival from transformation to death was 22 months.

Several staging algorithms for establishing prognosis in individual CTCL patients have been proposed since 1978. All are based on the principal risk factors for disease progression (extent of skin, nodal, and visceral involvement) and on histopathologic information from lymph node and bone marrow biopsies. In 1979, the Committee on Staging and Classification of Cutaneous T-cell Lymphoma proposed a system in which low, intermediate, and high risks were determined by differentiating 4 levels of skin involvement, 5 levels of nodal involvement, the presence or absence of palpable adenopathy, and the presence or absence of visceral involvement. Subsequently, Sausville et al at the NCI proposed a simplified version based on a multivariate analysis, which demonstrated that skin stage, histopathologic lymph node involvement, and visceral involvement were significant prognostic factors. On the basis of this classification system, 3 survival groups were identified: low-risk patients with skin patches or plaques and histopathologically uninvolved lymph nodes (stages IA, IB) had an excellent prognosis, whereas patients with visceral disease had a poor prognosis, irrespective of skin stage. Patients with skin tumors, histopathologically involved lymph nodes, and erythroderma had an intermediate prognosis, similar to that of patients with follicular B-cell lymphoma.

Bone marrow involvement was further defined in a retrospective study in which histopathologic staging of bone marrow based on presence of lymphoid aggregates or infiltrating lymphoma was performed. In this study, the presence of lymphoid aggregates had no independent prognostic significance, whereas diffuse lymphomatous infiltrates in the marrow were associated with an inferior outcome.

### Clinical Management

Initial management of CTCL is dependent on the extent of clinical manifestations and the impact of symptoms on quality of life (Tables 2 and 3). Almost all patients with MF/SS require treatment directed at the skin. Systemic therapies are used in MF/SS when patients become refractory to topical therapies or when they demonstrate signs of advanced systemic disease.

#### Skin-directed therapies

Topical corticosteroids frequently achieve good responses, particularly in early stage, providing symptomatic relief. Zackheim et al reported the largest experience with topical steroids in 79 patients with patch/plaque MF. With a median follow-up of 9 months, of the T1 patients 63% achieved complete remission and 31%, partial remission.

Topical chemotherapy using mechlorethamine (nitrogen mustard, HN2) has proved effective for cutaneous MF since its first use was reported in 1973. Re-
Table 3. New treatments for refractory cutaneous T-cell lymphoma (CTCL).

<table>
<thead>
<tr>
<th>Treatment</th>
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<tbody>
<tr>
<td>Alemtuzumab (CAMPATH 1-H)</td>
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<tr>
<td>EPOCH chemotherapy</td>
</tr>
<tr>
<td>Autologous/allogeneic bone marrow transplantation</td>
</tr>
<tr>
<td>FK228 (depsipeptide)</td>
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<tr>
<td>Temozolomide</td>
</tr>
<tr>
<td>Intermediate dose IL-2</td>
</tr>
<tr>
<td>IL-12 +/- low-dose IL-2</td>
</tr>
<tr>
<td>$^{90}$Y anti-CD25 antibody</td>
</tr>
<tr>
<td>Anti-Tac-pseudomonas immunoconjugates</td>
</tr>
</tbody>
</table>

Abbreviations: EPOCH, etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone; IL, interleukin.

Response rates range from 67-88% in patch stage disease, and 26% to 70% in stage II plaque disease. Topical chemotherapy using carmustine (BCNU) yields results similar to those of HN2. Both nitrogen mustard and carmustine can be used as an aqueous solution or formulated by a compounding pharmacy in a petroleum jelly base.

Topical bexarotene gel has recently been approved by the Food and Drug Administration for patients with CTCL. Bexarotene is a novel retinoid that selectively binds to the RXR (retinoid X-receptor) family of retinoid receptors. In Phase I/II and Phase III clinical trials, the complete response rates with bexarotene gel were reported to be 21-23%, respectively, with an overall response rate of 63% and a median time to progression of 149 days (range, 56-342 days). The response rate was highest in patients with patch and plaque disease. Toxicities included rash in 56% and pruritus in 18%.

Phototherapy using ultraviolet A (PUVA) with psoralen, or ultraviolet B (UVB), has been shown to be effective for treating early-stage disease. In a retrospective study of 30 patients, 25 (83%) achieved complete remission after a median of 5 months of UVB treatment 3 times per week. The median duration of remission was 22 months. The addition of low-dose interferon-α (IFN-α) had improved response rates in early-stage disease to 80%. The long-term disease-free survival of early-stage MF patients treated with PUVA is 15% to 20%, but toxicities include secondary skin cancers in up to 20% of patients.

Radiation therapy has been an important modality for treating both early and advanced MF/SS. Total skin electron beam therapy (TSEBT) consisting of a total of 30 to 36 Gy is used most commonly in patients with diffuse plaque involvement that is refractory to other skin-directed therapies, in tumor-stage MF, and in patients with SS. Complete response rates to TSEBT range from 56% to 96% in patients with stages IA to IIA CTCL. Patients with stage IA disease have a relapse-free survival rate of 33% to 52% at 10 years, compared to 16% for those with stage IB disease.

Toxicities associated with TSEBT include erythema, desquamation, temporary depilation, and temporary loss of fingernails, toenails, and sweat gland function. Several clinical trials have explored the efficacy of TSEBT combination therapies. In a trial of 103 previously untreated patients randomized to conservative (topical) therapy or combination chemotherapy with CAPO (cyclophosphamide, Adriamycin, etoposide, vincristine, prednisone) and TSEBT, the response rates were significantly higher in the combined modality arm, but with a median follow-up of 75 months, there was no difference in disease-free or overall survival.

Extracorporeal photopheresis (ECP), a systemic form of PUVA therapy, has been shown to be an effective immunoadjuvant therapy in CTCL. ECP involves exposure of leukapheresed mononuclear cells to a psoralen photoactivating agent (e.g., 8-MOP or UVADEX) and ultraviolet light (UVA) ex vivo followed by reinfusion of the treated cells. Studies suggest that ECP is most effective in patients with erythrodermic CTCL. The mechanism of action of ECP involves the induction of an anti-idiotype cytotoxic T-cell response against circulating tumor cells, which undergo apoptosis after exposure to UVA in the presence of methoxy-psoralen. The addition of IFN or retinoids to ECP has improved response rates and response durations in some patients.

In a recent pilot study, immune activation of lymphocytes and natural killer cells using ultra low doses of interleukin-2 along with ECP has been implemented and is associated in a small group of patients with a rapid decrease in circulating tumor cells and improvement in skin disease. Ongoing studies are exploring other potential adjuvants to ECP, including oral bexarotene (Targretin).

Systemic therapy for CTCL (Table 4)

Single-agent systemic cytotoxic chemotherapy has been used to treat patients with refractory MF. Initial therapy may consist of pulse steroids, alkylating agents, or methotrexate. Single-agent therapy can induce complete responses in up to 30% of patients, but remissions are typically of short duration. Methotrexate given orally twice weekly or by intravenous infusion has been reported to have activity in up to 72% of patients.

Purine analogs have demonstrated activity in both CTCL and other peripheral T-cell lymphomas. Response rates ranging from 20-40% have been reported in several small series of refractory CTCL patients treated with fludarabine or cladribine. Gemcitabine has demon-
Pentostatin (deoxycoformycin) has been shown to have activity in up to 60% of patients, with complete responses in 33%.44 Combination systemic chemotherapy has been associated with high response rates, but responses generally are not durable. In a recent Phase II evaluation of the EPOCH regimen (etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone), of 15 patients with advanced, refractory CTCL, including 6 patients with SS, the complete response rate was 27% and the partial response rate was 53%. Two of 6 patients with SS had complete disappearance of circulating Sézary cells.45 Another regimen, VICOP-B (idarubicin, etoposide, cyclophosphamide, vincristine, bleomycin, prednisone; EPOCH, etoposide, vincristine, doxorubicin, bolus cyclophosphamide, oral prednisone; IFN, interferon; ONTAK, denileukin diftitox)

Table 4. Systemic therapies for cutaneous T-cell lymphoma (CTCL).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Duration, months (median)</th>
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<tbody>
<tr>
<td>Pegylated liposomal doxorubicin</td>
<td></td>
</tr>
<tr>
<td>(PEG-DOXO)10</td>
<td>15</td>
</tr>
<tr>
<td>TSEB + CAPO31</td>
<td>13.7</td>
</tr>
<tr>
<td>VICOP-B</td>
<td>8.7</td>
</tr>
<tr>
<td>EPOCH45</td>
<td>8</td>
</tr>
<tr>
<td>IFN 3-18 mU48</td>
<td>5.4</td>
</tr>
<tr>
<td>IFN high dose 16</td>
<td>8</td>
</tr>
<tr>
<td>Fludarabine 17</td>
<td>3</td>
</tr>
<tr>
<td>2-CDA 18,19</td>
<td>4.3</td>
</tr>
<tr>
<td>Pentostatin 2-5 mg/m² x 320-22</td>
<td>1.3-8.3</td>
</tr>
<tr>
<td>ONTAK 9-18 μg/kg x 5 days 23</td>
<td>7.3</td>
</tr>
<tr>
<td>Pentostatin and Interferon 24</td>
<td>13.1</td>
</tr>
<tr>
<td>Fludarabine and Interferon 25</td>
<td>6.5</td>
</tr>
<tr>
<td>Bexarotene 300mg/m² daily 26</td>
<td>7.5</td>
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Abbreviations: TSEB, total skin electron beam; CAPO, cyclophosphamide, adriamycin, etoposide, vincristine, prednisone; VICOP-B, idarubicin, etoposide, cyclophosphamide, vincristine, bleomycin, prednisone; EPOCH, etoposide, vincristine, doxorubicin, bolus cyclophosphamide, oral prednisone; IFN, interferon; ONTAK, denileukin diftitox

Pentostatin (deoxycoformycin) has been shown to have activity in up to 60% of patients, with complete responses in 33%.44

Combination systemic chemotherapy has been associated with high response rates, but responses generally are not durable. In a recent Phase II evaluation of the EPOCH regimen (etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone), of 15 patients with advanced, refractory CTCL, including 6 patients with SS, the complete response rate was 27% and the partial response rate was 53%. Two of 6 patients with SS had complete disappearance of circulating Sézary cells.45 Another regimen, VICOP-B (idarubicin, etoposide, cyclophosphamide, vincristine, bleomycin, prednisone) was associated with an 80% response rate (36% CR) and a median duration of 8.7 months in 23 patients with MF, but there were no responses in patients with SS.9

Pegylated liposomal doxorubicin (PEG-DOXO) has been shown to have significant activity in advanced MF. Of 10 patients treated, 9 responded. The median time to progression was 15 months.10 Despite encouraging response rates with single agent or combination cytotoxic therapies, however, no significant survival benefit has been demonstrated with these therapies.

IFN-α has been used at a variety of doses and schedules in CTCL and response rates have ranged from 15-60%.46-48 A dose escalation study of doses ranging from 3-18 million units 3 times a week in 53 patients determined that response in some patients may be dose-dependent. Olsen and Bunn reported that the mean time to an objective response to IFN-α2a was 5.4 months, but that maximum response may take much longer as is indicated by a range of 0.6 months to 14.8 months.48

There is no evidence to date that combining IFN with other therapies improves response. Two trials in which IFN was combined with ECP yielded unconvincing results.48,49 Combination treatment using INF-α2a and fludarabine phosphate in 35 patients with advanced or refractory MF or SS demonstrated a 51% overall response rate, and a similar study using sequential IFN-α2a and pentostatin reported a response rate of 41%, with a median response duration of 13 months.50,51 Of note, several patients in these studies were in unmaintained complete response for greater than 10 years.

Interleukin-12 (IL-12) has also demonstrated activity in patients with early-stage CTCL, with a 50% objective response rate reported in a Phase II study.52 The benefit from IL-12 appears to be its potent stimulation of IFN-γ.53 Rook and colleagues demonstrated that Sézary leukemia cells express predominantly Th2 cytokines and that Th1 cytokine production by normal lymphocytes in CTCL patients is suppressed.12 After administration of IL-12 to CTCL patients treated on a Phase I clinical trial, Th1 cytokine secretion was restored and infiltrating CD8+ cytotoxic T-cells could be documented in involved skin lesions. In a Phase II trial of subcutaneously administered IFN-γ, 31% of CTCL patients experienced objective responses.54 A multicenter study is underway to further explore the efficacy of IL-12 alone and in combination with low-dose IL-2 in refractory CTCL patients.

Denileukin diftitox (DAB389IL-2, ONTAK) is a fusion toxin consisting of the enzymatically active moiety of diphtheria toxin and the full-length sequence of the IL-2 gene. This chimeric protein binds to and intoxicates high-affinity IL-2 receptor expressing cells. Immunohistochemical analysis of over 250 skin biopsies from CTCL patients demonstrates that IL-2 receptor expression, as measured by CD25 immunostaining, is present in 50-60% of cases.55,56 In a Phase I trial of denileukin diftitox in which 35 CTCL patients were enrolled, the response rate was 37%, with 5 (14%) CR.57 Seventy-one CTCL patients enrolled in a subsequent Phase III trial of 2 doses of denileukin diftitox (9 or 18
µg/kg/day × 5 doses q 21 days). Twenty percent of patients had partial responses and 10% experienced complete responses. The response rate and duration of response (median, 6.9 months; range, 2.7–46.1 months) did not differ significantly between the 2 dosage groups. Toxicities included infusion-related events in 69% and vascular leak syndrome in 23%. In a recent study combining corticosteroid premedication with ONTAK, the response rate in refractory CTCL patients was 60% and the frequency and severity of hypersensitivity reaction and capillary leak were significantly diminished.59

The role of retinoid therapy in CTCL has expanded recently with the availability of novel RXR retinoids. In early studies with the RAR (retinoid A receptor) retinoids, 13-cis-retinoic acid, responses were noted in up to 40% of patients in several small series.60–62 RAR retinoids have been combined with other therapies such as PUVA, IFN, and TSEBT, but such combinations have not been found to be significantly better than IFN or TSEBT alone. Bexarotene, an RXR ligand that selectively binds and activates retinoid X receptor subtypes (RXRα, RXRβ, RXRγ), has demonstrated activity both orally and topically in the treatment of CTCL. The exact mechanism of action of bexarotene in the treatment of CTCL is unknown, but bexarotene has been shown to induce apoptosis in selected epithelial tumor cell lines. In clinical trials of refractory CTCL patients treated at doses of bexarotene ranging from 6-650 mg/m², the overall response rate was 50%, with a time to progression of 30 weeks at 300 mg/m² and 74 weeks at > 300 mg/m².63 A significant response was reported in patients with Sézary syndrome, with > 70% clearing of skin by week 12. Significant adverse events included hyperlipidemia, hypercholesterolemia, and hypothyroidism, requiring dose reductions in most patients.

Recently, trials of combination therapies with bexarotene have been initiated. Because bexarotene has been demonstrated to upregulate expression of the high-affinity IL2R, a Phase I dose escalation trial of Tar gutrin with ONTAK was initiated. Of 14 patients treated on this trial, upregulation of IL2R was demonstrated in 13, even at low doses of bexarotene (150 mg/d). Responses have been observed in up to 60% of patients, including patients who had a suboptimal response to ONTAK alone. A Phase II study is under way.

Novel agents for refractory CTCL
Alemtuzumab (CAMPATH-1H) has demonstrated activity in CTCL. In 2 studies, 2 of 8 patients with MF had complete responses, and 2 others had partial responses.13,64 Another targeted therapy, 90Y-T101, a radioimmunoconjugate, demonstrated activity in 3 of 8 patients with CTCL, who had partial responses.65,66 Other T-cell targeted therapies include unmodified and 90Y anti-CD25 antibody and anti-Tac pseudomonas exotoxin immunocjugates.67 Investigational agents currently in Phase II clinical trials for CTCL include intermediate dose (11 m/IU) IL-2, temozolomide,14 IL-12 in combination with low-dose IL-2, and FK228 (depsipeptide).15 A number of studies have demonstrated the role of autologous and allogeneic bone marrow transplant for selected patients.68 Development of vaccine strategies for CTCL is also under way.

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