Non-Hodgkin’s Lymphomas

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NCCN.org
Classification and Staging
### Classification

**Table 1**

**WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2008)**

<table>
<thead>
<tr>
<th>Mature B-Cell Neoplasms</th>
<th>Diffuse large B-cell lymphoma (DLBCL), NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
<td>◦ T-cell/histiocyte-rich large B-cell lymphoma</td>
</tr>
<tr>
<td>• B-cell prolymphocytic leukemia</td>
<td>◦ Primary DLBCL of the CNS</td>
</tr>
<tr>
<td>• Splenic marginal zone lymphoma</td>
<td>◦ Primary cutaneous DLBCL, leg type</td>
</tr>
<tr>
<td>• Hairy cell leukemia</td>
<td>◦ EBV positive DLBCL of the elderly*</td>
</tr>
<tr>
<td>• Splenic lymphoma/leukemia, unclassifiable*</td>
<td>◦ DLBCL associated with chronic inflammation</td>
</tr>
<tr>
<td>◦ Splenic diffuse red pulp small B-cell lymphoma*</td>
<td>◦ Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>◦ Hairy cell leukemia-variant*</td>
<td>◦ Primary mediastinal (thymic) large B-cell lymphoma</td>
</tr>
<tr>
<td>• Lymphoplasmacytic lymphoma</td>
<td>◦ Intravascular large B-cell lymphoma</td>
</tr>
<tr>
<td>◦ Waldenström’s macroglobulinemia</td>
<td>◦ ALK-positive large B-cell lymphoma</td>
</tr>
<tr>
<td>• Heavy chain diseases</td>
<td>◦ Plasmablastic lymphoma</td>
</tr>
<tr>
<td>◦ Alpha heavy chain disease</td>
<td>◦ Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease</td>
</tr>
<tr>
<td>◦ Gamma heavy chain disease</td>
<td>◦ Primary effusion lymphoma</td>
</tr>
<tr>
<td>◦ Mu heavy chain disease</td>
<td>◦ Burkitt lymphoma</td>
</tr>
<tr>
<td>• Plasma cell myeloma</td>
<td>◦ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma</td>
</tr>
<tr>
<td>• Solitary plasmacytoma of bone</td>
<td>◦ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>• Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT type)</td>
<td></td>
</tr>
<tr>
<td>• Nodal marginal zone lymphoma</td>
<td></td>
</tr>
<tr>
<td>◦ Pediatric nodal marginal zone lymphoma*</td>
<td></td>
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<tr>
<td>• Follicular lymphoma</td>
<td></td>
</tr>
<tr>
<td>◦ Pediatric follicular lymphoma*</td>
<td></td>
</tr>
<tr>
<td>• Primary cutaneous follicle center lymphoma</td>
<td></td>
</tr>
<tr>
<td>• Mantle cell lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

*The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.
**Table 1 continued**

<table>
<thead>
<tr>
<th>Mature T-Cell and NK-Cell Neoplasms</th>
<th>Hodgkin Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• T-cell prolymphocytic leukemia</td>
<td>• Nodular lymphocyte-predominant Hodgkin lymphoma</td>
</tr>
<tr>
<td>• T-cell large granular lymphocytic leukemia</td>
<td>• Classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>▶ <em>Chronic lymphoproliferative disorder of NK-cells</em></td>
<td>▶ Nodular sclerosis classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>• Aggressive NK cell leukemia</td>
<td>• Lymphocyte-rich classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>• Systemic EBV-positive T-cell lymphoproliferative disorder of childhood</td>
<td>• Mixed cellularity classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>• Hydroa vacciniforme-like lymphoma</td>
<td>• Lymphocyte-depleted classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>• Adult T-cell leukemia/lymphoma</td>
<td></td>
</tr>
<tr>
<td>• Extranodal NK/T-cell lymphoma, nasal type</td>
<td></td>
</tr>
<tr>
<td>• Enteropathy-associated T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>• Hepatosplenic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>• Subcutaneous panniculitis-like T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>• Mycosis fungoides</td>
<td></td>
</tr>
<tr>
<td>• Sézary syndrome</td>
<td></td>
</tr>
<tr>
<td>• Primary cutaneous CD30-positive T-cell lymphoproliferative disorders</td>
<td></td>
</tr>
<tr>
<td>▶ Lymphomatoid papulosis</td>
<td></td>
</tr>
<tr>
<td>• Primary cutaneous anaplastic large cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>• Primary cutaneous gamma-delta T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>• <em>Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma</em></td>
<td></td>
</tr>
<tr>
<td>• <em>Primary cutaneous CD4-positive small/medium T-cell lymphoma</em></td>
<td></td>
</tr>
<tr>
<td>• Peripheral T-cell lymphoma, NOS</td>
<td></td>
</tr>
<tr>
<td>• Angioimmunoblastic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>• Anaplastic large-cell lymphoma, ALK positive</td>
<td></td>
</tr>
<tr>
<td>• Anaplastic large-cell lymphoma, ALK negative*</td>
<td></td>
</tr>
</tbody>
</table>

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*The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.

#These lesions are classified according to the leukemic or lymphoma to which they correspond.

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# Non-Hodgkin’s Lymphomas

## Lugano Modification of Ann Arbor Staging System*
(for primary nodal lymphomas)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Involvement</th>
<th>Extranodal (E) status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limited</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>One node or a group of adjacent nodes</td>
<td>Single extranodal lesions without nodal involvement</td>
</tr>
<tr>
<td>Stage II</td>
<td>Two or more nodal groups on the same side of the diaphragm</td>
<td>Stage I or II by nodal extent with limited contiguous extranodal involvement</td>
</tr>
<tr>
<td>Stage II bulky**</td>
<td>II as above with “bulky” disease</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Advanced</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>Nodes on both sides of the diaphragm</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Nodes above the diaphragm with spleen involvement</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Additional non-contiguous extralymphatic involvement</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

* Extent of disease is determined by PET-CT for avid lymphomas, and CT for non-avid histologies

Note: Tonsils, Waldeyer’s ring, and spleen are considered nodal tissue

**Whether II bulky is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Categorization of A versus B has been removed from the Lugano Modification of Ann Arbor Staging.

Classification

In 1956, Rappaport et al. proposed a lymphoma classification that was based on the pattern of cell growth (nodular or diffuse), and size and shape of the tumor cells.\(^1,2\) This classification, though widely used in the United States, quickly became outdated with the discovery and the existence of distinct types of lymphocytes (B, T and NK). The Kiel classification became the first and most significant classification that applied this new information to the classification of lymphomas.\(^3-5\) According to the Kiel classification, the lymphomas were divided into low-grade and high-grade based on the histological features. This classification was widely used in Europe. The use of different classification systems in clinical studies made it difficult to compare results from clinical studies. Hence, the International Working Formulation (IWF) for NHLs was developed to standardize the classification of lymphomas.

International Working Formulation Classification

The IWF classified NHL into three major categories as low, intermediate and high grade, based on the morphology and natural history.\(^6\) This classification divided DLBCL into intermediate and high grade groups. However, these distinctions were not reproducible. Since this classification did not include immunophenotyping, the categories were not reproducible.\(^7\) In addition, after this classification was published many new diseases were described that were not included in the IWF classification.

Revised European American Classification

In 1994, the International Lymphoma Study Group (ILSG) developed the REAL classification, which classified lymphomas based on the cell of origin (B, T, or NK) and included morphology, immunophenotype, genetic and clinical features to define diseases.\(^8\) In 1997, the International Lymphoma Classification Project performed a clinical evaluation of the Revised European American Classification (REAL) classification in a cohort of 1,403 cases of NHL.\(^9,10\) The diagnosis of NHL was confirmed in 1,378 (98.2%) of the cases. This study identified the thirteen most common histological types, comprising about 90% of the cases of NHL in the United States. The findings were as follows: DLBCL, 31%; follicular lymphoma (FL), 22%; small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), 6%; mantle cell lymphoma (MCL), 6%; peripheral T-cell lymphoma (PTCL), 6%; and mucosa associated lymphoid tissue (MALT) lymphoma, 5%. The remaining subtypes each occurred in less than 2% of cases. Importantly, in the United States more than 50% of cases of lymphoma are either DLBCL or FL. The study investigators concluded that the REAL classification can be readily applied and identifies clinically distinctive types of NHL.

World Health Organization Classification

In 2001, the World Health Organization (WHO) updated the classification of hematopoietic and lymphoid neoplasms.\(^11,12\) The 2001 WHO classification applied the principles of REAL classification and represented the first international consensus on classification of hematologic malignancies. The REAL/WHO classification of NHL includes many entities not recognized by the IWF.\(^11,12\) After consideration of cell of origin (B, T, or NK), the classification subdivides lymphomas into those derived from precursor lymphocytes versus those derived from mature lymphocytes. The classification is further refined based on immunophenotype, genetic, and clinical features. These considerations have aided in defining active treatment for specific subtypes of lymphoma.

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/28/2014.
In 2008, the International T-cell lymphoma Project evaluated the WHO classification of T-cell lymphoma in a cohort of 1,314 cases of PTCL and natural killer/T-cell lymphomas (NKTCL). The diagnosis of PTCL or NKTCL was confirmed in 1,153 cases (88%). The most common subtypes were PTCL-not otherwise specified (NOS; 25.9%), angioimmunoblastic lymphoma (18.5%), NKTCL (10.4%), adult T-cell leukemia/lymphoma (ATLL; 9.6%), anaplastic large cell lymphoma (ALCL), ALK-positive (6.6%) and ALCL, ALK-negative (5.5%). The findings of this study validated the utility of the WHO classification for defining subtypes of T-cell lymphomas.

The WHO classification was updated again in September 2008 to add new diseases and subtypes that have been recognized in the past decade, and to better define some of the heterogeneous and ambiguous categories based on the recent advances. Genetic features, detected by cytogenetics or fluorescence in-situ hybridization (FISH) are increasingly important in defining specific NHL subtypes. In addition, detection of viruses, particularly Epstein-Barr virus, HHV8 and HTLV1, is often necessary to establish a specific diagnosis.

**2008 WHO Classification of Mature B-cell Lymphomas**

**CLL/SLL**

The updated classification includes the definition issued by the International Working Group on CLL (IWCLL). The diagnosis of CLL requires the presence of monoclonal B lymphocytes ≥ 5 x 10⁹/L in peripheral blood and the clonality of B cells should be confirmed by flow cytometry. The presence of fewer than 5000/mm³ B-lymphocytes in the absence of lymphadenopathy, organomegaly or other clinical features is defined as monoclonal B-lymphocytosis (MBL). CLL requiring treatment develops in individuals with CLL-phenotype MBL and with lymphocytosis at the rate of 1.1% per year.

**Follicular Lymphoma**

In FL, pathological grading according to the number of centroblasts is considered to be a clinical predictor of outcome. In the 2001 WHO classification, three grades were recommended: FL1, FL2, and FL3; FL3 could be optionally stratified into 3A (centrocytes still present) or 3B (sheets of centroblasts). However, clinical outcomes for patients with FL1 and FL2 do not differ and this classification was deemed unreliable. Therefore, in the updated 2008 WHO classification, these grades are grouped under a single grade (FL1-2). Hans et al reported that there was no difference in survival outcomes between patients with Grade 3A and 3B FL, whereas patients with FL3 with more than 50% diffuse component have an inferior survival similar to the survival of those with DLBCL. FL3B with cytogenetic abnormalities of BCL6 (at 3q27) are thought to be genetically more akin to germinal center type DLBCL than FL1-3A, and is associated with a more aggressive clinical course. Patients with FL3B with BCL2 translocation appear to have a clinical course similar to patients with FL1-3A. Since FL3B is rare, the clinical behavior of FL3 in most studies is based mainly on FL3A cases. The 2008 WHO classification mandates stratifying FL3 into either 3A or 3B. FL is thus still divided into three grades (FL1-2, FL3A and FL3B) based on the number of centroblasts. Any diffuse areas in FL should be given a separate diagnosis of DLBCL, if it meets the criteria for FL3A or 3B. Pediatric-type FL, primary intestinal FL, other extranodal FLS and follicular lymphoma “in situ” (FLIS) are the other variants that are included under FL.

**Pediatric-type follicular lymphoma:** Pediatric-type FL is considered a rare variant of FL in the 2008 WHO classification and is generally characterized by lack of BCL2 rearrangement and t(14,18), which constitute the genetic hallmark of conventional FL seen in adults. Pediatric-type FL has a better prognosis than adult FL and is often cured with minimal therapy.
Primary intestinal follicular lymphoma: FL of the gastrointestinal tract is a recently described entity, which is common in the small intestine with the vast majority of cases occurring in the duodenum. The morphology, immunophenotype, and genetic features are similar to those of nodal FL. However, most patients have clinically indolent and localized disease. Survival appears to be excellent even without treatment.

Other extranodal follicular lymphoma: In many of the other extranodal sites, the morphology, immunophenotype, and genetic features are similar to those of nodal FL. Patients usually have localized disease and systemic relapses are rare.

Follicular Lymphoma “in situ”: FLIS is characterized by the preservation of the lymph node architecture, with the incidental finding of focal strongly positive staining for BCL2 (restricted to germinal centers) and CD10 in the involved follicles, and the detection of t(14;18) by FISH. FLIS has been reported in patients with prior FL or concurrent FL (at other sites), as well as in individuals with no known history of FL. The occurrence of FLIS in the general population appears to be rare.

Primary Cutaneous Follicle Center Lymphoma (PC-FCL)
This is a new category in the 2008 classification and is defined as a tumor of neoplastic follicle center cells, including centrocytes and variable numbers of centroblasts, with a follicular, follicular and diffuse or a diffuse growth pattern. PC-FCL is the most common B-cell lymphoma of the skin and it is classified as a distinct entity in the EORTC classification of cutaneous lymphomas. Gene expression profiling studies have also provided evidence in support of this classification. PC-FCL presents as a solitary or localized skin lesion on the scalp, forehead or the trunk. It is characterized by an indolent course and rarely disseminates to extracutaneous sites. PC-FCL is consistently BCL6-positive, may be CD10-positive in cases with a follicular growth pattern. BCL2 is often either negative or dim (predominantly seen in cases with a follicular growth pattern). PC-FCL has an excellent prognosis with a 5-year survival rate of 95%. PC-FCL must be distinguished from primary cutaneous DLBCL, leg type, which is not always possible histologically, and can be identified by expression of IRF4/MUM1, is strongly BCL2+ and has a more unfavorable prognosis.

Diffuse Large B-cell Lymphomas
Some of the new categories of DLBCL are defined by extranodal primary sites and the association with viruses such as EBV or HHV8. Two borderline categories have also been included to incorporate cases in which it is not possible distinguish between adult Burkitt lymphoma (BL) and DLBCL, and primary mediastinal large B-cell lymphoma (PMBL) and nodular sclerosis classical Hodgkin lymphoma (NSCHL). The ALK-positive DLBCL, plasmablastic lymphoma and primary effusion lymphoma are considered as distinct entities. The 2008 classification also has new category of large B-cell lymphoma arising in HHV8-associated multicentric Castleman’s disease.

DLBCL, Not Otherwise Specified (NOS)
The 2008 classification has included DLBCL, NOS as a new category to include GCB and ABC subtypes as well as other DLBCL cases that do not belong to any of the four specific subtypes (T-cell/histiocyte rich large B-cell lymphoma, primary CNS DLBCL, primary cutaneous DLBCL ("leg type") or EBV+ DLBCL of the elderly).

Gene expression profiling (GEP) has been used to identify distinct subtypes of DLBCL: germinal center B-cell (GCB) subtype, activated B-cell (ABC) subtype, primary mediastinal B-cell lymphoma (PMBL), and type 3 which includes cases that cannot be classified as GCB, ABC, or PMBL subtypes. GEP is not yet recommended for routine
clinical use. Immunostaining algorithms have been developed to
differentiate between GCB and ABC subtypes using a combination of
CD10, BCL6, IRF4/MUM1, GCET1 and FOXP1, and the outcome
appears improved in GCB patients, though subtype does not impact
choice of therapy at the present time.

B-cell Lymphoma, Intermediate between BL and DLBCL
BL is characterized by t(8;14), which results in the juxtaposition of
MYC gene from chromosome 8 with the immunoglobulin heavy chain
variable (IGHV) region on chromosome14 and variant translocations
involving MYC and the immunoglobulin light chain genes. Nevertheless,
MYC translocations also occur in DLBCL. GEP studies have confirmed that the distinction between BL and DLBCL is not
reliably reproducible with the use of the current criteria of morphology,
immunophenotype, and genetic abnormalities. Mature aggressive
B-cell lymphomas without a molecular BL signatures (non-mBL) with
MYC rearrangements as well as those with both t(8;14) and t(14:18)
translocations are associated with a poor prognosis.

This provisional category replaces the “Atypical Burkitt Lymphoma”
that was included in the 2001 WHO classification. The new category
includes lymphomas with features of both DLBCL and BL, but or
biological and clinical reasons should not be diagnosed as DLBCL or
BL. Lymphomas in this provisional category include those that are
morphologically intermediate between BL and DLBCL with
immunophenotype suggestive of BL (CD10-positive, BCL6-positive,
BCL2-negative and IRF4/MUM1-negative or weakly positive),
lymphomas that are morphologically similar to BL but are strongly
BCL2-positive and those with both MYC and BCL2 rearrangements
(“double hit”) and complex karyotypes.

B-cell Lymphoma Intermediate between PMBL and NSCHL
PMBL has been recognized as a subtype of DLBCL based on its
distinctive clinical and morphological features. NSCHL is the most
common form of HL. Both tumors occur in the mediastinum and affect
adolescents and young adults. GEP studies strongly support a
relationship between PMBL and CHL. About a third of the genes that
were more highly expressed in PMBL were also characteristically
expressed in CHL cells. Traverse-Glehen, et al., reported borderline
cases with biologic and morphologic features of both CHL and B-cell
NHL, known as "mediastinal gray zone lymphomas".

This provisional category includes lymphomas with overlapping
features between CHL and DLBCL, especially PBML. Those cases
that morphologically resemble NSCHL have a strong expression of
CD20 and other B-cell associated markers. Those cases that
resemble PBML may have dim or no expression of CD20, strong
expression of CD30 and CD15. These lymphomas have a more
aggressive course and poorer outcome than either CHL or PBML.

Primary Cutaneous DLBCL, Leg Type (PC-DLBCL)
PC-DLBCL, leg type, is an unusual form of DLBCL composed of large
transformed B cells most commonly arising on the leg (85-90%)
although it can arise at other sites (10-15%). These tumors arise
from post-germinal center B-cell with expression of CD20,
IRF4/MUM1, FOXP1, and BCL2; many cases express BCL6 and lack
expression of CD10. These tumors can disseminate to
non-cutaneous sites, including the CNS. Studies have reported the
development of extracutaneous relapse in 17-47% of patients with
PC-DLBCL. In a study in patients with PC-DLBCL (N=60), CNS
was the most common site of visceral progression, occurring in 27% of
patients with extracutaneous relapse (or in 12% of all patients on this
study). The high frequency of extracutaneous relapse in PC-DLBCL
results in a poorer prognosis than the other cutaneous B-cell lymphomas, especially when the presentation involves multiple cutaneous lesions.47

2008 WHO Classification of Mature T-cell and NK-cell Lymphomas

The 2008 WHO classification has adapted the EOTRC classification for cutaneous T-cell lymphomas.28 The new categories include primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous aggressive epidermotropic CD9-positive cytotoxic T-cell lymphoma and primary cutaneous small/medium CDE4-positive T-cell lymphoma. Anaplastic large cell lymphoma (ALCL), ALK-negative is now separated out from PTCL-NOS as a provisional entity.

**ALCL**

ALCL accounts for less than 5% of all cases of NHL. There are now three distinctly recognized subtypes of ALCL: ALCL, ALK-positive, ALCL, ALK-negative and primary cutaneous ALCL. Primary cutaneous ALCL is a distinct subtype of mature T-cell lymphoma. ALK-positive ALCL is most common in children and young adults. It is characterized by the over expression of anaplastic lymphoma kinase (ALK1) protein, resulting from t(2;5) in 40-60% of patients.49,50 Although clinically aggressive, it is highly curable with CHOP chemotherapy. The distinction between ALK-positive and ALK-negative ALCL was not required in the 2001 WHO classification. It is now clear that ALK-positive ALCL is a well-defined clinicopathologic entity. The International Peripheral T-Cell Lymphoma Project reported that patients with ALK-positive ALCL had a superior outcome compared with those with ALK-negative ALCL [5-year failure-free survival (FFS): 60% vs. 36%; and 5-year overall survival (OS): 70% vs. 49%].51 Contrary to prior reports, ALK-negative ALCL was associated with a better outcome than PTCL-NOS. The 5-year FFS (36% vs. 20%) and OS (49% vs. 32%) were superior compared with PTCL-NOS. A recent analysis from the GELA found that age and beta-2 microglobulin, not ALK1 expression, were the most significant prognostic factors of overall survival for patients with ALCL; however, age was very closely associated with ALK1 expression.52 Patients with primary cutaneous ALCL had a very favorable 5-year OS (90%) despite being negative for ALK1; the 5-year FFS rate was 55%. The findings of this study confirmed that ALK-negative ALCL should be separated from both ALK-positive ALCL and PTCL-NOS. Based on the recent findings, the 2008 WHO classification has included a provisional category for ALK-negative ALCL. It is morphologically identical to ALK-positive ALCL, with a strong and diffuse expression of CD30, no expression of B-cell antigens and absence of ALK1. The prognosis is intermediate between that of ALK-positive ALCL and PTCL-NOS.

**Response Criteria**

The International Working Group (IWG) published the guidelines for response criteria for lymphoma in 1999. These response criteria are based on the reduction in the size of the enlarged lymph node as measured by CT scan and the extent of bone marrow involvement that is determined by bone marrow aspirate and biopsy.53 These guidelines were revised in 2007 by the International Harmonization Project to incorporate IHC, flow cytometry and 18-fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans in the definition of response for lymphoma.54 In the revised guidelines, the response category of complete response uncertain (CRu) was essentially eliminated because residual masses were defined as a partial response (PR) or a complete response (CR) based on the result of a PET scan. Using the revised system, response is categorized as CR, PR, stable disease (SD) and relapsed disease or progressive disease (PD).
However, the application of PET to responses is limited to histologies where there is reliable FDG uptake in active tumor. However, the revised response criteria have thus far only been validated for DLBCL and Hodgkin lymphoma. The application of the revised response criteria to other histologies requires validation and the original IWG guidelines should be used. Of note, the IWG response criteria may not be applicable for several of the tumor subtypes included in the NCCN Guidelines. Tumor specific response criteria are included in the guidelines for CLL/SLL, MF/SS, ATLL, HCL and T-PLL.

**Diagnosis**

In all cases of NHL, the most important first step is an accurate pathologic diagnosis. The basic pathological evaluation is the same in each Guidelines (by tumor subtype), although some further evaluation may be useful in certain circumstances to clarify a particular diagnosis; these are outlined in the pathological evaluation of the individual Guidelines.

An incisional or excisional lymph node biopsy is recommended to establish the diagnosis of NHL. Core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of obtaining diagnostic tissue. Fine needle aspiration (FNA) biopsy is widely used in the diagnosis of malignant neoplasms, but its role in the diagnosis of lymphoma is still controversial. Since the revised REAL/WHO classification is based on both morphology and immunophenotyping, FNA alone is not acceptable as a reliable diagnostic tool for NHL. However, its use in combination with ancillary techniques may provide precise diagnosis thereby obviating the need for a more invasive biopsy in highly selected circumstances. Recent studies have shown that the diagnostic accuracy of FNA improves significantly when it is used in combination with IHC and flow cytometry.

In the NCCN Guidelines, FNA alone is not suitable for an initial diagnosis of NHL, though it may be sufficient to establish relapse. However, in certain circumstances, when a lymph node is not easily accessible, a combination of core biopsy and FNA in conjunction with appropriate ancillary techniques [PCR for \( IGHV \) and/or T-cell receptor (TCR) gene rearrangements; FISH for major translocations; immunophenotypic analysis] may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL. In other entities presenting in leukemic phase, such as FL or MCL, a biopsy is still preferred to clarify histological subtype.

Immunophenotypic analysis is essential for the differentiation of various subtypes of NHL to establish the proper diagnosis. It can be performed by flow cytometry and/or IHC; the choice depends on the antigens as well as the expertise and resources available to the hematopathologist. In some cases flow cytometry and IHC are complementary diagnostic tools. Cytogenetic or molecular genetic analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are characteristic of some NHL subtypes or to establish clonality.

After the publication of the 2008 WHO Classification, the NHL Guidelines panel developed a series of algorithms for the use of immunophenotyping in the diagnosis of mature lymphoid neoplasms. These algorithms were developed to provide guidance for surgical pathologists as well as an aid to the clinician in the interpretation of pathology reports and they should be used in conjunction with clinical and pathological correlation. See Immunophenotyping/Genetic Testing in the guidelines.
Workup

Essential workup procedures include a complete physical exam with particular attention to node bearing areas and the size of liver and spleen, symptoms present, performance status, laboratory studies including CBC, serum lactate dehydrogenase (LDH), hepatitis B virus testing (see below), comprehensive metabolic panel, and CT chest/abdominal/pelvic with oral and intravenous contrast (unless co-existent renal insufficiency). MUGA scan or echocardiograms are recommended when anthracyclines and anthracenedione containing regimens are used. Bone marrow biopsy with or without aspirate is essential in all cases where treatment is considered; however, there are circumstances where it may be deferred (see below). Due to the risk of hepatitis B reactivation, the panel has included hepatitis B testing (hepatitis B surface antigen and hepatitis B core antibody) as part of essential workup prior to initiation of treatment in all patients who will receive anti-CD20 monoclonal antibody-based regimens. Furthermore, hepatitis B reactivation has been reported with chemotherapy alone and testing should be considered in anyone with a risk factor (e.g. blood transfusion, IV drug abuse) or if from a region with a non-negligible prevalence of hepatitis B infection (see “Hepatitis B Reactivation” in the Supportive Care section below). Hepatitis C testing is needed in high-risk patients and patients with splenic marginal zone lymphoma.

Optional procedures (depending on specific lymphoma type) include beta-2-microglobulin, CT or PET-CT scans, endoscopic ultrasound (gastric MALT lymphoma), head CT or brain MRI and lumbar puncture to analyze cerebrospinal fluid (MCL and DLBCL). Discussion of fertility issues and sperm banking should be addressed in the appropriate circumstances.61

Bone marrow biopsy is usually included in the workup for all patients with NHL with the exception of SLL/CLL when there is a clonal lymphocytosis identified by flow cytometry. Bone marrow involvement occurs in 39% of low-grade, 36% of intermediate grade and 18% of high-grade lymphomas. Bone marrow involvement was associated with significantly shorter survivals in patients with intermediate or high-grade lymphomas.62 In a retrospective analysis, the incidence of bone marrow involvement and the parameters predicting bone marrow involvement were analyzed in 192 patients with stage I and II in DLBCL.63 Overall incidence of BM involvement was 3.6%. The authors concluded that bone marrow biopsy may be safely omitted in selected patients with early stage DLBCL.63 In cutaneous B-cell lymphomas, bone marrow biopsy is essential for PC-DLBCL, leg type, since this is an aggressive lymphoma that will probably require systemic treatment, whereas the role of bone marrow biopsy in the PC-FCL and PC-MZL subtypes is less clear. Recent studies have indicated that bone marrow biopsy is an essential component of staging in patients with PC-FCL first presenting in the skin, whereas it appears to have limited value in patients with MZL presenting in the skin, and may be considered only in selected cases.64,65

In the NCCN Guidelines, bone marrow biopsy with or without aspirate is included as part of essential workup for all lymphomas. However, in patients with low bulk indolent disease with radiographic clinical stage III disease, an initial staging bone marrow evaluation can be deferred if observation is recommended as it will not change the clinical recommendations. However, in the evaluation of potentially early stage indolent lymphoma (stage I or II), bone marrow biopsy is essential; some panel members advocate bilateral core biopsies in this situation.66 Bilateral cores are recommended if radioimmunotherapy is considered.
FDG-PET scan has been used for initial staging, restaging and follow-up of patients with NHL. In a meta-analysis study, PET showed a high positivity and specificity when used for the staging and restaging of patients with lymphoma. FDG-PET is nearly universally positive at diagnosis in Hodgkin lymphoma, DLBCL, and follicular lymphoma, about 90% in T-cell lymphoma and nodal MZL but less sensitive for extra-nodal MZL. However, a number of benign conditions including sarcoid, infection, and inflammation can result in false-positive PET scans complicating the interpretation. Lesions smaller than 1 cm are not reliably visualized with PET scans. PET scan is now part of pre-treatment evaluation in Hodgkin lymphoma and DLBCL and may be useful in selected cases in other histologies. The pre-treatment PET is particularly important to aid in the interpretation of post-treatment response evaluation according to new response criteria (see above). Although PET scans may detect additional disease sites at diagnosis, the clinical stage is modified only in 15-20% of patients and a change in treatment in only 8% of patients. PET scan has generally been used in conjunction with diagnostic CT scans.

Integrated PET-CT has largely replaced the dedicated CT scans in the United States. This diagnostic study has distinct advantages in both staging and restaging compared to full-dose diagnostic CT or PET alone. In a retrospective study, PET-CT performed with low-dose non-enhanced CT was found to be more sensitive and specific than the routine contrast-enhanced CT in the evaluation of lymph node and organ involvement in patients with Hodgkin disease or high-grade NHL. Preliminary results of another recent prospective study (47 patients; patients who had undergone prior diagnostic CT were excluded) showed a good correlation between low-dose unenhanced PET-CT and full-dose enhanced PET-CT in the evaluation of lymph nodes and extranodal disease in lymphomas. However, the lack of intravenous contrast and the diminished resolution can make it difficult in some cases to interpret the anatomical localization and significance of FDG-avid sites. Further studies are needed to determine if PET-CT scans can replace diagnostic CT scans in the initial staging and response evaluation of lymphomas. The panel has included PET-CT scan as an optional workup procedure for selected patients.

Supportive Care
Supportive care remains an important component of managing patients with NHL, particularly during active therapy. Supportive care measures for NHL may include (but are not limited to) management of infectious complications, management of tumor lysis syndrome, and use of myeloid growth factors or blood product transfusions. These measures may help to maximize the benefit of NHL therapy for patients by enhancing tolerability, reducing treatment-related toxicities, and ensuring timely delivery of planned treatment courses. Patients with hematologic malignancies are at increased risk for infectious complications due to profound immunosuppression stemming from myelosuppressive therapy and/or the underlying malignancy. For example, reactivation of latent viruses may occur in the setting of significant immunosuppression in patients with NHL.

Viral Reactivation and Infections
Hepatitis B Virus Reactivation
Hepatitis B virus (HBV) reactivation has been reported in patients treated with chemotherapy with or without immunotherapy agents. HBV carriers with lymphoid malignancies have a high risk of HBV reactivation and disease, especially those treated with anti-CD20 monoclonal antibodies (e.g., rituximab, ofatumumab). Cases of liver failure and death associated with HBV reactivation have occurred in patients receiving rituximab-containing regimens.
Testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) can determine the HBV status of an individual. Because of the widespread use of the hepatitis B vaccine, hepatitis B surface antibody (HBsAb) positivity is of limited value; however, in rare cases, HBsAb levels can help to guide therapy. Patients with malignancies who are positive for either HBsAg or HBcAb are at risk for HBV reactivation with cytotoxic chemotherapy; approximately 20% to 50% of patients with HBsAg positivity and 3% to 45% with HBcAb positivity develop HBV reactivation.\(^\text{74,75,77,80,83-90}\)

False-negative HBsAg results may occur in chronic liver disease; therefore, patients with a history of hepatitis in need of chemotherapy should be assessed by viral load measurement.\(^\text{91}\) HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in HBcAb-positive individuals.\(^\text{75,92}\) In patients with B-cell lymphoid malignancies treated with rituximab-containing regimens, HBV reactivation was observed in patients with HBcAb positivity (with or without HBsAb positivity), even among those who were HBsAg negative prior to initiation of treatment.\(^\text{77,85,90}\)

A recent meta-analysis and evaluation of the FDA safety reports concerning HBV reactivation in patients with lymphoproliferative disorders reported that HBcAb positivity was correlated with increased incidence of rituximab-associated HBV reactivation.\(^\text{84}\) Vaccination against HBV should be strongly considered in HBV-naïve patients (i.e., negative for HBsAg, HBsAb, and HBcAb).\(^\text{75,93}\)

Recommended strategies for the management of HBV reactivation in patients with hematologic malignancies undergoing immunosuppressive therapy include upfront antiviral prophylaxis or pre-emptive therapy. Prophylactic approaches involve treating patients who are HBsAg-positive or HBcAb-positive with prophylactic antiviral therapy, regardless of viral load or presence of clinical manifestations of HBV reactivation. The alternative strategy of pre-emptive therapy involves close surveillance with a highly sensitive quantitative assay for HBV, combined with antiviral therapy upon a rising HBV DNA load.\(^\text{75}\)

Antiviral prophylaxis with lamivudine has been shown to reduce the risks for HBV reactivation in HBsAg-positive patients with hematologic malignancies treated with immunosuppressive cytotoxic agents.\(^\text{81,94-97}\)

A small randomized study in HBsAg-positive patients with lymphoma (N=30) showed that antiviral prophylaxis with lamivudine was superior to deferred pre-emptive therapy (i.e., antivirals given at the time of serological evidence of HBV reactivation based on viral DNA in serum samples).\(^\text{94}\) HBV reactivation occurred in 53% of patients in the deferred therapy arm compared with none in the prophylaxis arm. In a meta-analysis of clinical trials evaluating the benefit of lamivudine prophylaxis in HBsAg-positive lymphoma patients treated with immunosuppressive regimens, prophylaxis resulted in significant reductions in HBV reactivation (risk ratio=0.21; 95% CI, 0.13–0.35) and a trend for reduced HBV-related deaths (risk ratio=0.68; 95% CI, 0.19–2.49) compared with no prophylaxis.\(^\text{97}\)

Recent studies have shown entecavir to be more effective than lamivudine in preventing rituximab-associated HBV reactivation.\(^\text{98-100}\) In a prospective study that compared the efficacy of antiviral prophylaxis with entecavir and lamivudine in HBsAg-positive patients with newly diagnosed DLBCL treated with R-CHOP chemoimmunotherapy (n = 229), entecavir was associated with significantly lower rates of hepatitis (8.2% vs 23.3%, \(P = .022\)), HBV reactivation (6.6% vs 30.0%, \(P = .001\)), delayed HBV-related hepatitis (0% vs 8.3%, \(P = .027\)) and disruption of chemotherapy (1.6% vs 18.3%, \(P = .002\)).\(^\text{98}\) The results of another randomized controlled trial also showed that entecavir prophylaxis (before initiation of chemotherapy to 3 months after completion of chemotherapy) was more effective in preventing HBV-reactivation than...
the control (initiation of entecavir therapy at the time of HBV reactivation and HBsAg reverse seroconversion after chemotherapy). The cumulative HBV reactivation rates at months 6, 12, and 18 after chemotherapy were 8%, 11.2%, and 25.9%, respectively, in the control group, and 0%, 0%, and 4.3% in the entecavir prophylaxis (P = .019).

Although prophylaxis with lamivudine has been evaluated in the setting of immunosuppressive anti-tumor therapy (as mentioned above), the optimal antiviral strategy remains unclear. Concerns over the development of resistance to lamivudine exist. Adefovir combined with lamivudine has been evaluated in patients with lamivudine-resistant HBV infections. Tenofovir has demonstrated superior antiviral efficacy compared with adefovir in randomized double-blind phase III studies in patients with chronic HBV infection, and may be the preferred agent in this setting, however, limited data are available regarding its use in patients with cancer. Entecavir and telbivudine have also been evaluated in randomized open-label studies with adefovir as the comparator in patients with chronic HBV infection, and both agents have shown improved antiviral activity compared with adefovir.

The panel recommends HBsAg and HBcAb testing for all patients planned for treatment with anti-CD20 monoclonal antibody-containing regimens. In individuals who test positive for HBsAg and/or HBcAb, baseline quantitative PCR for HBV DNA should be obtained to determine viral load. However, a negative baseline PCR does not preclude the possibility of reactivation. In patients from areas with high HBV prevalence (Asia, Africa, Eastern Europe, and portions of South America) or regions where the prevalence is not known, all patients receiving immunotherapy, chemotherapy, or chemoinmunotherapy should be tested for HBsAg and HBcAb. Patients receiving intravenous immunoglobulin (IVIG) may be HBcAb positive as a consequence of IVIG therapy, although HBV viral load monitoring is recommended.

Prophylactic antiviral therapy with entecavir is recommended for patients who are HBsAg positive and undergoing NHL therapy. Lamivudine prophylaxis should be avoided due to the risks for the development of resistance. For patients who are HBsAg negative but HBcAb positive, antiviral prophylaxis with entecavir is also the preferred approach; however, if these patients concurrently have high levels of HBsAb, they may be monitored with serial measurements of HBV viral load and treated with pre-emptive antivirals upon increasing viral load. During the treatment period, viral load should be monitored monthly with PCR and then every 3 months after completion of treatment. If viral load is consistently undetectable, prophylaxis with antivirals should be continued. If viral load fails to drop or a previously undetectable PCR becomes positive, consultation with a hepatologist and discontinuation of anti-CD20 antibody therapy is recommended.

As mentioned above, several antiviral agents are available for prophylactic measures. The optimal choice will be driven by institutional standards or recommendation from hepatology or infectious disease consultant. The appropriate duration of prophylaxis remains undefined, but the panel recommended that surveillance and antiviral prophylaxis should be continued for up to 12 months after the completion of oncologic treatment.

**Hepatitis C Virus-associated B-cell NHL**
Case-control studies have demonstrated a strong association between seropositivity for hepatitis C virus (HCV) and development of NHL, particularly for B-cell lymphomas. In large population-based or multicenter case-control studies, prevalence of HCV seropositivity was consistently increased among patients with B-cell histologies including DLBCL and marginal zone lymphomas. A retrospective study in patients with HCV infection (N=3209) showed that the cumulative incidence of developing malignant lymphomas was significantly higher.
among patients with persistent HCV infection compared with those who had sustained virologic response (SVR) to interferon-containing therapy (15-year incidence rate 2.6% vs. 0%; \( P=0.016 \)).\textsuperscript{121} Based on multivariate analysis, persistent HCV infection remained a significant independent factor associated with development of malignant lymphomas. This study suggested that achievement of SVR with interferon-based therapy may reduce the incidence of malignant lymphoma in patients with HCV infection.\textsuperscript{121} Several published reports suggested that treatment with antivirals (typically, interferon with or without ribavirin) led to regression of NHLs in HCV-positive patients, which provide additional evidence for the involvement of HCV infection in the pathogenesis of lymphoproliferative diseases.\textsuperscript{122-128} In a retrospective study in patients with NHL (N=343; indolent and aggressive histologies) who achieved a CR after chemotherapy, the subgroup of HCV-positive patients treated with antivirals (interferon and ribavirin; n=25) had significantly longer disease-free survival compared with HCV-positive patients who did not receive antiviral therapy (n=44); the probability of relapse-free survival at 5-year follow up was 76% and 55%, respectively.\textsuperscript{127} In addition, none of the patients with a SVR to antivirals (n=0 of 8) relapsed compared with 29% who did not respond to antivirals (n=5 of 17). In a multicenter retrospective study from a large series of HCV-positive patients with indolent NHL, antiviral therapy (interferon or pegylated interferon, with or without ribavirin), resulted in SVR in 78% of patients who received first-line antivirals (n=76) and in 56% of those who received antivirals as second-line therapy after failure of initial treatment (n=18).\textsuperscript{128} Patients in this analysis did not require immediate treatment for their lymphoma. The overall hematologic response was 78% among both subgroups treated with antivirals in first line (CR in 47%) and in second line (CR in 27%). In the group of patients who received antivirals in first line, hematologic response was significantly associated with achievement of SVR.\textsuperscript{128} Thus, in HCV-positive patients with indolent NHL not requiring immediate anti-tumor therapy with chemoimmunotherapy regimens, initial treatment with interferon (with or without ribavirin) appeared to induce lymphoma regression in a high proportion of patients. In HCV-positive patients with NHL who achieve a remission with anti-tumor therapy, subsequent treatment with antivirals may be associated with lower risk of disease relapse.

The optimal management of HCV-positive patients with NHL remains to be defined. Patients with indolent NHL and HCV seropositivity may benefit from antiviral treatment as initial therapy, as demonstrated in several reports.\textsuperscript{122,124,126,128,129} In patients with aggressive NHL, an earlier analysis of pooled data from Groupe d'Etude des Lymphomes de l'Adulte (GELA) clinical studies (prior to the rituximab era) suggested that HCV seropositivity in patients with DLBCL was associated with significantly decreased survival outcomes, due, in part, to severe hepatotoxicity among those with HCV infection.\textsuperscript{130} Subsequent studies in the rituximab era showed that HCV seropositivity was not predictive of outcomes in terms of PFS or OS in patients with DLBCL.\textsuperscript{131,132} However, the incidence of hepatotoxicity with chemoimmunotherapy was higher among HCV-positive patients, confirming the observation made from the GELA studies.

The treatment of chronic HCV infection has improved with the advent of newer antiviral agents, especially those that target carriers of HCV genotype 1. Direct acting antiviral agents (DAA) administered in combination with standard antivirals (pegylated interferon and ribavirin) have shown significantly higher rates of SVR compared with standard therapy alone in chronic carriers of HCV genotype 1.\textsuperscript{133-136} Telaprevir and boceprevir are DAA that were recently approved by the FDA for the treatment (in combination with pegylated interferon and ribavirin) of patients with HCV genotype 1 infection. The updated guidelines for the management of HCV infection from the American Association for the
Study of Liver Diseases (AASLD) recommended that DAAs be incorporated into standard antiviral therapy for patients infected with HCV genotype 1.\textsuperscript{137}

The panel recommends initial antiviral therapy in asymptomatic patients with HCV-positive low-grade B-cell NHL. For those with HCV genotype 1, triple antiviral therapy with inclusion of DAAs should be considered as per AASLD guidelines. Patients with HCV-positive aggressive B-cell NHL should initially be treated with appropriate chemoimmunotherapy regimens according to the NCCN Guidelines for NHL. Liver function and serum HCV RNA levels should be closely monitored during and after chemoimmunotherapy for development of hepatotoxicity. Antiviral therapy should then be considered in patients who achieve a CR after completion of chemoimmunotherapy.

**Cytomegalovirus Reactivation**

Cytomegalovirus (CMV) reactivation may occur among patients with lymphoproliferative malignancies (most commonly, CLL/SLL) receiving alemtuzumab therapy, and occurs most frequently between 3 to 6 weeks after initiation of therapy when T-cell counts reach a nadir.\textsuperscript{138,140} CMV reactivation is a well-documented infectious complication in patients receiving treatment with alemtuzumab, occurring in up to 25% of treated patients.\textsuperscript{138,141-145} Current management practices for prevention of CMV reactivation include the use of prophylactic ganciclovir (oral or IV) if CMV viremia is present prior to alemtuzumab therapy,\textsuperscript{140} or pre-emptive use of these drugs when the viral load is found to be increasing during therapy.\textsuperscript{139,146,147}

Several studies of alemtuzumab in patients with CLL have demonstrated the effectiveness of using routine CMV monitoring coupled with pre-emptive therapy with ganciclovir in preventing overt CMV disease.\textsuperscript{138,139} A small randomized study in patients with lymphoproliferative disease treated with alemtuzumab-containing regimens (N=40) showed that upfront CMV prophylaxis with oral valganciclovir significantly reduced the incidence of CMV reactivation compared with oral valacyclovir (0% vs 35%; \(P=0.004\)).\textsuperscript{140}

Patients with hematologic malignancies treated with alemtuzumab-containing regimens should be closely monitored and managed for potential development of CMV reactivation. To this end, periodic monitoring for the presence of CMV antigens using quantitative polymerase chain reaction (PCR) assays is an effective management approach.\textsuperscript{146} The panel recommends routine surveillance for CMV viremia (every 2–3 weeks) during the treatment course with alemtuzumab and for 2 months following completion of alemtuzumab treatment.

**Progressive Multifocal Leukoencephalopathy**

Progressive multifocal leukoencephalopathy (PML) is a rare but serious and usually fatal CNS infection caused by reactivation of the latent (John Cunningham) JC polyoma virus. Cases of PML generally occur in severely immunocompromised individuals, as in the case of patients with AIDS. Patients with hematologic malignancies who have profound immunosuppression (due to the underlying disease and/or immunosuppressive therapies) are also at risk of developing PML. In a report of 57 cases from the Research on Adverse Drug Events and Reports project, 52 patients with lymphoproliferative disorders developed PML after treatment with rituximab and other treatments which included hematopoietic stem cell transplantation or chemotherapy with purine analogs or alkylating agents.\textsuperscript{148} Median time from last rituximab dose to PML diagnosis was 5.5 months. Median time to death after PML diagnosis was 2 months. The case fatality rate was 90%.\textsuperscript{148} The use of rituximab may be associated with an increased risk of PML in immunocompromised patients with
lymphoproliferative malignancies. Cases of PML have been reported with rituximab treatment (usually in combination with chemotherapy regimens) in patients with CLL/SLL or other types of NHL. Patients with low CD4+ T-cells prior to or during anti-tumor treatment with rituximab-containing regimens may be particularly susceptible to PML. Patients with NHL receiving treatment with another anti-CD20 monoclonal antibody ofatumumab, or the anti-CD30 antibody-drug conjugate brentuximab vedotin, may also be at potential risk for PML.

Development of PML is clinically suspected based on neurological signs and symptoms that may include confusion, motor weakness or poor motor coordination, visual changes, and/or speech changes. PML is usually diagnosed with PCR of cerebrospinal fluid (CSF) or in some cases, by analysis of brain biopsy material. There is no effective treatment for PML. Patients should be carefully monitored for the development of any neurological symptoms. There is currently no consensus on pretreatment evaluations that can be undertaken to predict for the subsequent development of PML.

**Tumor Lysis Syndrome**

Tumor lysis syndrome (TLS) is a potentially serious complication of chemotherapy and is characterized by metabolic abnormalities caused by the abrupt release of intracellular contents into the blood resulting from cellular disintegration induced by chemotherapy. It is usually observed within 12 to 72 hours after start of chemotherapy. Untreated TLS can induce profound metabolic changes resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death.

Cairo and Bishop have classified TLS into laboratory TLS and clinical TLS. Laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels. Clinical TLS refers to laboratory TLS with clinical toxicity that requires intervention. Clinical complications may include renal insufficiency, cardiac arrhythmia, or seizures. The four primary electrolyte abnormalities of TLS are hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Symptoms associated with TLS may include nausea and vomiting, diarrhea, seizures, shortness of breath, or cardiac arrhythmias.

TLS is best managed if anticipated and when treatment is started prior to chemotherapy. The cornerstone of TLS management is hydration and the control of hyperuricemia. Allopurinol should be administered prior to the initiation of chemotherapy. Rasburicase is indicated in cases where the uric acid level remains elevated despite treatment with allopurinol or in patients with renal insufficiency. Electrolytes and renal function should be monitored every 6 to 8 hours with appropriate interventions for hyperkalemia and hyperphosphatemia. Careful clinical monitoring will help to preempt complications, and in many cases, admission to ICU may be appropriate. Cardiac monitoring or serial ECG may be beneficial to identify early electrolyte-related cardiac abnormalities. Dialysis may be necessary in cases of anuric acute renal failure.

Allopurinol is a xanthine analog and a competitive inhibitor of xanthine oxidase, thereby blocking conversion of purine metabolites to uric acid. Allopurinol will decrease the formation of uric acid production and has been shown to reduce the incidence of uric-acid uropathy. Since the drug inhibits new uric acid formation rather than reduce existing uric acid, it can take several days for elevated levels of uric acid to normalize after the initiation of treatment, which may delay the start of chemotherapy. Furthermore, allopurinol may lead to the accumulation of xanthine crystals in renal tubules leading to acute obstruc
Rasburicase is a recombinant urate oxidase, which catalyzes the oxidation of uric acid to a highly soluble non-toxic metabolite that is readily excreted. It has been shown to be safe and highly effective in the prevention and treatment of chemotherapy-induced hyperuricemia in both children and adults with hematologic malignancies. In an international compassionate use trial in patients at risk for TLS during chemotherapy (N=280 enrolled), rasburicase (0.20 mg/kg/day IV for 1–7 days) resulted in uric acid response in all evaluable patients (n=219; adults, n=97). Among the subgroup of adults with hyperuricemia (n=27), mean uric acid levels decreased from pretreatment levels of 14.2 mg/dL to 0.5 mg/dL 24 to 48 hours after administration of last dose of rasburicase. Among adult patients at risk for TLS (but without baseline hyperuricemia; n=70), mean uric acid levels decreased from 4.8 mg/dL to 0.4 mg/dL. The GRAAL1 trial evaluated the efficacy and safety of rasburicase (0.20 mg/kg/day IV for 3–7 days, started on day 0 or day 1 of chemotherapy) for the prevention and treatment of hyperuricemia in adult patients with aggressive NHL during induction chemotherapy (N=100). Prior to chemotherapy, 66% of patients had elevated lactate dehydrogenase (LDH) levels and 11% had elevated uric acid levels (>7.56 mg/dL). Uric acid levels were normalized and maintained within normal ranges during chemotherapy in all patients. Uric acid levels decreased within 4 hours after the first injection of rasburicase. In addition, serum creatinine levels and other metabolites were also controlled with the administration of rasburicase.

A prospective, multicenter randomized phase III trial compared the efficacy and safety of rasburicase and allopurinol in adult patients with hematological malignancies at high or potential risk for TLS (N=275). Patients were randomized to receive treatment with rasburicase alone (0.20 mg/kg/day IV for days 1–5; n=92), rasburicase combined with allopurinol (rasburicase 0.20 mg/kg/day IV for days 1–3; allopurinol 300 mg/day PO for days 3–5; n=92) or allopurinol alone (300 mg/day PO for days 1–5; n=91). The rate of uric acid response (defined as plasma uric acid levels ≤7.5 mg/dL for all measurements from days 3–5) was 87% for rasburicase, 78% for rasburicase combined with allopurinol and 66% for allopurinol. The incidence of clinical TLS was similar across treatment arms, occurring in 3%, 3% and 4% of patients, respectively. The incidence of laboratory TLS was 21%, 27%, and 41%, respectively, with significantly lower incidence observed in the rasburicase arm compared with allopurinol (P=0.003). The response rate with rasburicase was superior to allopurinol in the overall study population (87% vs. 66%, as above; P=0.001) as well as in patients with high risk TLS (89% vs. 68%; P=0.001) and in patients with baseline hyperuricemia (90% vs. 53%; P=0.015). The median time to control for serum uric acid in hyperuricemic patients was 4 hours for rasburicase, 4 hours for rasburicase combined with allopurinol and 27 hours for allopurinol. Potential hypersensitivity to study regimen was reported in 4% of patients in the rasburicase arm and 1% in the combination arm; no anaphylaxis or grade 4 hypersensitivity reactions were reported in this trial. However, rasburicase can induce anaphylactic reactions. Other adverse reactions include methemoglobinemia and severe hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. A single fixed dose of rasburicase (6 mg) or a single weight-based dose of rasburicase (0.05–0.15 mg/kg) has been shown to be effective in the management of uric acid levels in adult patients with hyperuricemia or with high-risk factors for TLS. A recent phase II randomized trial compared the efficacy of rasburicase administered as a single dose (0.15 mg/kg, followed by additional
days of dosing as needed) versus rasburicase (0.15 mg/kg/day) given for 5 days in adult patients at high risk or potential risk for TLS (N=80 treated).

The median pretreatment uric acid level was 8.5 mg/dL for high-risk patients (n=40) and 5.6 mg/dL for potential risk patients (n=40). Nearly all treated patients (99%) showed normalization of uric acid levels within 4 hours after the first dose of rasburicase; levels of uric acid were undetectable (<0.7 mg/dL) in 84% of patients. In the single-dose rasburicase arm, 85% of patients had sustained uric acid response compared with 98% of patients in the 5-day rasburicase arm. Among high-risk patients within the single-dose arm, 6 patients received a second dose of rasburicase to achieve uric acid response.

The risk factors for TLS include bone marrow involvement, bulky tumors that are chemosensitive, rapidly proliferative or aggressive hematologic malignancies, an elevated leukocyte count or pretreatment LDH, pre-existing elevated uric acid, renal disease or renal involvement of tumor. Patients diagnosed with lymphoblastic lymphoma or Burkitt lymphoma are at a higher risk of developing TLS. Occasionally, patients with bulky presentation of DLBCL and patients with CLL and high white blood cell count may experience TLS at a moderately high frequency.

The NCCN Guidelines recommend that allopurinol be started 2−3 days prior to chemotherapy and continued for 10−14 days. Rasburicase is recommended for patients with any of the following risk factors: presence of any high risk feature (i.e., Burkitt lymphoma or lymphoblastic lymphomas; spontaneous TLS; elevated WBC count; elevated uric acid levels; bone marrow involvement; renal disease or renal involvement by tumor); bulky disease requiring immediate therapy; patients in whom adequate hydration is not possible; allopurinol is ineffective; or acute renal failure. A single dose is adequate in most cases; repeat dosing should be given on an individual basis.