Editor

Anas Younes

Handbook of Lymphoma

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Anas Younes
Memorial Sloan Kettering Cancer Center
New York, NY
USA

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Editor
Anas Younes, MD
Memorial Sloan Kettering Cancer Center
New York, NY
USA

Contributors
Connie Batlevi, MD, PhD
Ahmet Dogan, MD
Neha Mehta-Shah, MD
Colette Owens, MD
Anastasios Stathis, MD

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Editor and author biographies

Anas Younes, MD, is the Chief of the Lymphoma Service at Memorial Sloan Kettering Cancer Center and Professor of Medicine at Weill-Cornell Medical College, New York, NY, USA. He has extensive experience in clinical and translational research in lymphoma. He was the Principal Investigator of the MD Anderson Cancer Center Lymphoma SPORE grant, and is currently the Principal Investigator of the Memorial Sloan Kettering Cancer Center Lymphoma SPORE grant. He has lead more than 60 clinical trials in lymphoma. He has lead, in collaboration with colleagues from around the world, the pivotal trials that resulted in the US FDA approval of brentuximab vedotin and nivolumab for the treatment of patients with relapsed Hodgkin lymphoma. He has published more than 250 papers on lymphoma.

Connie Batlevi, MD, PhD, Assistant Professor, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

Ahmet Dogan, MD, Chief, Hematopathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

Neha Mehta-Shah, MD, Assistant Professor, Division of Oncology, Washington University School of Medicine, St Louis, MO, USA.

Colette Owens, MD, Instructor, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

Anastasios Stathis, MD, Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland.

Abbreviations

aa-IPI	Age-adjusted IPI
ABC	Activated B-cell like
ABVD	Doxorubicin, bleomycin, vinblastine and dacarbazine
ADC	Antibody drug-conjugate
AIDS	Acquired immunodeficiency syndrome
ALCL	Anaplastic large cell lymphoma
AMC	AIDS Malignancy Consortium
AMP	Doxorubicin, ranimustine, and prednisone
ASCT	Autologous stem cell transplantation
ATLL	Adult T-cell leukemia/lymphoma
BCCA	British Columbia Cancer Agency
BCR	B-cell receptor
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
bFGF	Basic fibroblast growth factor
BL	Burkitt's lymphoma
BTK	Bruton's tyrosine kinase
cHL	Classical Hodgkin lymphoma
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CODOX-M/IVAC	Cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide, and cytarabine
COMPLETE	Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment
CNS	Central nervous system
COO	Cells of origin
CR	Complete response
CSF	Cerebrospinal fluid

CT	Computed tomography
CTCL	Cutaneous T-cell lymphomas
CVP	Cyclophosphamide, vincristine, and prednisolone
DA-EPOCH-R	Dose-adjusted toposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab
DFS	Disease-free survival
DHAP	Dexamethasone, cytarabine, and cisplatinum
DLBCL	Diffuse large B-cell lymphoma
EATL	Enteropathy-associated T-cell lymphoma
EBMT	European Group for Blood and Marrow Transplantation
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ECP	Extracorporal photopheresis
EFS	Event-free survival
ENKTL	Extranodal NK/T-cell lymphoma
EORTC	European Organisation for Research and Treatment of Cancer
ESR	Erythrocyte sedimentation rate
FC	Flow cytometry
FFP	Freedom from progression
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FLIPI	Follicular lymphoma International Prognostic Index
GC	Germinal center
GCB	GCB-cell like
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GELF	Groupe d’Etude des Lymphomes Folliculaires
GEP	Gene-expression profiling
GHSG	German Hodgkin Lymphoma Study Group
G-CSF	Granulocyte-colony stimulating factor
GVL	Graft versus lymphoma
H&E	Hematoxylin and eosin
HAART	Highly active antiretroviral therapy

HCV	Hepatitis C virus
HDACi	Histone deacetylase inhibitor
HIV	Human immunodeficiency virus
HHV8	Human herpes virus 8
HL	Hodgkin lymphoma
Hp	Helicobacter pylori
HTLV-1	Human retrovirus T-cell leukemia virus type 1
ICE	Ifosfamide, carboplatin, and etoposide
ICDE	Infusional cyclophosphamide, doxorubicin, and etoposide
IELSG	International Extranodal Lymphoma Study Group
IFN	Interferon
IFRT	Involved field radiation therapy
IgH	Immunoglobin heavy
IL	Interleukin
IPI	International Prognostic Index
IPS	International Prognostic Score
IPTCL	International peripheral T-cell lymphoma project
IV	Intravenous
LDH	Lactate dehydrogenase
LP	Lymphocyte predominant
LPL	Lymphoplasmacytic lymphoma
MACOP-B	Leucovorin, doxorubicin, cyclophosphamide, vincristine, and bleomycin
MALTL	Mucosa-associated lymphoid tissue lymphoma
mBACOD	Methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone, with folinic acid and GM-CSF
MBL	Monoclonal B-cell lymphocytosis
MCL	Mantle cell lymphoma
MF	Mycosis fungoides
MIPI	Mantle cell International Prognostic Index
MMAE	Monomethyl auristatin E
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition

MZL	Marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NF	Nuclear factor
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NLPHL	Nodular lymphocyte-predominant HL
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PB	Peripheral blood
PBSC	Peripheral blood stem cells
PCNSL	Primary central nervous system lymphoma
PCR	Polymerase chain reaction
PD1	Programmed death 1
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphatidylinositol-3 kinase
PIP3	Phosphatidylinositol 3,4,5,trisphosphate
PLL	Prolymphocytic leukemia
PMLBCL	Primary mediastinal large B-cell lymphoma
PO	Oral
PR	Partial response
PTCL	Peripheral T-cell lymphoma
PTLD	Post-transplant lymphoproliferative disorders
RCHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-CODOX-M/IVAC	Rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide, and cytarabine
RDHAP	Rituximab, dexamethasone, cytarabine, and cisplatin
RESHAP	Rituximab, etoposide, metilprednisolone, cytarabine, and cisplatin

RGDP	Rituximab, dexamethasone, gemcitabine, and cisplatin
RICE	Rituximab, ifosfamide, carboplatin, and etoposide
SCT	Stem cell transplantation
SLE	Systemic lupus erythematosus
SLL	Small lymphocytic lymphoma
SMZL	Splenic MZL
T-LL	T-cell lymphoblastic leukemia
TSEBT	Total skin electron beam therapy
TNF	Tumor necrosis factor
US FDA	United States Food and Drug Administration
UV	Ultraviolet
VACOP-B	Etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin
VCAP	Vincristine, cyclophosphamide, doxorubicin, and prednisone
VECP	Vindesine, etoposide, carboplatin, and prednisone
VEGF	Vascular endothelial growth factor
VIP-rABVD	Etoposide, ifosfamide, and cisplatin alternating with adriamycin, bleomycin, vinblastine, and dacarbazine
WHO	World Health Organization

Chapter 1

Introduction

Colette Owens and Anas Younes

Introduction

Lymphomas are a heterogeneous group of malignancies of the lymphoid system. Lymphomas are some of the most diverse and most curable human malignancies. They are defined as a group of tumors that develop from lymphocytes and can be thought of as 'solid tumors' of the immune system. These cancers come from the cells of the immune system at different stages of development, which causes a diverse range of morphologic and clinical findings.

There are three types of lymphocytes, which include natural killer (NK) cells, which function in cell-mediated, cytotoxic innate immunity, T cells for cell-mediated cytotoxic adaptive immunity, and B cells, for humoral antibody-driven adaptive immunity. Other parts of the lymphatic system include the tonsils, thymus, and spleen, and lymphatic tissue is also found in the stomach, skin, and small intestine. Because lymphatic tissue is in many parts of the body, lymphoma can develop anywhere.

There are two large subdivisions of lymphoma: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). In 2014 approximately 80,000 new cases of lymphoma were diagnosed in the US (9000 cases of HL and 71,000 cases of NHL) and 20,000 patients are expected to die from lymphoma per year [1]. NHL is the seventh most common cancer in the US with the age-adjusted incidence rising by 89.5% from 1975 to 2010 [1]. Worldwide NHL is the eighth most common cancer in men and 11th in

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women, accounting for 5.1% of all cancers and 2.7% of all cancer deaths [2]. The highest incidence of NHL occurs in North America, Europe, Australia and several African countries [1]. It is most frequently diagnosed in older people, with an average age of 65–74 years [1]. However, specific, less common subtypes such as HL and Burkitt lymphoma are more frequently diagnosed in younger patients. NHL is broadly classified into B-cell lymphoma, T-cell lymphoma, and NK-cell lymphoma (Figure 1.1).

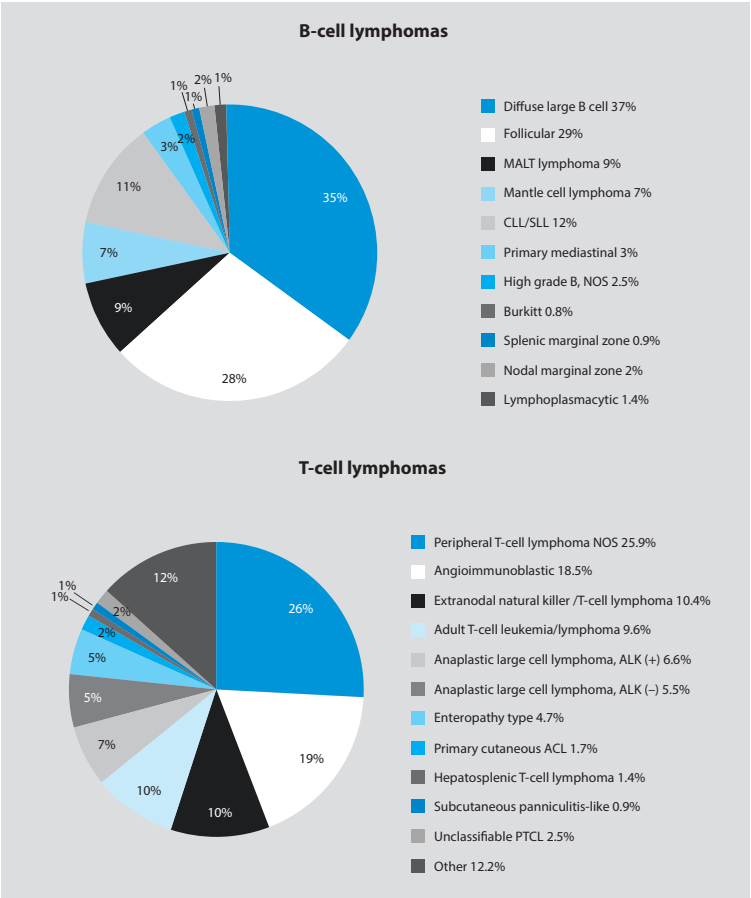

Figure 1.1 Frequencies of B-cell and T-cell lymphomas by subtype. (A) B-cell lymphoma subtype frequencies across eight countries representative of geographic regions from January 1, 1988 and December 31, 1990. Data from [3]. (B) T-cell lymphoma subtype frequencies by consensus diagnosis of International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study. Data from [4].

About 90% of people will have a B-cell lymphoma and 10% will have a T-cell lymphoma (though this number is higher in Asia). Less than 1% of people will have a NK-cell lymphoma [1]. However, there is a large variation in the geographical distribution of subtypes, with higher proportions of follicular and diffuse large B-cell lymphoma in North America and Europe, and T-cell lymphomas in Asia [2].

The incidence of HL is lower than that of NHL. HL is an uncommon disorder with an annual incidence of 2–3 per 10,0000 in Europe and the US. It has a bimodal age distribution in early adulthood (20–30 years of age) and late adulthood (over 55 years of age). The nodular sclerosis subtype is more common in younger people, while mixed cellularity subtype is more common in older people. The 1-year relative survival rate of patients with HL is 92% [1]. The 5-year and 10-year relative survival rates are 85% and 80%, respectively [1].

Different lymphomas arise from cells of the immune system at different stages of differentiation. NHLs were separated from HLs in the early 20th century due to the recognition of Reed-Sternberg cells. The World Health Organization (WHO) classified lymphomas based on morphologic, clinical, immunologic, and genetic information, and attempted to divide NHLs and other lymphoid malignancies into entities with clinical and therapeutic relevance (for more detailed information see Chapter 3).

Risk factors

The risk of NHL increases with age and most commonly occurs in people in their 60s and 70s, and typically more often in men than women. HL has a bimodal age distribution and typically has a male predominance as well. The cause of lymphomas is not clearly understood, but there have been some associations with the development of lymphoma. Both bacterial and viral infections have been associated with lymphoma (reviewed in Chapter 2). For example, mucosa-associated lymphoma tissue (MALT) of the stomach is frequently associated with Helicobacter pylori infection, and antibiotic therapy can lead to lymphoma regression. Hepatitis C infection has also been associated with an increased risk of marginal zone lymphomas. Epstein-Barr virus (EBV) is associated with Burkitt lymphoma, high-grade B-cell lymphoma, primary effusion lymphoma, NHL

in older people (60–90 years of age), and lymphoproliferative disorders post organ transplant. Patients with a history of EBV-related infectious mononucleosis are at a two- to three-fold higher risk for development of HL [5]. Human immune deficiency virus (HIV) infection is associated with several types of aggressive B-cell lymphoma. Another human herpes virus, HHV8, is also associated with the development of primary effusion lymphoma that tends to affect HIV-positive patients. Adult T-cell leukemia/lymphoma (ATLL) is associated with human T-cell lymphotropic virus (HTLV-1), which is a human retrovirus. ATLL is endemic in parts of Japan, the Caribbean, South America, and Central and West Africa, which parallels the highest incidences of HTLV-1.

Patients with autoimmune disorders also appear to have an increased risk of lymphoma, including rheumatoid arthritis, celiac disease, systemic lupus erythematosus, and Sjogren's syndrome. Some of the medications that treat these disorders may increase this risk as well, such as the tumor necrosis factor (TNF) inhibitors. There may also be a further risk for patients taking immunosuppressant medications that are used after organ transplantation.

Diagnosis

The standard for diagnosis of lymphoma is a biopsy. Typically, an excisional biopsy with an intact lymph node is preferred and can be examined under the microscope by a pathologist. However, core needle biopsies may be helpful in situations where an excisional biopsy is unable to be performed. In addition to routine histology and immune phenotyping by immunohistochemistry, flow cytometry, polymerase chain reaction (PCR) for B- and T-cell clonality and T-cell receptors, cytogenetics for specific translocations and clonality, and fluorescence in situ hybridization (FISH) for specific translocations are performed on the tissue and have now become an essential part of lymphoma diagnosis, classification and prognostication.

90% of lymphomas are of B-cell origin and they express HLADR, CD10, CD19, CD20, CD21, CD22, CD5, CD38, and Tdt. They also express immunoglobulin heavy and light chain gene rearrangements, which distinguish B cells and lymphomas [6]. CD1, CD2, CD3, CD4, CD5, CD6, CD7,

CD8, CD38, CD71, and T-cell receptor gene rearrangements distinguish T cells [6]. Cytogenetic analysis is now a routine part of the diagnosis and management of a significant number of lymphoid malignancies. Many recurring cytogenetic abnormalities have been identified, and significant correlations with these abnormalities, morphology, immunophenotyping, and clinical outcomes have been recognized. Unfortunately, not all lymphoma subtypes have specific cytogenetic patterns and those that do, do not always express these patterns

Once there is a diagnosis of lymphoma further staging is done to assess the extent of disease. This typically includes imaging with computed tomography (CT) scans of the chest, abdomen and pelvis, or positron emission tomography (PET)/CT scan, and this may or may not include a bone marrow biopsy. The Ann Arbor Staging Classification (Table 1.1) is used to classify the extent of disease, and the International Prognostic Index has been used to prognosticate groups of patients with NHLs. The International Prognostic Score (IPS) is used to risk stratify advanced HL.

Clinical presentation

HL typically presents with painless lymphadenopathy with or without splenomegaly, fevers, night sweats, weight loss, and pruritis. Pain in a lymph node can be associated with alcohol consumption. It can also be associated with HIV and EBV infections. There are two major subdivisions within HL: classical HL (95%) and lymphocyte predominant HL (5%).

Grade	Description
I	Involvement of a single lymph node or a group of nodes in the same region. Single extranodal lesion without nodal involvement
II	Involvement of two or more lymph node regions on the same side of the diaphragm. Stage I or II by nodal extent with limited contiguous extranodal involvement
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm. Nodes above the diaphragm with spleen involvement.
IV	Involvement of more than one extranodal site at any location.
A	No symptoms
B	B symptoms: weight loss >10% body weight during prior 6 months, recurrent fevers >38°C during prior month, recurrent drenching night sweats in prior month

Table 1.1 The Ann Arbour lymphoma staging system. Adapted from © American Society of Clinical Oncology, 2014. All rights reserved. Cheson et al [7].

Within classical HL there are four subtypes: nodular sclerosis (60%), mixed cellularity (20%), lymphocyte-rich (15%), and lymphocyte-depleted (5%) [6,8]. Classical HL has the classic Reed-Sternberg cells ('owl eyes') that express CD15 and CD30, but typically no B-cell markers. Lymphocyte-predominant HL typically has 'popcorn' or lymphocytic and histiocytic cells that express typical B-cell proteins such as CD20, CD79a, CD45, but do not express CD15 or CD30. This is typically a slow progressive disease associated with prolonged survival.

HL at any stage is curable in the majority of patients. The standard treatment for classical HL is a combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and the number of cycles varies with stage. Involved field radiation is also used in early stage classical HL, typically following short-course chemotherapy. In the relapsed/refractory setting, a complete or partial response is not achieved in 10–20% of people and 10–30% of people relapse after an initial complete response [6]. Different combinations of chemotherapies may treat relapses successfully, but high-dose therapy with an autologous stem cell transplantation is the standard of care for relapsed chemosensitive disease. More recently, brentuximab vedotin, an anti-CD30 monoclonal antibody conjugated to a mitotic spindle inhibitor has been approved for relapsed/refractory disease.

NHL subtypes are divided into indolent (low grade-slow growing), aggressive (intermediate grade – fast growing), and highly aggressive types (high grade – very rapidly growing). Indolent lymphomas include: follicular (grade 1, 2, and 3a), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone, and lymphoplasmacytic (Waldenströms) lymphoma. These lymphomas grow slowly and are not considered curable, but typically respond well to treatment and can go into remission and people live for several years. Many times, people can be asymptomatic and can defer treatment and be monitored expectantly. Indications for treatment include The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, which include B symptoms, cytopenias, large mass >7 cm, multiple lymph nodes >3cm in size, splenomegaly, or end organ damage. However, because indolent lymphomas cannot be cured they are characterized by treatment, remission, and then relapse. Mantle cell lymphoma is more of an intermediate lymphoma than can behave

like an indolent lymphoma, but more often behaves more aggressively and is not curable. Aggressive lymphomas include: diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, lymphoblastic, and double hit large cell lymphomas and B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt/Gray zone. These lymphomas grow rapidly and require treatment. They differ in that they are curable with treatment. Most relapses occur within the first 2 years, but relapsed/refractory disease is more difficult to treat and cure.

Prognostic factors

Diffuse large B-cell lymphoma

The International Prognostic Index (IPI) is based upon a multivariate analysis of survival of 2031 patients with aggressive NHLs. Several histological subtypes were included, and patients were treated with various doxorubicin-containing chemotherapy combinations [9]. In addition to Ann Arbor stage, the characteristics that were found to be significant were age, elevated serum lactate dehydrogenase (LDH), performance status, and the number of extranodal sites of disease [9]. One point is assigned for each of these risk factors:

- age >60 years;
- stage III or IV disease;
- elevated serum LDH;
- Eastern Cooperative Oncology Group (ECOG) performance status of >1; and
- extranodal site >1.

The sum of the points correlates with the following risk groups:

- low risk (0–1 points): 5-year survival of 73%;
- low–intermediate risk (2 points): 5-year survival of 51%;
- high–intermediate risk (3 points): 5-year survival of 43%; and
- high risk (4–5 points): 5-year survival of 26%.

There have been additional IPI risk scores and adaptations. A simplified risk score is the age-adapted IPI that only includes three factors and is used for groups older or younger than 60 [9]:

- stage;
- LDH;

- performance status;
- low risk (0 points): 5-year survival of 83%;
- low–intermediate risk (1 point): 5-year survival of 69%;
- high–intermediate risk (2 points): 5-year survival of 46%; and
- high risk (3 points): 5-year survival of 32%.

Follicular lymphoma and mantle cell lymphoma

There are also FLIPI and MIPI scores for follicular and mantle cell lymphoma respectively. The prognostic factors that were significant in follicular lymphoma were age, stage, number of lymph node areas involved, serum hemoglobin level, and serum LDH; for mantle cell lymphoma they were age, performance status, LDH, and white blood cell count. Although, oncologists continue to use the IPI scoring system for risk stratification, it should be noted that these risk models were developed prior to the advent of rituximab, which has significantly improved outcomes for patients with lymphoma. However, the addition of rituximab improves survival across risk groups and the IPI remains a valid tool.

Hodgkin Lymphoma

The IPS score gives 1 point for each of the following factors [10]:

- albumin <4g/dL;
- hemoglobin <10.5 g/dL;
- male;
- age ≥45;
- stage IV disease;
- leukocytosis (white blood cell count at least 15,000 mm^3); and
- lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600mm^3).

Freedom from progression (FFP) at 5 years is directly related to the number of factors present in a patient. The 5-year FFP for patients with zero factors is 84%. Each additional factor lowers the 5-year FFP rate by 7%, such that the 5-year FFP for a patient with 5 or more factors is 42% [10]. Other reported unfavorable risk factors include: mixed-cellularity or lymphocyte-depleted type, male sex, large number of involved nodal sites, age over 40 years, the presence of B symptoms, advanced stage,

high erythrocyte sedimentation rate (ESR), bulky disease (widening of the mediastinum by more than one third, or the presence of a nodal mass measuring more than 10 cm in any dimension) [10].

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Chapter 2

Risk factors, etiology, and pathogenesis

Anastasios Stathis and Colette Owens

Lymphomas are a heterogeneous group of neoplastic disorders that originate from lymphatic cells. Clinical and epidemiological studies have revealed some risk factors that are associated with the development of lymphomas while molecular biology studies have elucidated mechanisms that drive the malignant transformation of lymphatic cells. In this chapter we review current knowledge of the risk factors and of the molecular pathogenesis of the most common lymphomas.

Risk factors and causes

Immune deregulation plays a major role in the pathogenesis of lymphomas. In this context, some infectious agents, autoimmune diseases, and immunosuppression represent well-established risk factors for the development of specific lymphoma subtypes.

Infection

Growing epidemiological and biological evidence has linked infections to the development of lymphomas (Table 2.1). A strong association between human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and several B-cell lymphoma subtypes has been reported by several studies. The risk is higher for non-Hodgkin lymphoma (NHL)

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Infectious agent	Lymphoid malignancy
EBV	Burkitt lymphoma
	Post organ transplant lymphoma
	Primary CNS DLBCL
	Hodgkin's disease
	Extranodal NK/T-cell lymphoma, nasal type
HTLV-1	Adult T-cell leukemia/lymphoma
Helicobacter pylori	Gastric MALT lymphoma
Human herpesvirus 8	Primary effusion lymphoma
	Castleman's disease
HIV	Diffuse large B cell lymphoma
	Burkitt lymphoma
Hepatitis C	Lymphoplasmacytic lymphoma
Chlamydia psitacci	Orbital adnexal lymphoma
Campylobacter jejuni	Immunoproliferative small bowel disease
Borrelia burgdorferi	Cutaneous MALT lymphoma

Table 2.1 Infectious agents associated with lymphoma. CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HTLV-1, Human T-cell lymphotropic virus; MALT, mucosa-associated lymphoma tissue; NK, natural killer.

with a 60–200 times increased risk for all subtypes of NHL in HIV-positive patients [1,2]. The most common HIV-associated lymphomas include diffuse large B cell lymphoma (DLBCL; with up to one third of cases presenting as primary central nervous system lymphomas), Burkitt lymphoma, primary effusion lymphoma, and plasmablastic lymphoma. Hodgkin lymphoma (HL) is also increased in the setting of HIV. The pathogenesis of HIV-associated lymphomas includes several mechanisms, among them chronic antigen stimulation, genetic abnormalities, cytokine deregulation and infections by Epstein-Barr virus (EBV) and human herpes virus 8 (HHV8) [3]. The incidence of HIV-associated lymphomas has significantly decreased with the advent of highly active antiretroviral therapy (HAART).

Other viruses can have impact on lymphoma risk. The human retrovirus T-cell leukemia virus type 1 (HTLV-1) is an established cause for the development of adult T-cell leukemia/lymphoma (ATLL), a peripheral T-cell neoplasm that is endemic in Japan, the Caribbean, and parts of Central Africa. The distribution of the disease is linked to the prevalence of HTLV-1 in the population. The cumulative incidence of ATLL

is estimated to be approximately 3% in HTLV-1 carriers [4]. EBV was initially identified in cases of endemic Burkitt's lymphoma from Africa. Subsequently EBV was detected in cases of sporadic BL, HIV-associated lymphomas, and post-transplant lymphoproliferative disorders. In contrast to endemic BL where EBV is invariably associated, EBV is associated to approximately one third of sporadic BL cases [5,6]. In HIV-associated lymphomas, EBV is detected in approximately 40% of all cases (80–100% of primary central nervous system [CNS] lymphoma and primary effusion lymphoma, 80% of DLBCL with immunoblastic features, and 30–50% of BL and nearly all cases of HL) [6,7]. The HHV8, known also as Kaposi's sarcoma herpesvirus was initially identified in tissues of patients with AIDS-related Kaposi's sarcoma and was subsequently linked to the development of a peculiar type of lymphoma known as primary effusion lymphoma [8]. HHV-8 has been also linked to a significant fraction of multicentric Castleman's disease.

Epidemiological studies have associated hepatitis C chronic infection with some B-cell NHL subtypes including marginal zone lymphomas (MZLs), in particular splenic MZLs (SMZLs), extranodal (mainly non-gastric) MZL of mucosa-associated lymphoid tissue (MALT), lymphoplasmacytic lymphoma (LPL), and DLBCL. While a causal relationship remains controversial, the most convincing proof is the observation, mainly limited to some indolent subtypes, of B-cell lymphoma regressions after hepatitis C virus (HCV) eradication with interferon (IFN) and ribavirin [9]. Bacterial infections have also been associated in the context of chronic inflammation to the development of certain lymphoma subtypes.

Extranodal marginal zone B-cell lymphomas of the MALT arise from lymphoid populations that are induced by chronic inflammation in extranodal sites. The most frequently affected organ is the stomach, where MALT lymphoma is incontrovertibly associated with a chronic gastritis induced by Helicobacter pylori (Hp). The initial observation in a few cases that this lymphoma can regress following Hp eradication was subsequently confirmed by a large number of clinical trials and Hp eradication therapy represents today the standard first line of treatment for Hp-positive localized gastric MALT lymphoma. Other bacterial infections have since been found to be implicated in the pathogenesis

of MZL arising in the skin (Borrelia burgdorferi), in the ocular adnexa (Chlamydophila psittaci), in the small intestine (Campylobacter jejuni), and possibly in the lung (Achromobacter xylosoxidans) [10].

Immune deficiency

Some rare inherited genetic syndromes that cause primary immune disorders are associated with an increased risk of serious infections and a higher risk of developing NHLs. The primary immune disorders that are most frequently associated with lymphoproliferative diseases are ataxia telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency, severe combined immunodeficiency, X-linked lymphoproliferative disorder, Nijemen breakage syndrome, hyper-IgM syndrome, and autoimmune lymphoproliferative disorder. With the exception of common variable immunodeficiency these diseases present primarily in the pediatric age [11].

Additionally, it is now well established that lymphoproliferative disorders can arise as a consequence of immunosuppression in recipients of solid organ, bone marrow, or stem cell allograft. Post-transplant lymphoprolifertaive disorders (PTLD) can develop with different frequency among patients receiving solid organ transplant, the higher being in those receiving heart-lung/lung, or intestinal allografts (5% of patients) and lower in those receiving renal, hepatic, and cardiac allografts (approximately 1% of patients) [12]. Stem cell and bone marrow allografts have a risk of approximately 1% [13]. The majority of PTLD are associated with EBV infection.

Autoimmune disease

Some autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE or lupus), Sjögren disease, celiac sprue (gluten-sensitive enteropathy), and others have been linked with an increased rate of NHL. The frequency of these lymphomas is not well known and it is difficult to determine if they are related to the underlying condition or to the treatment. Indeed, methotrexate, and some anti-tumor necrosis factor (TNF) therapies used for some of these diseases may cause an increased risk for the development of a lymphoma [14].

Other risk factors

Increased age, familiarity, previous treatment for cancer, and exposure to some chemicals and to radiation have all been proposed as possible risk factors but their exact link with the development of lymphoma is not clearly defined.

Pathogenesis of non-Hodgkin lymphoma

NHLs are a heterogeneous group of lymphatic tumors with distinct histological, immunophenotypic, genetic, and clinical features that originate from B lymphocytes, less commonly from T lymphocytes, while extremely rare are those originating from natural killer (NK) cells.

Over the past years, there has been significant improvement in our knowledge of the molecular pathogenesis of NHL as a clonal expansion of lymphatic cells. B and T lymphocytes, undergo under physiological circumstances, profound DNA rearrangements that permit expression of the functional B- and T-cell receptors, which determine the specificity of the immune response. This process involves multiple DNA double-strand breaks, which can form the basis for genomic lesions that contribute to lymphomagenesis.

Most mature lymphoid tumors present recurrent genetic lesions including non-random chromosomal translocations, somatic mutations, DNA gains, or losses. Some of these genetic changes can be preferentially observed in individual lymphoma entities but the vast majority are shared by different lymphoma subtypes. At the molecular level, these genetic lesions can result in activation of oncogenes by chromosomal translocations, as well as inactivation of tumor suppressor genes by chromosomal deletion and mutation. In addition, it is now known that the genome of certain lymphoma subtypes can be altered by the introduction of exogenous genes by oncogenic viruses and in particular the most studied for the development of some NHL are represented by EBV, HHV8, and HTLV-1.

The cytogenetic abnormalities discovered and their subsequent molecular characterization have permitted the identification of specific genes that are altered in NHL. Currently, while not sufficient alone to pose a diagnosis of a specific lymphoma subtype, genetic features of lymphomas,

detected by cytogenetics or fluorescence in situ hybridization (FISH) are increasingly important in defining specific NHL subtypes, together with histopathology and clinical presentation of the disease (Table 2.2).

Diffuse large B-cell lymphoma

DLBCL has a high degree of genomic complexity with different somatic mutations and unbalanced genomic lesions as well as few chromosomal translocations. Two main biologically different DLBCL subtypes have been identified by gene-expression profiling (GEP) studies resembling two types of normal B cells, likely to represent the lymphoma cells of origin (COO): germinal center (GC) B-cell like (GCB) subtype and activated B-cell like (ABC) subtype [15].

These two different types of DLBCL have different outcomes with standard current treatments with the ABC type having the worst prognosis. Given the prognostic importance of the definition of the DLBCL type, and due to technical difficulties in applying GEP studies in the daily practice, surrogate immunohistochemistry algorithms using monoclonal antibodies against a limited number of molecules (CD10, BCL6, MUM1, GCET1, FOXP1) have been developed but a total overlap with GEP signature has not been reached yet [16].

Lymphoma subtype	Translocation	Genes involved	Main sites/frequency
MALT lymphoma	t(11;18)(q21;q21) t(1;14)(p22;q32) t(14;18)(q32;q21) t(13;14)(p14.1;q32)	API2/MALT BCL-10/ IgH IgH /MALT1 FOXP1/ IgH	Lung, stomach Ocular adnexae, salivary gland Thyroid, ocular adnexae, skin
Mantle cell lymphoma	t(11;14)(q13;q32)	CCND1-IgH	90% of cases
Follicular lymphoma	t(14;18)(q32;q21)	IgH/BCL-2	90% of cases
Diffuse large B cell lymphoma	t(14;18)(q32;q21) t(3;-)(q27;-) t(8;-)(q24;-)	IgH/BCL-2 BCL-6 C-MYC	20–45% of cases 25% of cases 20% of cases
Burkitt's lymphoma	t(8;14)(q24;q32) t(8;22)(q24;q11) t(8;2)(q24;p12)	C-MYC/IgH C-MYC/Igλ C-MYC/Igκ	Most cases Rare variant Rare variant
Anaplastic large cell lymphoma, ALK positive	t(2;5)(p23;q35)	ALK/NPM	Virtually all cases

Table 2.2 Recurrent chromosomal translocations in lymphoma. MALT, mucosa-associated lymphoid tissue.

Genetic aberrations have been reported, which are associated with poor outcome in DLBCL patients. These lesions include BCL2 translocation, and TP53 inactivation (both apparently restricted to the GCB type), MYC translocations, gains at 3q, and losses at 8p and 9p21 (CDKN2A). A particularly poor prognosis seems to be associated with the concomitant involvement of MYC, BCL2, BCL6, or CCND1 (cyclin D1) in the so-called 'double' and 'triple-hit' lymphomas [17,18].

Follicular lymphoma

Follicular lymphoma (FL) is the most common indolent subtype of NHL and the second most common NHL. Up to 90% of FL cases have the t(14;18)(q32;q21) translocation, which juxtaposes the BCL2 gene to the IGHV locus resulting in the overexpression and accumulation of its transcript and protein. FISH is the best approach to detect the presence of the translocation [19].

Mantle cell lymphoma

The main genetic feature of mantle cell lymphoma (MCL) is the t(11;14)(q13;q32) chromosomal translocation with the deregulated ectopic expression of CCND1, coding for the cyclin D1, due to the juxtaposition to IGHV region. FISH is the technique of choice to demonstrate the presence of the translocation [20]. Approximately 10% of MCL lack the translocation. An indolent signature of MCL has been reported consisting in the lack or low levels of the transcriptional factor SOX11 [21].

Mucosa-associated lymphoid tissue lymphoma

The most common translocation is the t(11;18)(q21;q21), fusing BIRC3 (cIAP2) on 11q21 with MALT1 on 18q21. The presence of t(11;18) is associated with a low probability of response to antibiotics. The t(14;18)(q32;q21) translocation is cytogenetically virtual identical to the one involving BCL2 in FL or DLBCL, but in MALT lymphoma it brings MALT1 under the control of the promoter region of the IGHV genes with subsequent deregulation of MALT1 expression. The t(1;14)(p22;q32) translocation determines high levels of BCL10 expression due to its juxtaposition to

the IGHV promoter region. The presence of this translocation is associated with resistance to lymphoma eradication with antibiotics [22].

Burkitt lymphoma

BL is characterized by the t(8;14)(q24;q32) chromosomal translocation, juxtaposing the MYC to the IGHV genes. Rare variants are the t(2;8)(p12;q24) involving the Igk locus or the t(8;22)(q24;q11) involving the Igl locus. The differential diagnosis between BL and other aggressive lymphomas has important clinical consequences due to the specific regimes that can be given [23].

Pathogenesis of Hodgkin lymphoma

Hodgkin lymphoma (HL) is an uncommon B-cell lymphoma that accounts for ~10% of all lymphomas and comprises two disease entities: nodular lymphocyte-predominant HL (NLPHL) and classical HL (cHL), which is further divided into four subtypes: nodular sclerosis cHL, mixed cellularity cHL, lymphocyte-depleted cHL, and lymphocyte-rich cHL [24].

Classical HL accounts for 95% and NLPHL accounts for 5% of all HL. Studies of rearranged immunoglobulin variable-region heavy-chain (VH) genes from lymphoma cells isolated from patients with HL, have established that both lymphocyte-predominant cells (LP cells – the noplastic cells of NLPHL) as well as Hodgkin and Reed–Sternberg cells (HRS – the neoplastic cells of cHL) are of B-cell origin deriving from germinal centre B cells [25,26].

Despite their origin from germinal center B cells, HRS cells infrequently express B-cell genes, including CD20 antigen and the B-cell transcription factors OCT2, BOB1, and PU.1, presumably due to epigenetic reprogramming [27,28]. In cHL, deregulated transcription factors such as the nuclear factor kappa B (NFkB) and Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signaling pathway promote proliferation and abrogate apoptosis in HRS cells [29,30].

In contrast to some subtypes of NHL, no recurrent specific chromosomal translocations have been described in HL. Comparative genomic hybridization reveals recurrent gains of the chromosomal sub-regions on chromosomal arms 2p, 9p, and 12q and high-level amplifications on

4p16, 4q23-24 and 9p23-p24 [24]. Amplifications on 9p24.1 represent a recurrent genetic abnormality in the nodular sclerosis type of HL and have gained great interest in recent years with the development of monoclonal antibodies targeting programmed cell death 1 (PD-1) due to the fact that the genes encoding PD-1 ligands are key targets of chromosome 9p24.1 amplification [31].

cHL has been clearly associated with Epstein–Barr virus (EBV). In the Western World, HRS cells are infected with the EBV in ~40% of HL patients, and in 100% of HL patients who are infected with the human immunodeficiency virus (HIV) [32].

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Chapter 3

World Health Organization classification

Anas Younes and Ahmet Dogan

One of the most important steps in the management of patients with lymphoma, is establishing an accurate diagnosis. To do so, an adequate amount of tissue should be obtained for analysis and diagnostic work-up. Ideally, an excisional biopsy of a disease site or an enlarged lymph node should be performed. A less invasive, large core needle biopsy can also be sufficient in many cases to establish a diagnosis. However, fine needle aspiration is not considered appropriate for establishing a specific diagnosis of lymphoma.

A biopsy should be processed and interpreted by an expert hematopathology team. A few decades ago, simple hematoxylin and eosin (H&E) stains were the only available method to describe different entities of lymphomas. Not surprisingly, such a primitive method resulted in a simple and inaccurate classification. In contrast, the current World Health Organization (WHO) lymphoma classification utilizes a panel of immunostains and molecular tools to produce a more accurate and precise classification [1]. Furthermore, the WHO classification provides a common language among pathologists and clinicians from around the world. Such a common language is critical for communicating prognosis to patients and for guiding management options. Furthermore, the WHO classification enables assessing clinical trials results in a homogeneous patients population (Table 3.1) [1].

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Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Lymphoplasmacytic lymphoma
• Waldenström macroglobulinemia
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue
Nodal marginal zone B-cell lymphoma (MZL)
• Pediatric type nodal MZL
Follicular lymphoma
• Pediatric type follicular lymphoma
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Table 3.1 Common sub-types of lymphoid tumors according to the World Health Organization classification (continues overleaf).

Hodgkin lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma

Classical Hodgkin lymphoma

- Nodular sclerosis classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

Mature T-cell neoplasms

T-cell prolymphocytic leukemia

T-cell large granular lymphocytic leukemia

Chronic lymphoproliferative disorder of natural killer (NK) cells

Aggressive NK-cell leukemia

Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)

Hydroa vacciniforme-like lymphoma

Adult T-cell leukemia/lymphoma

Extranodal NK/T cell lymphoma, nasal type

Enteropathy-associated T-cell lymphoma

Hepatosplenic T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides

Sézary syndrome

Primary cutaneous CD30+ T-cell lymphoproliferative disorder

- Lymphomatoid papulosis
- Primary cutaneous anaplastic large-cell lymphoma

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

Primary cutaneous gamma-delta T-cell lymphoma

Primary cutaneous small/medium CD4+ T-cell lymphoma

Peripheral T-cell lymphoma, not otherwise specified

Angioimmunoblastic T-cell lymphoma

Anaplastic large cell lymphoma (ALCL), ALK+

Anaplastic large cell lymphoma (ALCL), ALK–

Table 3.1 Common sub-types of lymphoid tumors according to the World Health Organization classification (continued). Adapted from © American Society of Hematology, 2009. All rights reserved. Vardiman et al [1].

Broadly, WHO classification of lymphoid tumors, includes: (1) mature B-cell neoplasms, (2) Hodgkin lymphoma, and (3) mature T-cell neoplasms (Table 3.1) [1]. Of the approximately 80,000 new cases of non-Hodgkin lymphoma (NHL) that are diagnosed in the US this year, approximately 70,000 will have B-cell lymphoma and 10,000 will have T-cell lymphoma. Approximately, 8000 patients will be diagnosed with Hodgkin lymphoma this year. The most common NHL subtypes are diffuse large B cell lymphoma (DLBCL) and follicular lymphoma, accounting for approximately 50% to 60% of all NHL cases (Figure 3.1) [2]. Although the WHO classification allows hematopathologists to more precisely identify different lymphoma subtypes, it is important to note that almost all these histologically well-defined entities are heterogeneous at the molecular levels. For example, using gene expression profiling methods, DLBCL can be sub-divided into two major molecular subtypes, the germinal center type (GCB) and the activated B-cell type (ABC). These subsets have different clinical outcomes, as they are associated with different genetic alterations and underlying oncogenic mechanisms.

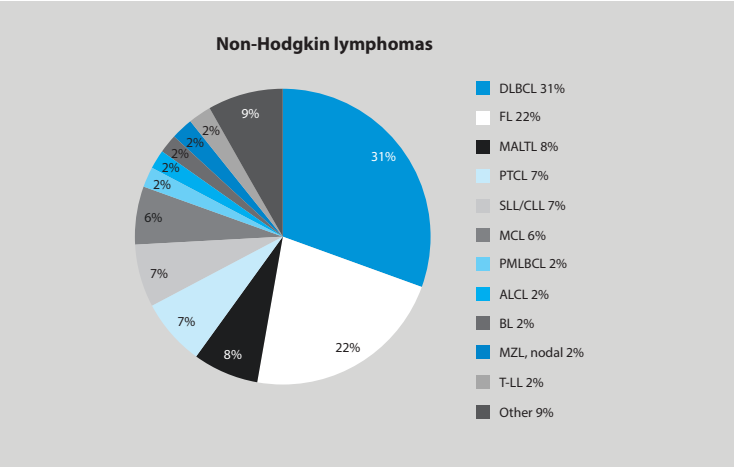

Figure 3.1 Frequency of non-Hodgkin lymphoma subtypes. ALCL, anaplastic large cell lymphoma; BL, Burkitt's lymphoma; CLL, chronic lymphocytic leukemia; MALTL, mucosa-associated lymphoid tissue lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PMLBCL, primary mediastinal large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic lymphoma; T-LL, T-cell lymphoblastic leukemia. Data from [2].

Finally, as the sensitivity of different diagnostic methods continues to improve, there is an increased ability to identify early clonal expansion of lymphoid cells that may represent a pre-malignant early step in the malignant transformation process. The best example is the entity of monoclonal B-cell lymphocytosis (MBL). In this example, clonal B cell proliferation is detected in otherwise asymptomatic, healthy individuals, but with absolute lymphocytosis below the threshold of 5 x 10^9/L that is required for establishing a diagnosis of B-cell chronic lymphocytic leukemia (CLL).

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Chapter 4

Staging

Colette Owens and Anas Younes

Introduction

Tissue analysis of tumor samples is required to establish a lymphoma diagnosis. Once a diagnosis is established, imaging studies should be performed to assess the extent of disease (tumor stage). Depending on the choice of therapy, additional tests will be needed to ensure the safety of the selected therapy.

Biopsy

Ideally, an excisional biopsy should be obtained to ensure adequate tissue for morphologic and molecular analysis. More recently, a less invasive, core needle biopsy is increasingly being used with success. Initially, a morphologic examination of tissue sections is performed by an expert hematopathologist. This initial examination provides important information on the growth pattern and lymph node architecture. For example, lymphoma cells may grow in a nodular (or follicular) pattern, or a diffuse pattern. Additional biomarker and genetic tests are typically used to further classify the type of lymphoma, establish clonality, identify therapeutic targets, and assess prognosis.

Immunohistochemistry

A panel of immunostains is typically used to determine the tumor lineage (B, T, or natural killer cell of origin). To do so, the expression pattern of

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several lineage-specific proteins is examined using a battery of monoclonal antibodies. Table 4.1 lists the most frequently protein biomarkers. In addition to establishing lineage, additional immunostains are used to sub-classify different types of lymphomas. Frequently, the expression pattern of several proteins can be associated with specific lymphoma subtypes, as shown in Table 4.2. Finally, immunohistochemistry (IHC) studies are also used to asses prognosis, identify therapeutic targets, and to select patients for specific clinical trials (Table 4.3).

Flow cytometry

Multi-parameter flow cytometry (FC) analysis of tumor cells can provide valuable information to assist in establishing the diagnosis, sub-classify the lymphoma type, and assess prognosis. This diagnostic tool is particularly helpful for examining circulating lymphoma cells in peripheral blood and in bone marrow. FC analysis is also used to analyze cells obtained by a

B cell	T cell
CD10	CD3
CD19	CD4
CD20	CD7
κ and λ light chain	CD8
	αβ and γδ T-cell receptor proteins

Table 4.1 Common lineage-specific proteins that are included in diagnostic immunohistochemistry diagnostic panels.

	Typically expressed	Not expressed
Classical Hodgkin lymphoma	CD30, CD15	CD10
Mantle cell lymphoma	CD20, CD5	CD10
Anaplastic large cell lymphoma	CD30, ALK	CD10
Diffuse large B cell lymphoma	CD10, CD20	CD 5 (rare), CD30 (rare)

Table 4.2 Correlation between protein expression and non-Hodgkin lymphoma subtypes.

Biomarker	Relevant disease	Prognostic implication
SOX11	Mantle cell	Poor
Myc and Bcl2 coexpression	Diffuse large B cell	Poor
CD10	Diffuse large B cell	Good
ALK	Anaplastic large cell	Good

Table 4.3 Correlation between protein expression status and prognosis in different subtypes of non-Hodgkin lymphoma.

fine needle aspiration from diseased sites. Most antibodies that are used for IHC on paraffin-embedded tissues can also be used for FC analysis. However, the advantage of FC is the ability to evaluate the expression of several proteins in the same cell. FC is also used to assess the presence of lymphoma cells in the cerebral spinal fluid.

Molecular diagnostics

In lymphoid malignancies, clonality is typically established by the presence of a dominant clone with identical gene rearrangement involving the immunoglobin heavy (IgH) chain in B-cell lymphomas, or T-cell receptors in T cell lymphoma. This test can be performed using polymerase chain reaction (PCR) assay, and most recently by DNA-sequencing methods. Characteristic chromosomal translocations can be detected by fluorescent in situ hybridization (FISH). For example, chromosomal rearrangement involving the Bcl2 gene is frequently observed in follicular lymphoma and diffuse large B cell lymphoma (DLCLC), whereas those involving the Bcl1 gene are observed in mantle cell lymphoma. Myc rearrangement is characteristic of Burkitt lymphoma, but can also be seen in rare cases of DLBCL. Finally, gene rearrangement involving ALK, is typically observed in ALK+ anaplastic large cell lymphoma (Table 4.4). As DNA and RNA sequencing assays are increasingly utilized in the clinical settings, these assays can also detect clonal genetic alterations, including mutations, and copy number changes.

Assessment of disease stage

Once a lymphoma diagnosis is established, the next step is to determine the extent of disease and assigning a disease stage [1]. There are four

Chromosomal translocation	Gene involved	Typical disease
t (14;18) (q32;q21)	Bcl-2	Follicular lymphoma
t (11;14) (q13;q32)	Bcl-1	Mantle cell lymphoma
t (8;14) (q24;q32)	Myc	Burkitt's lymphoma
t (2;5) (p23;q35)	ALK	Anaplastic large cell lymphoma

Table 4.4 Common chromosomal translocations observed in non-Hodgkin lymphoma subtypes.

lymphoma stages, with stage I being the least advanced (early stage) and stage IV being the most advanced stage. Staging is determined by imaging studies that may involve computed tomography (CT) or magnetic resonance imaging (MRI) scans, a positron emission tomography (PET) scan, and frequently requires a bone marrow biopsy. In general, involvement of one lymph node region or one extra nodal site is defined as stage I and IE, respectively. Stage II is established when more than one nodal involvement as long as they are on one side of the diaphragm. Stage III, lymph node involvement (regardless of the number or size) on both sides of the diaphragm. Stage IV, when both nodal and extra nodal sites (such as liver, bone, bone marrow, lungs) are involved. A bone marrow biopsy is frequently needed to complete the staging work up, and to determine disease response at the end of therapy. A bone marrow biopsy is not required in patients with early stage classical Hodgkin lymphoma who are adequately staged with imaging studies, including PET scan, as the bone marrow is rarely involved in these situations.

Lumbar puncture

In special cases of non-Hodgkin lymphoma, lumbar puncture is indicated to determine whether the lymphoma is spread to the spinal canal. This is particularly important for patients with Burkitt's lymphoma, testicular lymphoma, and aggressive B-cell lymphoma involving the para nasal sinuses. Additionally, patients with advanced stage diffuse large B-cell lymphoma, with multiple extranodal involvement, high lactate dehydrogenase (LDH), and poor performance status, are also at a higher risk for central nervous system involvement, and should be considered for a diagnostic lumbar puncture before initiating therapy. Patients with the above mentioned risk groups are candidates for prophylactic intrathecal chemotherapy.

Additional tests

After establishing the diagnosis and assigning a disease stage, a management plan is formulated. In many cases, the treatment involves chemotherapy, or a combination of chemotherapy and radiation therapy. Depending on the treatment recommendation, additional diagnostic tests

are performed to determine the patient's ability to tolerate treatment, and to monitor for unexpected toxicity. For example, before initiating an anthracyclin-based regimen, the patient's cardiac function, including the left ventricular ejection fraction, should be determined. Patients with evidence of hepatitis B or C infection should be adequately treated with anti-viral therapy, and monitored for liver toxicity. Similarly, patients with human immunodeficiencey virus (HIV) infection should be treated to decrease their viral load and to restore CD4 T cell counts before initiating therapy. Finally, women of childbearing age should be evaluated for possible pregnancy before initiating therapy, and should practice adequate birth control during therapy.

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Chapter 5

Treatment overview

Anastasios Stathis

Goals of treatment

In recent years, advances in the understanding of the biology of the lymphomas together with the development of new effective treatments have resulted in significant improvements in the outcomes for most common lymphoma subtypes. A definitive cure is the goal for patients with Hodgkin lymphoma (HL), diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, anaplastic large T-cell lymphoma, in addition to most subtypes of lymphoma when presented in a localized stage. When a cure is not achievable, which is currently the case for patients with advanced stage follicular lymphoma and mantle cell lymphoma (MCL), the goal of therapy should to improve survival and/or the quality of life [1,2]. Accordingly, the goals of treatments depend on the histologic subtype and patients characteristics, such as age and the existence of other comorbidities. Here we review the principles of treatment strategies for patients affected by the most common lymphomas.

Pre-treatment evaluation

Before planning a treatment for a patient with a newly diagnosed lymphoma, the extension of the disease together with prognostic factors and comorbidities of the patient must be known in order to establish the most appropriate treatment. Pre-treatment evaluations must include medical history with questions about the presence of B-symptoms (fever, weight

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loss, night sweats), performance status and comorbidities, a complete physical exam with particular attention to the superficial lympnodes, Waldeyer ring, size of the liver and spleen. Laboratory tests should include complete blood cell counts, chemistry, electrophoresis, erythrocyte sedimentation rate, serum lactate deydodrogenase, b2-microglobulin, hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) testing. The extension of the disease is established by positron emission tomography (PET)-computed tomography (CT) scan and bone marrow biopsy in most cases. Head CT or brain magnetic resonance imaging (MRI) and lumbar puncture to analyze cerebrospinal fluid is indicated in some cases of aggressive lymphoma with risk of dissemination in central nervous system ([CNS]; like Burkitt lymphoma and high-risk DLBCL). Multi-gated acquisition (MUGA) scans or echocardiograms are recommended when anthracyclines containing regimes are used.

Overview of types of treatment

The treatment of lymphomas has evolved over the past decade. Combination chemotherapy represents the backbone of treatment for most lymphomas. The addition to chemotherapy of the anti-CD20 monoclonal antibody rituximab has significantly improved the outcome of patients with B-cell non-Hodgkin lymphomas (NHLs). Radiotherapy is used in the treatment of different lymphomas, either a single treatment modality (in some early stage indolent lymphomas), or most commonly in combination with chemotherapy. Over the past decade, a significant expansion of new cancer therapeutics has permitted the development of new monoclonal antibodies and targeted agents with innovative mechanisms of action and some of them have been recently added for the treatment of patients with lymphoma (Table 5.1).

Cytotoxic agents

Among cytotoxic agents, alkylating agents were the first to show activity in lymphomas. The list of alkylating agents used to treat lymphomas comprise several drugs, the most commonly used being chlorambucil, bendamustine, cyclophosphamide, ifosfamide, melphalan, and dacarbazine. Other classes of cytotoxic drugs commonly used in the treatment

of lymphomas comprise anthracyclines (doxorubicin), glycopeptides (bleomycin), vinca alkaloids (vincristine, vinblastine), platin derivatives (cisplatin, oxaliplatin), purine analogues (fludarabine), topoisomerase inhibitors (etoposide), and antimetabolites (methotrexate). Corticosteroids are frequently used together with chemotherapy as they have both a lympholytic and antiemetic effect. Cytotoxic agents may be used as single agents but most commonly they are used in various combinations. The major toxicities of chemotherapeutic agents used for the treatment of lymphomas include: bone marrow failure, infertility, myelodysplasia (alkylating agents, purine analogs, toposidomerase inhibitors), cardiomyopathy (anthracyclines), pulmonary fibrosis (bleomycin), peripheral neuropathy (vinca alcaloids), renal failure, and peripheral neuropathy (platin derivatives).

Surgery

The role of surgery in the management of lymphomas is mainly limited to diagnostic purposes as most of the lymphomas are treated with systemic therapy and radiotherapy. Splenectomy may represent a treatment option in some cases of lymphomas with spleen involvement [3]. Gastrectomy for gastric lymphomas is reserved only in emergency situations where establishment of an appropriate treatment is not possible due to excessive bleeding.

Drug	Class	Indication	Year of approval
Brentuximab Vedotin	Anti-CD30 immunoconjugate	HL relapsed after ASCT or after two lines of chemotherapy; ALCL relapsed after 1 prior chemotherapy	2011
Lenalidomide	Immunomodulator	MCL after 2 lines of treatment	2013
Obinutuzumab	Type II anti-CD20 monoclonal antibody	In combination with chlorambucil for untreated CLL	2013
Ibrutinib	BTK inhibitor	MCL after failure of 1 prior treatment; CLL failing one prior line of treatment	2013; 2014
Idelalisib	PI3K delta inhibitor	In combination with rituximab in previously treated CLL; FL or SLL failing at least two prior systemic therapies	2014

Table 5.1 New therapeutic agents approved over the past 5 years for lymphomas. ALCL, anaplastic large cell lymphoma; ASCT, autologous stem cell transplantation; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; PI3K, phophatidylinositol-3 kinase; SLL, small lymphocytic lymphoma.

Radiotherapy

Lymphomas are highly radiosensitive. Over the years, the dose and field of radiation have been significantly modified to reduced late toxic effects of radiation therapy. Radiation therapy is typically used as a single treatment modality for some early presentations of indolent lymphomas, such as follicular lymphoma, or as consolidation after chemotherapy. Radiation therapy is also used as a single modality in many patients with relapsed lymphoma for palliation of symptoms, when other effective treatments are exhausted [4]. Specific indications are detailed in Chapters 6, 7, and 8.

Stem cell transplantation

High-dose chemotherapy followed by autologous or allogeneic hematopoietic stem cell transplantation can be curative in some forms of chemotherapy-sensitive relapsed lymphomas. Peripheral blood (PB) stem cells (PBSC) have become the main source of stem cells in hematopoietic transplantation. In autologous stem cell transplantation (ASCT), the patient's own stem cells are collected from PB following mobilization with the use of growth factors alone or in combination with chemotherapy. Collected blood is processed in the laboratory in order to purify and concentrate stem cells and then cryopreserved. Stem cells are reinfused after the administration of high-dose chemotherapy to rescue the patient from high-dose chemotherapy-induced aplasia [5]. In allogeneic transplantation, compatible donor stem cells are used to rescue the patient from conditioning-induced (chemo/radiotherapy) aplasia. Donor stem cells not only rescue from aplasia, but they also generate a powerful immune reaction against residual lymphoma cells (a graft versus lymphoma [GVL] effect). It is the combination of dose-intense lymphoma killing and GVL that explain the potentially curative effect of allogeneic transplantation [6]. However, allogeneic transplantation is associated with a number of toxicities (severe organ toxicity from dose-intensive conditioning, graft rejection, opportunistic infections, and graft versus host disease) and a significant mortality rate [7]. The use of non-ablative conditioning regimens to decrease toxicity and achieve engraftment of an allogeneic blood stem cell transplant allowing a GVL effect, has been used and can be considered in selected patients with indolent and aggressive NHLs

as well as in chemosensitive HLpatients in good general condition who relapse after high-dose chemotherapy and ASCT [8–11]. More commonly patients with relapsed lymphomas may be offered an autologous transplantation. The two major indications where there is clear evidence of benefit from ASCT are represented by relapsed DLBCL and HL [12–14]. However, for patients with relapsed DLBCL previously treated with rituximab, outcome following ASCT is significantly worse in comparison with rituximab-naive patients [15]. No randomized trials have ever shown a benefit from ASCT in other forms of relapsed or refractory lymphomas. On the other hand, ASCT is usually included in the first-line treatment of young patients with high-risk MCL [16]. First line consolidation ASCT in DLBCL has been evaluated in several randomized trials, failing to demonstrate an improvement in overall survival. Retrospective analyses suggest a benefit of upfront HSCT in high-risk International Prognostic Index (IPI) patients. In the absence of prospective confirmatory data, the use of first-line ASCT in DLBCL should be considered experimental or reserved only for selected high-risk IPI young patients. Improvements in supportive care have significantly reduced the toxicities from ASCT and its mortality is estimated at approximately less than 1% of cases. ASCT is associated with increased risk of myelodysplasia and second cancers.

Monoclonal antibodies

Unconjugated antibodies

The introduction of the anti-CD20 monoclonal antibody rituximab in the treatment of the most common subtypes of B-cell NHLs has significantly improved treatment outcomes [17]. Rituximab is a chimeric monoclonal antibody with a variable Fab segment of murine origin, which recognizes CD20 on the surface of the lymphoma cells. The activity of rituximab varies in different B-cell lymphomas. It can be given as single agent, in combination with chemotherapy or as maintenance. Over the past years advances in monoclonal antibodies techniques have permitted the development of second and third generation human and humanized anti-CD20 monoclonal antibodies such as ofatumumab (approved for chronic lymphocytic leukemia [CLL]) which is a second generation human and obinutuzumab (approved for CLL) a third generation

humanized monoclonal antibody. There are three main mechanisms through which these monoclonal antibodies cause the death of lymphoma cells: complement-dependent cytotoxicity, direct apoptosis, and antibody-dependent cell-mediated cytotoxicity [18].

The above reported monoclonal antibodies are also called 'naked' to distinguish them from a class of monoclonal antibodies, which are conjugated to either a chemotherapy (called also immunotoxins) or radioisotopes (radioimmunotherapy), where the antibody acts as a vector bringing to the target cell the toxin.

Radio-immune therapy

Radiolabeled antibodies directed to antigens present on the surface of lymphoid cells represent an interesting technique to selectively irradiate multiple tumor sites. When the antibody binds to the antigen on the surface of the cell, it irradiates both the cell and the adjacent tumor. Two radio-immunoconjugates based on anti-CD20 antibodies were approved for relapsed follicular lymphoma: the 90-Yttrium-labeled ibritumomab tiuxetan and the 131-iodine-labeled tositumomab. Currently, only ibritumomab tiuxetan is commercially available.

Antibody-drug conjugates

Several immunoconjugates have been developed in the past years, but the most significant results have been obtained with brentuximab vedotin an anti-CD30 immunoconjugate which has been recently approved for the treatment of HL and anaplastic large cell lymphoma (ALCL). Brentuximab vedotin is generated by conjugating the humanized anti-CD30 monoclonal antibody SGN-30 to the cytotoxic agent monomethyl auristatin E (MMAE) via a valine-citrulline peptide linker. Upon administration and internalization by CD30-positive tumor cells, brentuximab vedotin undergoes enzymatic cleavage, releasing MMAE into the cytosol; MMAE binds to tubulin and inhibits tubulin polymerization, which may result in G2/M phase arrest and tumor cell apoptosis. Brentuximab vedotin is approved for the treatment of patients with HL after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for ASCT and for the treatment of

patients with systemic ALCL after failure of at least one prior multi-agent chemotherapy regimen [19].

Immune checkpoint inhibitors

More recently, monoclonal antibodies targeting immune checkpoints have been evaluated in different tumor types including lymphomas. The programmed death 1 (PD-1) pathway serves as a checkpoint to limit T-cell-mediated immune responses. Both PD-1 ligands, PD-L1 and PD-L2, engage the PD-1 receptor and induce PD-1 signaling and associated T-cell 'exhaustion', a reversible inhibition of T-cell activation and proliferation. By expressing PD-1 ligands on the cell surface and engaging PD-1 receptor-positive immune effector cells, tumors can co-opt the PD-1 pathway to evade an immune response. Nivolumab and pembrolizumab, two monoclonal antibodies targeting PD-1, have shown significant activity in HL patients refractory to standard treatments, including ASCT and brentuximab vedotin [20].

Targeted small molecules

The following small molecules are currently approved for the treatment of some lymphoma subtypes.

Bortezomib

Bortezomib is a boronic acid analogue that reversibly inhibits the 26S proteasome, a large protease complex that degrades ubiquinated proteins. Specifically, the agent inhibits nuclear factor (NF)-kappaB, a protein that is constitutively activated in some lymphomas, thereby interfering with NF-kappaB-mediated cell survival, tumor growth, and angiogenesis. Bortezomib is approved for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy [21]. Recently a Phase III trial in previously untreated patients with MCL who were ineligible or not considered for stem-cell transplantation, showed that bortezomib added to combination chemotherapy (VR-CAP regimen, with bortezomib replacing vincristine in the standard R-CHOP regimen), resulted in significant improvements of progression-free survival in comparison to R-CHOP. This study led to its approval in newly diagnosed MCL patients [22].

Lenalidomide

Lenalidomide is a thalidomide analog with antineoplastic activity through different mechanisms. Lenalidomide inhibits tumor necrosis factor (TNF)-alpha production, stimulates T cells, reduces serum levels of the cytokines vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), and inhibits angiogenesis. It also promotes G1 cell cycle arrest and apoptosis of malignant cells. Lenalidomide is approved for the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib [23].

Ibrutinib

The B-cell receptor (BCR) signaling functions as the receptor for antigen; upon activation, it recruits numerous kinases and adaptor proteins for signal propagation. B-cell receptor signaling subsequently leads to the activation of various downstream effectors responsible for B-cell life cycle management which play prominent roles in promoting cell growth, proliferation, and survival of normal and malignant B cells.

Ibrutinib is a first-in-class small-molecule inhibitor of Bruton's tyrosine kinase (BTK) that binds to and irreversibly inhibits BTK activity, thereby preventing both B-cell activation and B-cell-mediated signaling. This leads to an inhibition of the growth of malignant B cells. BTK, a member of the src-related BTK/Tec family of cytoplasmic tyrosine kinases, is required for B-cell receptor signaling, plays a key role in B-cell maturation, and is overexpressed in a number of B-cell malignancies. Ibrutinib is approved for the treatment of patients with MCL who have received at least one prior therapy and for the treatment of patients with CLL who have received at least one prior therapy [24].

Idelalisib

Phosphatidylinositol-3 kinases (PI3K) are intracellular signal transducer enzymes that are essential for many cellular functions. The delta isoform is generally restricted to hematopoietic cell types. Upon activation via cell-surface receptor–ligand interactions, PI3Kδ phosphorylates the second messenger phosphatidylinositol to generate phosphatidylinositol 3,4,5,trisphosphate (PIP3). PIP3 enables the transmission of cell-surface

receptor signaling by acting as a scaffold for the recruitment and activation of numerous intracellular signaling enzymes, including the serine/threonine protein kinase Akt. Akt is an initiator of specific pathways that ultimately mediate positive pleotropic effects on cell survival, proliferation, growth, and metabolism. PI3Kδ is a signaling molecule in normal and malignant B lymphocytes involved in several signaling pathways, such as the B-cell receptor, CD40, B-cell-activating factor receptor, chemokine receptors CXCR4 and CXCR5, interleukin (IL)-6 receptor, and integrins. These pathways may be involved in B-cell proliferation, motility, and in homing to and maintenance of the tumor microenvironment in B-cell malignancies. Idelalisib, is an orally bioavailable, small molecule inhibitor of the delta isoform of class I PI3K. Idelalisib inhibits the production of the second messenger PIP3, preventing the activation of the PI3K signaling pathway and inhibiting tumor cell proliferation, motility, and survival. Unlike other isoforms of PI3K, PI3K-delta is expressed primarily in hematopoietic lineages. Idelalisib is approved for the treatment of patients with relapsed CLL in combination with rituximab and for the treatment of patients with relapsed follicular B-cell NHL or relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies [25,26].

After treatment

After achieving remission, patients should undergo follow-up with regular history, physical examination, blood counts, and biochemistry analysis. There is no evidence to support regular surveillance by CT or other imaging techniques. Surveillance with PET scans can possibly detect relapses a few months earlier but there is no evidence that this could have an impact on survival.

New research and emerging treatment options

The improved knowledge of the molecular biology has permitted the development of a high number of new therapeutic compounds and some of them have shown significant clinical activity and have been approved for the treatment of specific lymphoma subtypes. The most significant results have been obtained in the treatment of HLwhere the

immunoconjugate brentuximab vedotin and more recently the anti-PD-1 monoclonal antibody nivolumab will likely further improve treatment outcomes and will be incorporated in the standard treatment combinations. For NHLs, significant improvements have been obtained in both supportive treatments and in the discovery of new therapeutic compounds. However, many patients are still incurable with available treatments. A major challenge for the treatment of lymphoma in the next decade, together with the development of new therapeutic compounds, will be the identification of genetic and molecular signatures able to predict the activity of a molecularly targeted therapy. This will allow for the development of a personalized medicine for patients with lymphoma [27]. Current research aims at designing basket trials selecting patients based on shared genetic alterations rather than histologic subtype. This can be possible through the application of next generation genomic sequencing assays that can describe the spectrum and incidence of genetic alterations across different lymphoma subtypes. A prospective study of 103 cases of lymphoma using a comprehensive DNA-/RNA-targeted sequencing of genes commonly found in hematologic malignancies to define the distribution of genetic alterations across all lymphoma subtypes established the feasibility of this approach. The most common genetic alterations were TP53 (28%), BCL2 (23.3%), MLL2 (22%), BCL6 (16%), and TNFAIP3 (15%). 85% of samples had clinically relevant genetic alterations with potential prognostic and therapeutic implications. The most common clinically relevant genetic alterations were TP53, BCL2, CDKN2A/B, and CREBBP [28].

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Chapter 6

Treatment of B-cell lymphomas

Anastasios Stathis and Ahmet Dogan

Diffuse large B-cell lymphoma

Newly diagnosed patients

Standard therapy

The standard treatment for patients with diffuse large B-cell lymphoma (DLBCL) is based on clinical stage. Clinical and biologic prognostic factors are used to select or stratify patients enrolled on clinical trials and are not currently used to guide the selection of standard therapy. In general, the most widely used regimen is a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP), but other regimens are also used (Table 6.1). Patients with stage I or II disease can be treated with three cycles of RCHOP plus involved field radiation therapy or six to eight cycles of the RCHOP regimen without radiation therapy. Patients with advanced stage DLBCL are typically treated with six cycles of RCHOP [1]. Consolidation radiotherapy to the site of previous bulky disease must be taken into account.

Prognostic factors

The most important prognostic tool is represented by the International Prognostic Index (IPI) score which divides DLBCL patients into low, low–intermediate, intermediate–high or high-risk disease categories based on the presence of 0–1, 2, 3, and 4–5, respectively risk factors, represented by age >60 years, performance status >1, lactate dehydrogenase (LDH)

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>normal value, number of extranodal sites involved >1, and Ann Arbor stage >II. For patients younger than 60 years the age-adjusted IPI (aa-IPI) score divides patients in the same risk groups in the presence of 0, 1, 2, 3 risk factors represented by LDH >normal values, Ann Arbor stage >II, and performance status >1. The validity of the IPI score to predict the outcome of newly diagnosed DLBCL has been confirmed also for patients treated with RCHOP or RCHOP-like chemotherapy [2].

Gene-expression profiling (GEP) can define at least two major subtypes of DLBCL, the germinal center (GC) B-cell like (GCB) and the activated B-cell like (ABC) subtype (Figure 6.1) [3]. While these two subtypes have different outcomes with a better prognosis for the GCB subtype, the application of GEP studies to predict the outcome of patients with DLBCL is not currently applied in clinical practice.

Role of functional imaging

Positron emission tomography-computer tomography (PET-CT) has become the standard for both pretreatment evaluation and final response assessment in DLBCL. Regarding interim restaging, while a negative PET scan after two to four cycles of chemotherapy is clearly associated with a favorable outcome, treatment decisions based on interim PET are not recommended, due mainly to the possibility of false positive results [4]. In addition, PET-CT has a high sensitivity for bone marrow involvement and the most recent recommendation is that in DLBCL, a bone marrow biopsy is not necessary if PET-CT indicates bone or marrow involvement. If PET-CT is negative, a bone marrow biopsy should be performed only to exclude involvement by a different lymphoma subtype if this information is relevant (eg, requested for participation in a clinical trial) [5].

Risk for central rervous system disease

Some patients with high-risk lymphoma and specific extranodal localizations (renal, adrenal, and nasopharingeal) benefit by adding central nervous system (CNS) prophylaxis with high-dose methotrexate or intrathecal methotrexate ot cytarabine [6]. Patients with DLBCL of the CNS are treated with high-dose methotrexate containing regimens, usually together with high dose cytarabine [7]. Primary DLBCL of the

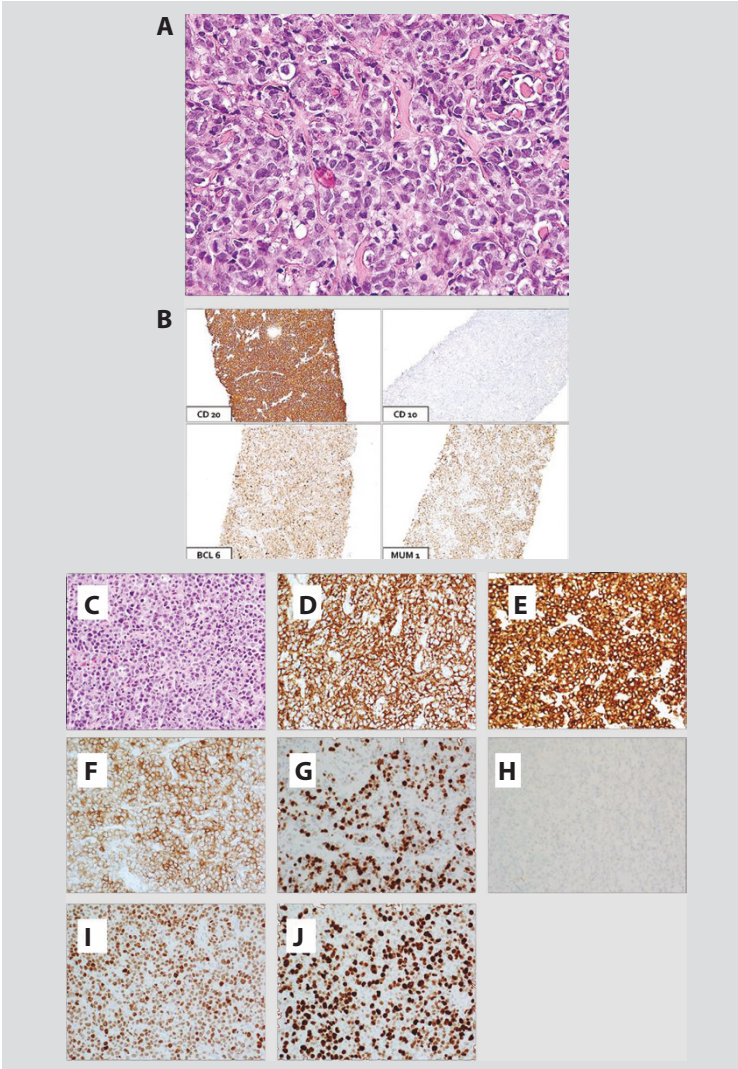

Figure 6.1 Diffuse large B cell lymphoma. Top panel: lymph node core biopsy showing involvement of a diffuse large B-cell lymphoma with an activated B-cell (ABC) phenotype. There is a diffuse infiltrate of large atypical lymphocytes (A). The composite image (B) shows that neoplastic lymphocytes express CD20, BCL6, and IRF4/MUM1 but not CD10 consistent with an activated B-cell (ABC) phenotype. Bottom panel: lymph node core biopsy showing involvement of a diffuse large B-cell lymphoma with a germinal center B-cell (GCB) phenotype, and dual expression of BCL2 and MYC. There is a diffuse infiltrate of large atypical lymphocytes with predominantly centroblastic morphology (C). The neoplastic lymphocytes express CD20 (D), BCL2 (E), CD10 (F), BCL6 (G) but not IRF4/MUM1 (H). They are also positive for MYC (I) and show a high proliferation fraction with Ki67 (J) suggesting an aggressive biological behavior.

testis must be treated with R-CHOP together with CNS prophylaxis and contralateral testis irradiation [8].

Primary mediastinal large B-cell lymphoma

Gene expression profiling has established that primary mediastinal large B-cell lymphoma (PMLBCL) is distinct from DLBCL and is more similar to Hodgkin lymphoma (HL) [9]. The optimal first-line treatment for this rare disease occurring in young patients with a slight female prevalence has still to be defined. In the pre-rituximab era dose-intensified regimes like the combination of methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine and bleomycin (MACOP-B regimen) or etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin (VACOP-B regimen) were superior when compared with CHOP chemotherapy [10]. The benefit of adding rituximab to CHOP chemotherapy in PMLBCL derives mainly from retrospective data and is less clear than other DLBCL types, due mainly to the rarity of the disease. An open question in the management of PMLBCL remains the utility of adjuvant mediastinal radiotherapy following induction immunochemotherapy. A large prospective randomized Phase III trial currently conducted by the International Extranodal Lymphoma Study Group (IELSG) is evaluating the role of mediastinal radiotherapy in patients achieving complete metabolic PET response after systemic therapy. More recently significant activity was reported with the infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) regimen in a single arm Phase II study (Table 6.1) [11].

Double hit diffuse large B-cell lymphoma

Double hit lymphomas with concurrent MYC and BCL2 rearrangement are highly aggressive and carry poor outcomes when treated with standard R-CHOP chemotherapy [12]. Currently, no standard treatment exists for these patients and they should be treated in clinical trials when possible. In a retrospective study, the R-EPOCH regimen resulted in higher rate of complete responses in comparison to R-CHOP [13].

Diffuse large B-cell lymphoma in older patients or in patients with co-morbidities

Patients older than 80 years or patients with significant co-morbidities may be treated with rituximab in combination with attenuated chemotherapy regimens such as the R-miniCHOP regimen [14]. A geriatric assessment should be performed in older patients before the decision for a specific treatment.

Treatment of relapsed and refractory diffuse large B-cell lymphoma

Relapsed or progressing patients can still be cured with salvage chemotherapy and autologous stem cell transplant (ASCT). Autologous stem cell transplant can however be curative only in patients that are chemosenstive to salvage therapy. With regards to salvage treatments, there are currently several options including the regimes rituximab, dexamethasone, cytarabine, and cisplatin (RDHAP), rituximab, ifosfamide, carboplatin, and etoposide (RICE), rituximab, dexamethasone, gemcitabine, and cisplatin (RGDP), and rituximab, etoposide, metilprednisolone, cytarabine, and cisplatin (RESHAP) (Table 6.1). In a randomized study, both RDHAP and RICE demonstrated similar efficacy. In the pre-rituximab era, patients with relapsed/refractory DLBCL who responded to second line regimens and received consolidation ASCT had a cure rate of 40%-60%. The cure rate of second-line regimens/ASCT in patients who receive rituximab-based initial therapy is lower in comparison with pre-rituximab era. In an international randomized study that evaluated second-line therapy of relapsed or refractory DLBCL with RICE versus RDHAP the 3-year overall survival was 49% [15].

Patients relapsing after autologous stem cell transplant or refractory to salvage chemotherapy and/or not a candidate for ASCT should be offered participation in clinical trials, as there is no standard of care for these patients. Furthermore, there are no new agents approved for relapsed DLBCL.

Follicular lymphoma

Newly diagnosed patients

In general, follicular lymphoma, is less aggressive than DLBCL, with an indolent clinical course (Figure 6.2). In patients presenting with early non-bulky stage I-II disease at diagnosis, involved field radiotherapy (24–36Gy) is the standard of choice and can be curative [16]. For patients with advanced stage disease, a distinction should be made among patients not symptomatic and patients requiring immediate treatment. In fact randomized trials show that a watch and wait policy allows chemotherapy to be delayed without any survival disadvantage when compared with immediate treatment. In asymptomatic patients for whom a watch and wait strategy is not acceptable, monotherapy with rituximab results in high response rates without impairing the quality of life [17,18].

Symptoms that require the establishment of treatment include: B symptoms, hematopoietic impairment, bulky disease, vital organ

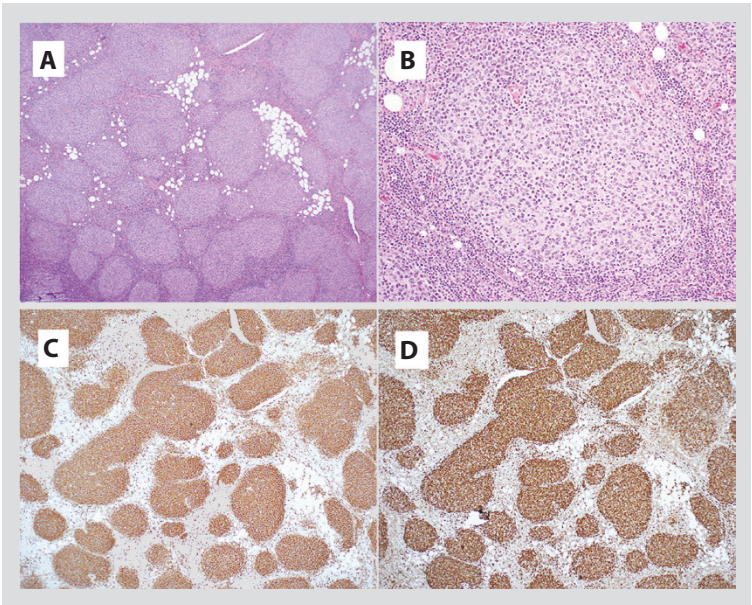

Figure 6.2 Lymph node showing involvement by a follicular lymphoma, Grade 3A. The lymph node architecture is effaced by a nodular proliferation of atypical lymphoid cells (A). On high power view the neoplastic cells are mixture of atypical centrocytes and centroblasts (B). The neoplastic cells express CD20 (C), BCL2 (D).

compression, ascites, pleural effusion, or rapid lymphoma progression. Combination treatment is the standard of care for patients with advanced disease. Rituximab in combination with chemotherapy such as cyclophosphamide, vincristine, and prednisolone (CVP) or CHOP are valid treatment options for patients with advanced disease (Table 6.1) [19].

Recently, the combination of rituximab with the alkylating agent bendamustine resulted in the same clinical activity but with less side effects in patients with grade I and II follicular lymphoma and has now been adopted as the standard of care for the first-line treatment in many institutes [20]. Generally the R-CHOP regimen is reserved for grade III follicular lymphoma.

Less intensive treatments (rituximab, radioimmunotherapy, or chlorambucil plus rituximab) represent an alternative in patients with low risk profile or contraindications to a more intensive chemoimmunotherapy.

Rituximab maintenance for two years following induction chemoimmunotherapy improves progression free survival following treatment with RCHOP [21].

Patients with relapsed disease should always undergo biopsy of PET-positive lesions to rule out transformation to a more aggressive DLBCL. Observation is an accepted approach in patients with low tumor burden. For patients requiring treatment, a non-cross-resistant scheme in comparison with the first line should be preferred. Rituximab is generally added to chemotherapy especially if relapse occurred after more than 6 months. High-dose chemotherapy followed by ASCT may be offered to young patients with short previous remission [22]. In selected young patients relapsing after ASCT, allogeneic transplantation can be considered.

Treatment of relapsed follicular lymphoma

Patients in relapse should also be considered for clinical trials evaluating new drugs. Recently, the PI3Kdelta inhibitor idelalisib was approved in EU and US for patients with follicular lymphoma resistant to rituximab and alkylating chemotherapy.

Regimen/Drugs	Dose	Days	Repeat
RCHOP			
Rituximab	375 mg/m^2	1	q21 days
Doxorubicin	50 mg/m^2	1	
Cyclophosphamide	750 mg/m^2	1	
Vincristine	1.4 mg/m^2	1	
Prednisone	100 mg po	1–5	
RDHAP			
Rituximab	375 mg/m^2	1	q21 days
Dexamethasone	40 mg	1–4	
Cytarabine	2000 mg/m^2 x2	2	
Cisplatin	100 mg/m	1	
RICE			
Rituximab	375 mg/m^2	1	q21 days
Ifosfamide	5000 mg/m^2 ci 24/h	2	
Carboplatin	AUC 5	2	
Etoposide	100 mg/m^2	1–3	
RGDP			
Rituximab	375 mg/m^2	1	q21 days
Gemcitabine	100 mg/m^2	1 and 8	
Dexamethasone	40mg po	1–4	
Cisplatin	75 mg/m^2	1	
REPOCH (*)			
Rituximab	375 mg/m^2	1	q21 days
Etoposide	50 mg/m^2 ci	1–4	
Prednisone	60mg po	1–5	
Vincristine	0.4 mg/m^2 ci	1–4	
Cyclophosphamide	750 mg/m^2 ci	1–4	
R-Bendamustine			
Rituximab	375 mg/m^2	1	q28 days
Bendamustine	90 mg/m^2	1–2	
R-miniCHOP			
Rituximab	375 mg/m^2	1	q21 days
Doxorubicin	20 mg/m^2	1	
Cyclophosphamide	400 mg/m^2	1	
Vincristine	1 mg/m^2	1	
Prednisone	40 mg/m^2 po	1–5	

Table 6.1 The most common chemotherapy regimes in non-Hodgkin lymphomas. *In DA-EPOCH, the doses of etoposide, doxorubicin and cyclophospamide in each subsequent cycle: increase 20% if in the previous cycle nadir of neutrophils was ≥0.5 G/l; given same dose as in previous cycle if nadir of neutrophils <0.5 G/l in two separate measurements; and reduce 20% if in the previous cycle nadir of neutrophils was <0.5 G/l in 3 or more measurements. Ci, continuous infusion; po, per os.

Mantle cell lymphoma

Newly diagnosed patients

Young patients should be treated with induction chemotherapy followed by ASCT. Different regimens have been used for the induction treatment [23]. Regimes should contain high-dose cytarabine. A possible combination is represented by three cycles of R-CHOP alternated to three cycles of R-DHAP (total 6 cycles of treatment) [24]. Patients not fit to undergo ASCT should be treated with 6 cycles of either R-CHOP or six cycles of rituximab plus bendamustine. A maintenance treatment with rituximab for two years can be considered. Patients with localized disease (stage I or stage II) may be treated with four cycles of R-CHOP followed by involved field radiotherapy.

Treatment of relapsed mantle cell lymphoma

Young patients relapsing following ASCT should be considered for allogeneic transplantation. Recently, two small molecules have been approved for relapsed mantle cell lymphoma and can be offered to patients. The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib and the immunomodulating agent lenalidomide. Other treatment options for relapsing patients include bortezomib, temsirolimus, or inclusion in a clinical trial evaluating new drugs.

Small B-cell lymphocytic lymphoma and chronic lymphocytic leukemia

Early stage small lymphocytic lymphoma (SLL) is usually managed as follicular lymphoma; radiation therapy can be an appropriate treatment in these patients. Advanced stage small lymphocytic lymphoma (SLL) is managed as chronic lymphocytic leukemia (CLL). The treatment of patients with CLL depends on the stage, risk of the disease, presence of genetic alterations, and the conditions of the patient, given that the disease usually presents in older patients (median age of diagnosis is 72 years). Inclusion of the patient in a clinical trial should always be considered, for all indications, as CLL is not a curable disease with available treatments. A watch and wait policy is appropriate for patients with early stage and low-risk disease (Binet A). Treatment must be established in

symptomatic patients with Binet B and patients with Binet C. Patients without high-risk genomic alterations (del(17p)/TP53), are treated with the combination of rituximab and fludarabine-cyclophosphamide or rituximab-bendamustine [25,26]. Fragile patients can be treated with a single alkylating agent (chlorambucil, bendamustine) or in combination with rituximab. For patients that relapse after first line, treatment decisions depend on the status of the patient and the duration of first response. Combination chemoimmunotherapy is offered to younger and fit patients. For older patients or young patients with comorbidities, combination chemoimmunotherapy at reduced doses, single agent ofatumumab, or the recently approved ibrutinib and idelalisib with rituximab can be considered [27]. Selected, young patients without comorbidities and with short duration of first response can be considered for allogeneic transplantation [28].

Patients with high-risk genomic alterations have a poor outcome. These patients should be included in clinical trials when possible. In the absence of clinical trials, ibrutinib and idelalisib in combination with rituximab or alemtuzumab are valid treatment options [29–31]. Young patients without comorbidities who achieve remission following first-line therapy must be considered for allogeneic transplantation.

A transformation to a high-grade lymphoma (Richter's syndrome) may develop in the course of the disease in up to 5% of patients. These patients are treated with a combination chemoimmunotherapy as for aggressive lymphoma (most commonly DLBCL). Auto-transplant is usually used following first-line therapy as consolidation. Young patients should be also considered for allogeneic transplantation.

Marginal zone lymphoma

For gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Helicobacter pylori (Hp) eradication therapy (proton pump inhibitor + clarithromycin-based triple therapy with either amoxicillin or metronidazole for 10–14 days) must be given to all patients, independently of stage or histological grade. Hp-negative patients with gastric MALT lymphoma may also receive eradication treatment. Eradication therapy with antibiotics in MALT lymphoma arising outside the stomach remains investigational.

Involved field radiotherapy may be a reasonable option only for localized MALT lymphomas (gastric not responding to eradication and for the other sites). Chemotherapy, immunotherapy, or in combination are effective in patients with MALT lymphoma of all stages.

In patients with disseminated disease, rituximab plus chemotherapy (chlorambucil or bendamustine) would be the best choice when treatment is needed. If clinical trials are available, patients should be included. Nodal marginal zone lymphoma (NMZL), is usually disseminated and treatment should be planned according to the therapeutic principles adopted for follicular lymphoma.

For splenic marginal zone lymphoma (SMZL), therapeutic options include splenectomy, chemotherapy, rituximab alone, or rituximab–chemotherapy (bendamustine, chlorambucil).

In patients with NMZL or SMZL and concurrent HCV-related chronic hepatitis who do not need immediately conventional treatment of lymphoma, antiviral treatment with pegylated interferon and ribavirin should be considered as first treatment [32].

Burkitt's lymphoma

Burkitt lymphoma (BL) can be curative in a high proportion of patients. The principles of treatment of this lymphoma are based on intensive chemoimmunotherapy and CNS prophylaxis [33]. Some accepted chemotherapy regimes in combination with rituximab that are used based on institutional preferences include the CODOX-M (cyclophosphamide, vincristine, doxorubicin, high dose methotrexate), alternating with IVAC (ifosfamide, etoposide and high dose cytarabine), the hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine, including intrathecal methotrexate) or the DA-EPOCH regimen.

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Chapter 7

Treatment of T-cell lymphomas

Neha Mehta-Shah and Ahmet Dogan

Overview of T-cell lymphomas

The mature T-cell and natural killer (NK)-cell lymphomas represent 10–15% of the non-Hodgkin lymphomas (NHL) by incidence and comprise 23 clinicopathologic entities in the most recent World Health Organization (WHO) classification (see Chapter 3) [1]. They are commonly subdivided into two categories: cutaneous T-cell lymphomas (CTCL) and systemic T-cell lymphomas (Table 7.1).

The systemic T-cell lymphomas or peripheral T-cell lymphomas (PTCL) have highly variable courses, and are typically aggressive and frequently less responsive to conventional chemotherapy than their B-cell lymphoma counterparts. The most common systemic T-cell and NK-cell lymphomas worldwide include peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL), and ALK-negative ALCL, which in sum represent approximately 60% of all systemic T-cell lymphomas [2–4]. There is considerable geographic variation in the incidence of certain entities, such as adult T-cell leukemia/lymphoma (ATLL) and extranodal NK/T-cell lymphoma (ENKTL) (Table 7.2).

Given the rarity of systemic T-cell and NK-cell disorders, large randomized trials are lacking to guide therapies. With the exception of ALK-positive ALCL, prognosis of systemic T-cell lymphomas remains relatively poor and can be risk stratified using the international prognostic index (IPI)

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Systemic	Primary cutaneous
Peripheral T-cell lymphoma, NOS	Mycosis fungoides
Angioimmunoblastic T-cell lymphoma	Sézary syndrome
Anaplastic large cell lymphoma, ALK-positive	Subcutaneous panniculitis-like T-cell lymphoma
Anaplastic large cell lymphoma, ALK-negative	Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma*
Enteropathy-associated T-cell lymphoma	Primary cutaneous gamma-delta T-cell lymphoma
Adult T-cell leukemia/lymphoma	Primary cutaneous small/medium CD4+ T-cell lymphoma*
Hydroa vacciniforme-like lymphoma	Primary cutaneous CD30+ T-cell lymphoproliferative disorder
T-cell prolymphocytic leukemia	Lymphomatoid papulosis
T-cell large granular lymphocytic leukemia	Primary cutaneous anaplastic large-cell lymphoma
Hepatosplenic T-cell lymphoma	
Extranodal NK/T-cell lymphoma, nasal type	
Aggressive NK cell leukemia	
Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)	
Chronic lymphoproliferative disorder of NK-cells*	

Table 7.1 2008 World Health Organization classification of mature T-cell and NK-cell neoplasms. *provisional entities. ALK, anaplastic lymphoma kinase; EBV, Epstein Barr virus; NK, natural killer; NOS, not otherwise specified. Adapted from © International Agency for Research on Cancer. All rights reserved. Swerdlow et al [1].

Sub-type	Registry	PTCL-NOS (%)	AITL (%)	ALCL, ALK+ (%)	ALCL, ALK– (%)	NK/T (%)	ATL (%)	EATL (%)
North America	IPTCL	34	16	16	8	5	2	6
	BCCA	59	5	6	9	9	NA*	5
	COMPLETE	34	15	11	8	6	2	3
Europe	IPTCL	34	29	6	9	4	1	9
	Swedish	34	14	9	15	4	NA*	9
Asia	IPTCL	22	18	3	3	22	25	2

Table 7.2 Incidence of lymphoma subtypes by geographic region. *ATLL patients were excluded in both the BCCA and Swedish Registry Studies. AITL, angioimmunoblastic T-cell lymphoma; ALCL ALK–, anaplastic large cell lymphoma anaplastic lymphoma kinase negative; ALCL ALK+, anaplastic large cell lymphoma anaplastic lymphoma kinase positive; ATL, adult T-cell leukemia/lymphoma; BCCA, British Columbia Cancer Agency; COMPLETE, Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment; EATL, enteropathy-associated T-cell lymphoma; IPI, International prognostic index; IPTCL, International peripheral T-cell lymphoma project; NA, not available; NK/TL, natural killer cell/T-cell lymphoma; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma. Data from [2–4].

or the prognostic index for T-cell lymphoma (PIT) (Table 7.3). Treatment strategies are generally based upon the best data available, which include prospective Phase II studies and retrospective analyses. The most frequently used regimens for the more common entities, PTCL-NOS, AITL, and ALCL are cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)-based, although long-term outcomes are often unsatisfactory. Therefore, ongoing clinical trials are aimed at improving upon CHOP by adding novel agents or using alternate regimens. Although controversial, patients are often considered for consolidation with autologous stem cell transplantation (ASCT) in first remission to improve remission durations. Recently, targeted agents specific for particular T-cell and NK-cell lymphomas, such as brentuximab vedotin for ALCL and crizotonib for ALK-positive ALCL, are now allowing the investigation of more individualized therapy for these entities. Furthermore, for a considerable portion of the T-cell and NK-cell lymphoma entities, including ENKTL and ATL, CHOP-based therapy is ineffective, and treatment strategies are disease-specific. There is still much to learn about the biology and potential drug targets for these diseases and ongoing studies using gene expression profiling and genomics may help answer some of these questions. In addition, ongoing clinical trials evaluating disease-specific treatment approaches and employing novel and often targeted agents will hopefully lead to improved outcomes for people with these diseases.

Cutaneous T-cell lymphomas (CTCL) represent approximately 4% of all NHLs and are a heterogeneous group of disorders [5,6]. Some forms of CTCL are histologically and immunophenotypically unique compared with other forms of T-cell lymphoma. However, others histologically resemble their counterparts in the lymph nodes but carry a different prognosis, clinical behavior, and phenotype. The most common types of CTCL include mycosis fungoides (MF), cutaneous peripheral T-cell lymphoma, and cutaneous CD30+ T-cell lymphoma, which represent 54%, 29%, and 14% of cases, respectively (Table 7.4) [6].

The majority of CTCL consists of indolent disorders that are treated with observation and intermittent skin-directed therapy to control the burden and the symptoms from disease. For example, those with stage IA MF, which represents 40% of those with MF, have similar life expectancy

PTCL Subtype	N	Median age	IPI (%) 0–1	2–3	4–5	5-yr OS[A] (%)	5-yr PFS[A] (%)	5-yr OS by IPI (%) 0–1	4–5
PTCL-NOS									
• IPTCL	229	60	28	57	15	32	20	50	11
• BCCA	117	64	30	47	22	35	29	64	22
• Swedish	256	69	17	59**	24**	28	21	NA	NA
AITL									
• IPTCL	213	65	14	59	28	32	18	56	25
• BCCA	10	66	0	30	70	36	13	NA	NA
• Swedish	104	70	4**	69**	27**	31	20	NA	NA
ALCL ALK–									
• IPTCL	72	58	41	44	15	49	36	74	13
• BCCA	18	55	44	22	33	34	28	66	25[B]
• Swedish	115	67	34	42	24	38	31	NA	NA
ALCL ALK+									
• IPTCL	76	34	49	37	14	70	60	90	33
• BCCA	12	32	67	25	8	58	28[B]	66B	25[B]
• Swedish	68	41	55**	39**	6**	79	63	NA	NA
EATL									
• IPTCL	62	61	25	63	13	20	4	29	15
• BCCA	9	61	0	30	70	22	22	NA	NA
• Swedish	68	68	42	44	14	20	18	NA	NA
NK/T									
• IPTCL									
extranasal	35	44	26	57	17	9	6	17	20
nasal	92	52	51	47	2	42	29	57	0
• BCCA	17	47	47	24	29	24	15	38	20
• Swedish	33	62	33	63	4	21	14	NA	NA

◀ **Table 7.3 Characteristics and outcomes in common peripheral T-cell lymphoma subtypes (table overleaf).** [A]Data from International T-cell lymphoma project in which >85% patients received an anthracycline based regimen without upfront transplant. [B]BCCA ALCL reported as both ALK + and –. **Distribution of patients with the given IPI scores is based on the number of patients for whom the score could be completely calculated. AITL, angioimmunoblastic T-cell lymphoma; ALCL ALK–, anaplastic large cell lymphoma anaplastic lymphoma kinase negative (–); ALCL ALK+, anaplastic large cell lymphoma anaplastic lymphoma kinase positive (+); ATL, adult T-cell leukemia/lymphoma; BCCA, British Columbia Cancer Agency; COMPLETE, Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment; EATL, enteropathy-associated T-cell lymphoma; IPI, International prognostic index; IPTCL, International peripheral T-cell lymphoma project; N, number; NA, not available; NK/T, Natural killer cell/T-cell lymphoma; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma. Data from [2–4].

to those of age, race, and sex matched controls [7,8]. However, the more aggressive forms of CTCL, such as advanced stage MF (stage IIB–IVB) and Sezary Syndrome, are often treatment refractory and require aggressive management as 5-year survival is 20–50% [8].

Approach to treatment of systemic T-cell lymphomas

Given the rare nature of these disorders, there are no randomized controlled clinical trials to drive treatment decisions in PTCL. Our knowledge of the expected outcomes for patients with PTCL is largely based upon three large retrospective series: the International T-cell lymphoma

Histology	Frequency (%)	5-year survival
Mycosis fungoides	54	88
Sézary syndrome	3	25
Subcutaneous panniculitis-like T-cell lymphoma	1	82
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma*	<1	18
Primary cutaneous gamma-delta T-cell lymphoma	<1	NA
Primary cutaneous small/medium CD4+ T-cell lymphoma*	2	72
Primary cutaneous CD30+ T-cell lymphoproliferative disorder		
• Lymphomatoid papulosis	12	100
• Primary cutaneous anaplastic large-cell lymphoma	8	95

Table 7.4 Prevalence and survival of patients with cutaneous T-cell lymphomas. Data from [6].

project (ITLCP), the British Columbia Cancer Agency (BCCA) series and the Swedish series, which reported outcomes on 1314 cases, 199 cases, and 755 cases, respectively [2–4]. The Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE) is a registry of 253 patients from the US, which has also been reported [9]. Confirmation of the diagnosis is critical to management as T-cell lymphomas are often characterized by antigen aberrancy that may vary within a subtype or even over the course of disease [10,11]. In the ITCLP, a consensus diagnosis (three out of four expert pathologists arriving at the same diagnosis) was only reached between 74 and 81% of the time for ALK negative-ALCL, PTCL-NOS, and AITL. When clinical information was added 12% of diagnoses were then refined [2]. Additionally, reactive non-malignant conditions may mimic PTCL [12–14].

Approach to initial therapy in peripheral T-cell lymphomas

Extrapolated from our knowledge of B-cell lymphomas, CHOP has remained the backbone of upfront therapy in PTCL. In the ITCLP, more than 85% of patients received CHOP-based therapy, and in contrast to ALK-positive ALCL where the 5-year failure free survival (FFS) was 60%, the 5-year FFS rates for PTCL-NOS, AITL, and ALK-negative ALCL, were only 20%, 18%, and 36%, respectively (Table 7.3). Several prospective clinical trials in PTCL are available to inform us on the expected response rate to CHOP. In a Phase II study evaluating CHOP induction therapy followed by ASCT for untreated PTCL, the overall response rate (ORR) to CHOP was 79% with a complete response (CR) rate of 39% [15]. Similarly, studies of more aggressive regimens such as etoposide, ifosfamide, and cisplatin alternating with adriamycin, bleomycin, vinblastine, and dacarbazine (VIP-rABVD) showed no difference in outcome compared to CHOP [16].

While the majority of patients will receive CHOP, there is no currently agreed upon standard front-line treatment or approach for PTCL. In general, efforts to augment the efficacy of CHOP by adding agents to a CHOP backbone have not led to significant improvement in outcome or have led to significant toxicity. Several Phase II studies of the anti-CD52 antibody alemtuzumab to CHOP demonstrated impressive CR rates

of 65–71%. However, the addition of alemtuzumab carried significant toxicity including J-C virus encephalitis, invasive aspergillosis, pneumocystis carinii pneumonia, sepsis, Epstein Barr virus (EBV)-related lymphoma, and cytomegalovirus reactivation [17–19]. Similarly, in a Phase II study of denileukin diftitox plus CHOP, the ORR and CR rates were 65% and 55%, respectively; however three deaths occurred following one cycle of therapy and four other patients were taken off study due to toxicity [20].

There is evidence for the addition of etoposide to CHOP-based therapy in PTCL. The German high-grade non-Hodgkin lymphoma (NHL) study group (DSHNHL) analyzed a subset of patients with PTCL treated on seven different prospective Phase II or Phase III protocols [21]. The authors found that younger patients (<60 years old) with normal lactate dehydrogenase (LDH) had a significant improvement in outcome if they received CHOP plus etoposide (CHOEP) compared with CHOP alone, with 3-year event free survival (EFS) of 75.4% versus 51%, although no difference in OS was observed. The benefits were greatest in the more favorable ALK-positive ALCL subtype but there was a trend towards improved EFS in favor of CHOEP in the other subsets as well ($p=0.057$). However, the addition of etoposide in elderly patients led to significant toxicity. The Nordic group adopted CHOEP induction in a prospective study evaluating upfront stem cell transplantation for PTCL [22]. In this Phase II study, patients received bi-weekly CHOEP followed by ASCT for the responders. The ORR to CHOEP was 82% with a CR rate of 51%. While one must be cautious when comparing results from different study populations, Reimer et al published findings that showed that patients treated with CHOP followed by ASCT achieved CR in 39% of cases [15].

With regards to the role of ASCT in first remission, there are no randomized trials to support this treatment approach and it remains controversial. Nevertheless, several prospective studies suggest benefit from upfront ASCT. The aforementioned Nordic study enrolled 160 patients with PTCL, including 39% with PTCL-NOS, 19% with ALK-negative ALCL, and 19% with AITL, and excluded ALK-positive ALCL [22]. Patients were treated with CHOEP for six cycles and those in CR or with a partial response (PR) proceeded to high-dose therapy and

ASCT. By intent-to-treat analysis, 71% of patients underwent ASCT and the 5-year OS and progression-free survival (PFS) rates were 51% and 44%, respectively. Reimer et al conducted the second largest prospective study evaluating ASCT in first remission post-CHOP, which enrolled 83 patients [15]. By intent-to-treat analysis, 3-year OS rate was 48% and amongst the 66% of patients who were transplanted 30-year OS was 71% [15]. In a retrospective analysis performed at Memorial Sloan Kettering Cancer Center to evaluate patients who were treated with the intent-to-transplant in first remission, the most powerful predictor of outcome was interim positron emission tomography (PET) scanning. Of the 53% of patients who had a negative interim PET after four cycles, 59% were progression free at 5 years including 53% of those with IPI of ≥3 [23].

Approach to relapsed or refractory peripheral T-cell lymphomas

In the setting of relapsed or refractory disease, there is an absence of randomized data and no standard of care to guide treatment [24]. In the largest series of patients with PTLC treated from 1976 to 2010, patients with relapsed or refractory disease who did not proceed to hematopoietic stem-cell transplant demonstrated a median OS of 5.5 months [25]. However, recently a number of newer agents have been approved for relapsed and refractory PTCL. Those who are eligible for transplant and have a possible donor identified may consider salvage chemotherapy options such as ifosfamide, carboplatin, and etoposide (ICE) or dexamethasone, cytarabine, and cisplatinum (DHAP), which have a higher potential to induce remission [26]. However, these regimens are only tolerated for up to three to four cycles and should be followed by consolidation. For those who are not transplant-eligible, the goals of treatment are palliative and therapy should be geared towards maintaining quantity and quality of life. In addition to traditional chemotherapeutic options, newer agents have been approved for this patient population including romidepsin, belinostat, and pralatrexate [27–31]. Additionally, in CD30-positive T-cell lymphomas, brentuximab vedotin is National Comprehensive Cancer Network (NCCN) compendium-listed for relapsed or refractory disease [26,32–34]. Brentuximab vedotin should be the first

choice for relapsed ALCL for patients who have not previously received it given the high response rates (Table 7.5) [32–34]. Other options for treatment include, but are not limited to, gemcitabine, bendamustine, and alemtuzumab [26,35–37].

For patients who are transplant-eligible, allogeneic transplant should be considered in the relapsed/refractory setting. Many have shown that the use of ASCT for relapsed PTCL rarely results in long-term disease control with the exception of those with ALCL [38,39]. While the Center for International Blood and Marrow Transplant Research registry data points to better results with ASCT at relapse, this series may be skewed due to a high proportion of patients with ALCL [40]. With regards to allogenic transplant, both myeloablative and reduced intensity ASCT have demonstrated up to a 60% 3-year PFS [41–43]. While ASCT may be appropriate for some patients with relapsed ALCL who did not receive ASCT in the front-line setting, allogeneic transplant is more likely to be curative [43].

Given the heterogeneity of PTCL, there is an increasing interest in individualizing therapy based on histology and other factors. Key examples of this strategy include brentuximab vedotin. Similarly, crizotinib, an ALK inhibitor, demonstrated significant activity in a small number of patients with relapsed ALK-positive ALCL and is being further investigated [44–46]. The histone deacetylase (HDAC) inhibitors, such as belinostat and romidepsin, appear to have preferential activity and duration of response in patients with AITL (Table 7.5) [28,30,31].

Histologic Subtype	**Agents approved for relapsed/refractory peripheral T-cell lymphoma**			
	Pralatrexate[A]	Romidepsin[B]	Belinostat[C]	Brentuximab vedotin[D*]
PTCL-NOS	31%	29%	23%	33%
AITL	8%	30%	46%	50%
ALCL	29%	24%	15%	86%

Table 7.5 Overall response rate to agents approved for relapsed/refractory peripheral T-cell lymphoma. *Brentuximab vedotin is NCCN Compendium listed for relapsed/refractory CD30+ PTCL. AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified. [A]Data from [27]; [B]data from [28]; [C]data from [29,30]; and [D]data from [32,33].

Special considerations in the treatment of peripheral T-cell lymphomas: anaplastic lymphoma kinase-positive anaplastic large cell lymphoma

ALK-positive ALCL is the most chemosensitive of the T-cell lymphomas with rates of survival and response similar to diffuse-large B-cell lymphomas (Figure 7.1). Given the high incidence of ALCL in the pediatric population, intensive anthracycline-based chemotherapy regimens have been studied in children [47,48]. Approximately 90% of patients with ALK-positive ALCL treated with anthracycline-based chemotherapy achieve a tumor response, with 65–75% of pediatric patients remaining relapse free at 5 years [49,50]. Amongst adults, treatment with CHOP-based therapy has remained the most commonly used therapy as more intensive regimens have not shown superiority to CHOP-based therapy [51,52]. The IPTCL reported that the prognosis for patients with ALK-positive ALCL is superior to that with ALK-negative ALCL: 5-year FFS and OS were 60% and 70%, respectively [2]. IPI appears to be particularly helpful to risk stratify those with ALK-positive ALCL and some suggest that those with

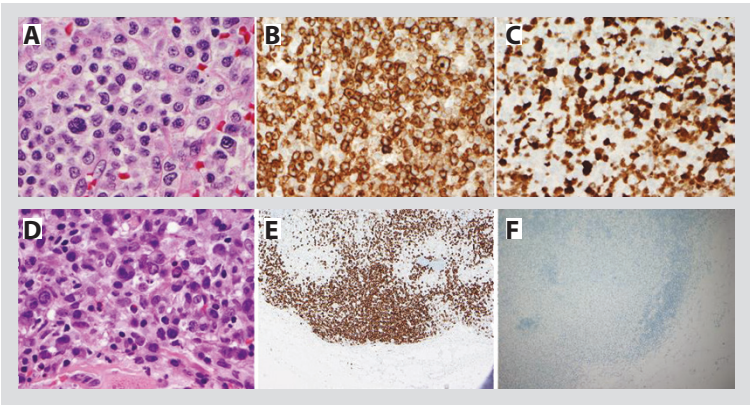

Figure 7.1 High power view of anaplastic lymphoma kinase-positive and -negative anaplastic large cell lymphoma (ALCL-ALK+/–). Top: ALCL-ALK-positive lymphoma; lymph node showing involvement by a systemic anaplastic large cell lymphoma, ALK-positive. On high power view, the cells have large bean-shaped nuclei and abundant pink cytoplasm, so-called hallmark cells (A). The neoplastic cells are strongly positive for CD30 (B) and for ALK (C). Bottom: ALCL-ALK-negative lymphoma; lymph node showing involvement by a systemic anaplastic large cell lymphoma, ALK-negative. On high power view, the cells have large bean-shaped nuclei and abundant pink cytoplasm, so-called hallmark cells (D). The neoplastic cells are strongly positive for CD30 (E) but negative for ALK (F).

high risk ALK-positive ALCL should be treated more similarly to those with other forms of PTCL (Table 7.3) [2,3,53]. The DSGNHL retrospectively assessed that in patients with ALK-positive ALCL who were ≤60 years and had a normal LDH, the addition of etoposide led to improved EFS but not OS [21]. The Groupe d'Etude des Lymphomes de l'Adulte (GELA) group has suggested that the prognostic significance of ALK expression is limited to those over age 40 [52]. After relapse, it appears that patients can be cured with intensive salvage therapy, which includes ASCT at a higher rate than with other T-cell lymphomas.

Brentuximab vedotin, which combines an anti-CD30 antibody with monomethylauristatin E (MMAE) has demonstrated responses greater than 80% in patients with relapsed/refractory ALK-positive and ALK-negative ALCL as a single agent in a Phase II trial [33]. The US Food and Drug Administration (FDA) approved brentuximab vedotin for the treatment of relapsed ALCL in 2011 [54]. Brentuximab vedotin in combination with chemotherapy is being explored as a first-line therapy in ALCL. Additionally, crizotinib is an inhibitor of ALK tyrosine kinase and is FDA-approved for the treatment of ALK-positive non-small cell lung cancer (NSCLC). Responses of ALK-positive ALCL with crizotinib have been reported in small case series, leading to ongoing trials in relapsed/refractory ALCL [45,46,55].

In comparison, ALK-negative ALCL tends to be less responsive to chemotherapy and treatment strategies are controversial. It has been common practice to treat patients with CHOP-like therapy as with other forms of PTCL as discussed in the previous overview section. However, there is evidence that expression of CD56 and DUSP22 may carry a similar prognosis to those with ALK-positive ALCL [56,57]. DUSP22 gene likely functions as a tumor suppressor and potentially identifies a unique entity within ALK-negative ALCL, which carries a better prognosis [56].

Special considerations in treatment of peripheral T-cell lymphomas: extranodal natural killer/T-cell lymphoma

Extranodal NK/T-cell lymphomas make up 7–9% of PTCL and typically present with a clinically apparent or radiographically apparent nasopharyngeal mass [2–4,58]. Outcomes of localized NK/T-cell lymphoma

are best with combined chemotherapy and radiation therapy. In studies of radiation therapy alone, responses are 75–100%, however systemic relapse rates are as high as 25–40% [59,60]. Previously, patients were treated with CHOP-based therapy in combination with radiation with a complete response rate of 59% and 3-year disease free survival of 25% [61–63]. However, as L-asparaginase was found to have significant single agent activity in NK/T-cell lymphomas, it has been incorporated into multiple other regimens with durable responses [64]. L-asparaginase has been combined with gemcitabine and oxaliplatin combined with radiation therapy, with an overall response rate of 96% and a local and systemic relapse rate of 10–15% in a Phase I study [65]. Similarly, studies of vincristine, prednisolone in combination with L-asparaginase carry an overall response rate of 89% when combined with radiation therapy. SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) in combination with radiation therapy has demonstrated an 82% response rate with a complete response rate of 78% [66]. In patients with localized ENKTL, it is reasonable to consolidate asparaginase-based chemotherapy with radiation therapy. In the setting of patients with advanced stage or relapsed/refractory disease, combination chemotherapy remains the standard treatment [68]. Studies of SMILE demonstrate an overall response rate of 25–80% [66,68]. L-asparaginase has also been studied in combination with methotrexate and dexamethasone with an overall response rate of 78% [69]. NK-cell leukemia which is characterized by widespread systemic dissemination and involvement of the marrow and peripheral blood carries an extremely poor survival measured only in weeks.

EBV DNA PCR measured in plasma has been found to correlate with tumor burden and serial EBV PCR monitoring is useful for assessing responses and disease recurrence [70,71]. Given the improved efficacy of L-asparaginase based regimens, the role of ASCT remains unclear.

Special considerations in the treatment of peripheral T-cell lymphoma: adult T-cell leukemia/lymphoma

In the US, the incidence of ATL is approximately 0.05 cases per 100,000 people but there is significant geographic variation in disease incidence

worldwide (Table 7.2) [72]. The acute or lymphoma variants of this disorder carry particularly poor prognosis with median survival being less than 1 year, for those with the aggressive subtypes.

Despite its limited efficacy, cytotoxic chemotherapy remains the mainstay of therapy for this disease. The Japanese group developed a multi-drug regimen called LSG15, which consists of seven cycles of vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP). LSG15 was compared with CHOP in a randomized Phase III and demonstrated superior CR rate (40 versus 25%) and 3-year OS (24 versus 13%). However, the median survival was only 13 months in the LSG15 arm [73].

The role of antiviral therapy remains controversial. In a retrospective analysis of patients with leukemic ATL, those treated with or without antiviral therapy during their first line therapy had a 5-year OS of 28% compared with 10%, respectively. Additionally, maintenance antiviral therapy in patients treated with first-line chemotherapy also conferred an improved OS. This has not yet been prospectively validated [74].

Additionally, mogamulizumab (an anti-CCR4 monoclonal antibody) has been approved in Japan for the treatment of relapsed or refractory ATL. In a multi-center Phase II study of 28 patients with relapsed/refractory ATL, the ORR with mogamulizumab resulted in a 50% response rate and median OS of 13.7 months [75]. A randomized Phase II study of modified LSG15 with or without mogmulizumab showed that the combination was well tolerated and demonstrated a CR rate of 52% compared with 33% with LGS15 alone [76].

With regards to the role of stem cell transplantation (SCT), a large nationwide Japanese retrospective report of 386 patients with ATL who underwent allogeneic hematopoietic SCT (HSCT) showed that the 3-year OS for the entire cohort was 33%. Among patients who underwent related transplantations, donor human T-cell leukemia/lymphoma virus type 1 (HTLV-1) seropositivity adversely affected disease-associated mortality [77]. In patients who are transplant-eligible, this is a reasonable strategy. ASCTs have been found to be ineffective in managing ATL [78,79].

Approach to treatment of cutaneous T-cell lymphomas

The approach to treatment of patients with CTCL is directed by the stage of the disease, impact of the disease on a patient's quality of life, and extent of the disease. MF serves as a model for how to approach patients with CTCL. However, disease-specific considerations must be taken into account, particularly for those diseases with a more aggressive course.

For early stage disease (stage IA-IIB), skin-directed therapy or expectant management are the most common courses. In some patients, lesions may not have an impact on quality of life and may relapse and remit particularly with seasonal variation. In these patients expectant management is appropriate [5]. Early aggressive therapy for initial treatment of MF with combination electron beam therapy and chemotherapy has not been shown to be superior to topical therapy for early stage disease [80]. For advanced stage disease, systemic therapy may be necessary. The only potential curative treatment option remains ASCT with a 54% 3-year OS but with a 20–30% rate of non-relapse mortality (Table 7.6) [81,82].

Skin-directed therapy in cutaneous T-cell lymphoma

Topical steroids are commonly used in early MF and have been associated with induction of apoptosis, downregulation of key transcription factors and cytokines, and growth factor production [83,84]. A large prospective study of patients with patch stage disease found that 63% and 25% of patients with T1 and T2 disease, respectively showed a complete response. Responses are only maintained if steroids are not discontinued [85]. Steroids are also effective in reducing pruritus, which is a frequent manifestation of disease.

Topical nitrogen mustard, which is an alkylating agent, has been shown to demonstrate a CR in up to 72% of cases at concentrations of 0.01–0.02% and is approved in a gel formulation for patients with stage IA/IB MF who have failed previous skin directed therapy [86]. Up to 11% of patients maintain a remission at 10 years [87].

Topical retinoids, such as bexarotene and tazarotene, are also effective in the treatment of early stage MF. Topical bexarotene is approved for the treatment of early stage MF and in clinical trials has shown an

ORR of 63% at a median of 20 weeks [88]. Topical tazarotene has demonstrated a 58% ORR in MF in a pilot study [90]. Both agents are known to cause skin irritation.

Another frequently used modality for treatment of MF, particularly in patients with patch disease with greater than 20% total body surface area involvement, is phototherapy. Phototherapy can be given as ultraviolet (UV)-A in combination with a photosensitizing agent, such as psorlen, or as narrow band UV-B. UV-A in combination with psorolen can lead to CR in up to 71% and ORR in up to 95% of patients with some responses lasting over 10 years [90–92]. UV-A has been combined with treatment with interferon for increased efficacy [93]. Given the increased risk of skin cancer with UV-A treatment, narrowband UV-B

Early stage mycosis fungoides (stage IA–IIA)	
Topical/skin-directed therapy	Steroids
	Phototherapy
	Nitrogen mustard
	Topical bexarotene
	Local radiation
	Total skin electron beam treatment
Refractory early stage MF (stage IA-IIA)	Phototherapy with interferon
	Phototherapy with low dose oral bexarotene
Advanced stage mycosis fungoides/Sezary syndrome (IIB–IVB)	
Topical/skin-directed therapy	Total skin electron beam therapy
Immunomodulatory therapy	Interferons
	Oral retinoids
	Extracorporeal photopheresis
Combined modality therapy	Phototherapy with interferon
	Phototherapy with oral retinoids
Biologic therapies	Alemtuzumab
	Histone deacetylase inhibitors (romidepsin, belinostat, and vorinostat)
Chemotherapies	Liposomal doxorubicin
	Gemcitabine
	Pralatrexate
	Antifolates (methotrexate or pralatrexate)
	Multiagent chemotherapy regimens
Stem cell transplantation	Allogeneic

Table 7.6 Treatment options in cutaneous T-cell lymphomas.

is frequently used for treatment of patch stage disease and carries similar efficacy to UV-A [94,95]. Narrowband UV-B has been safely and effectively combined with low dose oral bexarotene as well [96]. Both UV-A and UV-B treatment are less effective for tumor stage (T3) or plaque (T2) stage disease.

Total skin electron beam therapy (TSEBT) involves administration of ionizing radiation to the entire surface area of the skin and can penetrate deeper than nitrogen mustard or phototherapy. Therefore, this remains a useful option for patients who have rapidly progressing disease, extensive plaque disease, or tumor disease [97,98].

Systemic therapy in cutaneous T-cell lymphoma

Systemic therapy should be considered in patients with a high burden of disease or higher stage of disease, including those with tumor stage disease. Additionally for those who have more aggressive forms of CTCL such as Sezary syndrome, systemic therapies are a first line option.

For patients with advanced stage MF, oral retinoids such as bexarotene are a well-tolerated option; bexarotene is approved for CTCL of all stages. The ORR for bexarotene ranges from 40 to 60% with variable durations of response [99,100]. Addition of interferon, UV therapy, extracorporeal photopheresis, and radiation to bexarotene have all been shown to be safe but not more effective than bexarotene monotherapy [101–104]. Bexarotene has also been shown to be effective with durable responses in subcutaneous panniculilitis-like T-cell lymphoma [105].

For patients with advanced stage disease, low dose oral methotrexate is also a commonly used regimen that is generally well tolerated by patients. Low dose oral methotrexate (approximately 25 mg weekly) has been associated with an ORR of 33% in plaque disease and 58% in erythrodermic disease [106,107].

Prior to the advent of more recent therapies for advanced CTCL, interferon-α (IFNα) and extracorporal photopheresis (ECP) have been used. IFNα has shown efficacy in all stages of MF and in Sezary syndrome with single agent ORR ranging from 29 to 80% [108,109]. IFNα has been safely combined with UV-A therapy [94]. However, the systemic side effects of IFNα including fatigue and depression make this

therapy difficult to tolerate for extended periods of time. ECP, which involves leukapheresis and exposure of mononuclear cells to UV-A, was approved for the palliative treatment of CTCL in 1988, and is most effective for patients with erythrodermic CTCL with an ORR up to 73% in that population [110].

More recently, for patients who are refractory to skin-targeted therapy or have advanced stage disease refractory to retinoids, histone deacetylase inhibitors (HDACi) are considered. Vorinostat, an HDACi, was approved for CTCL that has progressed after two systemic therapies and showed an ORR of 25 to 30% in its registration trials [111,112]. Similarly, romidepsin, another HDACi, is approved for refractory CTCL with Phase II studies demonstrating a 36% ORR [113,114]. These therapies are generally well tolerated with major side effects being gastrointestinal upset and cytopenias, and therefore, can be used until intolerance or disease progression.

Additional agents that can be considered for treatment of advanced CTCL include denileukin difitox, which is a fusion of interleukin (IL)-2-diphteria toxin and alemtuzumab, a CD52 antibody. These agents have response rates of up to 50% and 84%, respectively but also have significant toxicities. Therefore, these are considered if patients have been refractory to other better tolerated treatments such as HDACi [115–117].

For those who have been refractory to retinoids, oral methotrexate, and HDACi, one may also consider sequential single-agent chemotherapeutic agents to maintain disease control and balance quality of life. Agents that have been found to be effective in CTCL include pralatrexate, gemcitabine, and liposomal doxorubicin [97]. Multi-agent chemotherapy regimens may also be considered [20,118,119]

As discussed previously, the only curative treatment for CTCL is consolidation with ASCT. ASCT is associated with a 54% 3-year OS but with a 20–30% rate of non-relapse mortality [81,82], therefore, this is a reasonable strategy in selected patients. There are no large series in ASCTs and relapses are commonly seen within 6 months of completion of the transplant [120,121]. However, there are some reports of durable remissions with this approach [122].

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Chapter 8

Treatment of Hodgkin lymphoma

Anas Younes

Introduction

Hodgkin lymphoma (HL) is a relatively rare cancer, with an estimated 8000 new cases per year in the United States. In the Western world, approximately 95% of patients with HL have a classical HL histology, whereas only 5% have the nodular lymphocyte-predominant HL (NLPHL) histologic subtype. The majority of patients are diagnosed in their late 20s to early 30s, with a fewer patients being diagnosed at a later age. HL is a B-cell lymphoid malignancy, originating from germinal center B lymphocytes. Although the malignant Hodgkin and Reed-Sternberg (HRS) cells of HL are of B-cell origin, they typically do not express most B-cell-typical genes. From a diagnostic point of view, lymphocyte-predominant (LP) cells of NLPHL, and HRS cells of classical HL have a different morphology, different phenotype, and different infection pattern with the Epstein-Barr virus (EBV) [1]. LP cells express typical B-cell antigens, including CD20, whereas HRS cells display CD15 positive, CD30 positive, and rarely express CD20. Furthermore, EBV infection which is frequently observed in the HRS cells of classical HL, is almost never seen in LP cells [1,2].

Early stage Hodgkin lymphoma

The management of early stage HL evolved over the years to become one of the most successful stories of modern oncology. Decades ago, the

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primary treatment was radiation therapy. Today, combined chemotherapy and radiation therapy is considered the standard of care. More recently, radiation therapy-free chemotherapy programs are being investigated, with promising results. Using modern treatment approaches, over 90% of patients with early stage HL are expected to be cured.

The treatment of early stage HL is based on risk classification. The most widely used prognostic factors model is based on the German Hodgkin Lymphoma Study Group (GHSG) and the European Organisation for Research and Treatment of Cancer (EORTC) as shown in Table 8.1. Patients with early stage HL are classified as 'favorable' if they did not have any of these risk factors. In contrast, the presence of at least one risk factors results in 'unfavorable' designation.

In general, doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy remains the most widely used chemotherapy regimen for newly diagnosed patients with HL in the US. A different number of chemotherapy cycles are used depending on the disease stage, prognostic factors, and the combined use with radiation therapy. Dose intense regimens such as escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) are more commonly used in Europe.

Based on the GHSG HD10 study in favorable early stage HL, the current standard of care treatment is two cycles of ABVD followed by 20Gy of involved field radiation therapy (IFRT). This regimen results in progression-free survival (PFS) of 92% and overall survival (OS) of 97% at 5 years [3]. Patients with unfavorable early stage HL are treated with four cycles of ABVD followed by 30Gy of IFRT, resulting in 5-year PFS of 87%, and an OS of 94.5% [4].

EORTC	GHSG
1. Bulky mediastinal mass	1. Bulky mediastinal mass
2. Elevated ESR	2. Elevated ESR
3. Nodal regions ≥4	3. Nodal regions ≥3
4. Age ≥50 years	4. Extra-nodal disease

Table 8.1 Prognostic factors in early stage Hodgkin lymphoma. EORTC, European Organisation for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Lymphoma Study Group. Data from [5].

Concerns about long-term toxicity of radiation therapy generated interests in the development of equally effective, and potentially less toxic, radiation therapy-free regimens for the treatment of early HL [6,7]. Although these studies will require long-term follow-up to determine the safety of this approach, early results from randomized trials suggested that the omission of radiotherapy may be associated with a slightly lower PFS, but had no impact on OS. More recently, functional imaging using 2-(18F) fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) was used to select patients with early stage HL for therapy with chemotherapy alone. Using this response-adapted approach, two clinical studies reported early promising, and practically similar results. The United Kingdom National Cancer Research Institute RAPID study randomized patients with non-bulky early stage disease who had a negative interim PET after three cycles of ABVD to either 30Gy IFRT or no further therapy, and found that the 3-year PFS and OS were not significantly different [8]. Similarly, the EORTC H10 study compared two strategies of therapy: standard treatment with ABVD and IFRT, stratified according to baseline prognostic factors, versus a non-radiotherapy approach but using further chemotherapy for those with negative FDG-PET scans after two cycles of ABVD [9]. The results with short follow-up suggested inferior disease control in the experimental PET-directed arms, although the number of progressions was small and much longer follow-up will be required to determine whether there is any detrimental effect on survival.

Advanced stage Hodgkin lymphoma

Patients with advanced stage HL are typically treated with combination chemotherapy regimens (Table 8.2). The most widely used regimen is ABVD. Typically, patients with advanced stage HL are treated with six to eight cycles of ABVD, resulting in an approximately 70% cure rate. As an alternative to ABVD, the Stanford V regimen was developed as a short duration regimen combined with radiation therapy [10]. However, recent randomized trials comparing ABVD to Stanford V found no difference in response rate, failure-free survival (FFS), or OS between the regimens [11,12].

The escalated BEACOPP regimen is more frequently used in Europe (Table 8.2) [13]. Six cycles of escalated BEACOPP is considered the standard for advanced HL, as eight cycles resulted in more toxicity without any additional benefit. A recent randomized trial compared treatment outcome of ABVD versus escalated BEACOPP in patients with advanced stage HL [14]. Patients with residual or progressive disease after initial ABVD or escalated BEACOPP were treated with salvage therapy including stem cell transplantation. The freedom from first progression significantly favored patients receiving escalated BEACOPP when compared with patients treated with ABVD (85% compared with 73%, $p=0.004$). However, after completion of all planned therapy including salvage

Regimen/drug	Dose	Route	Schedule (day)	Cycle length (days)
ABVD				
Doxorubicin (adriamycin)	25 mg/m^2	IV	1, 15	28
Bleomycin	10 units/m^2	IV	1, 15	
Vinblastine	6 mg/m^2	IV	1, 15	
Dacarbazine	375 mg/m^2	IV	1, 15	
BEACOPP (baseline)				
Etoposide	100 mg/ m^2, 200 mg/m^2 if PO	IV	1–3, or PO days 2–3	21
Doxorubicin	25 mg/m^2	IV	1	
Cyclophosphamide	650 mg/m^2	IV	1	
Vincristine	1.4 mg/m^2 (cap at 2 mg/m^2)	IV	8	
Bleomycin	10 units/m^2	IV	8	
Procarbazine	100 mg/m^2	PO	1–7	
Prednisone	40 mg/m^2	PO	1–14	
Escalated BEACOPP				
Etoposide	200 mg/m^2	IV	1–3	21
Doxorubicin	35 mg/m^2	IV	1	
Cyclophosphamide	1250 mg/m^2	IV	1	
Vincristine	1.4 mg/m^2 (cap at 2 mg/m^2)	IV	8	
Bleomycin	10 units/m^2	IV	8	
Procarbazine	100 mg/m^2	PO	1–7	
Prednisone	40 mg/m^2	PO	1–14	

Table 8.2 Common front-line regimens for the treatment of patients with Hodgkin lymphoma. IV, intravenous; PO, oral.

therapy for those with residual or progressive disease, the 7-year rate of freedom from second progression was not significantly different (88% in the escalated BEACOPP group and 82% in the ABVD group, $p=0.12$) and the 7-year OS rate was 89% and 84%, respectively ($p=0.39$). Because severe adverse events were more commonly observed in patients treated with escalated BEACOPP, many oncologists continue to favor the use of the less toxic ABVD regimen as the initial therapy, as relapsing patients may be salvaged with subsequent intensive therapy [15]. In a subsequent study, the EORTC randomized patients with advanced stage HL with poor risk features to either ABVD or BEACOPP. The study showed no difference in event-free survival (EFS) [16].

Management of patients with relapsed and refractory Hodgkin lymphoma

Patients with relapsed or treatment refractory HL are typically treated with a second-line chemotherapy followed by autologous stem cell transplantation (ASCT) [17,18]. This approach is based on two randomized Phase III studies demonstrating improved PFS in patients receiving high-dose chemotherapy and ASCT compared with those treated with standard-dose salvage chemotherapy [19,20]. Several second-line regimens are used to induce a remission prior to ASCT, including platinum-based and gemcitabine-based combination regimens, but there are no randomized studies comparing the efficacy of these salvage regimens [21–31]. The overall approach for the treatment of patients with relapsed and refractory HL is shown in Figure 8.1.

The goal of salvage chemotherapy is to reduce the tumor burden and establish chemo sensitivity, to enable patients to proceed to ASCT. The optimal number of cycles of salvage chemotherapy is poorly defined. However, it is widely acceptable that two to three cycles of treatment are usually given to establish a response and to reduce the risk of further toxicity. Most second-line regimens produce an average overall response rate of 60–70%. Patients who do not achieve a response to salvage chemotherapy usually do not have a significant benefit from ASCT, and are typically offered a third-line chemotherapy regimen (Figure 8.1). At best, responding patients who receive consolidation with ASCT have an average EFS of 60% (Table 8.3).

Management of patients with relapsed Hodgkin lymphoma after stem cell transplant

Approximately 30% of patients with HL will not be cured with currently available therapy, including ASCT, and will require additional therapy. The median survival of HL patients following relapse from ASCT is estimated to be less than 3 years [32]. Because of the poor prognosis, several novel agents are being evaluated for this patient population. To date, brentuximab vedotin remains the only drug approved by the US Food

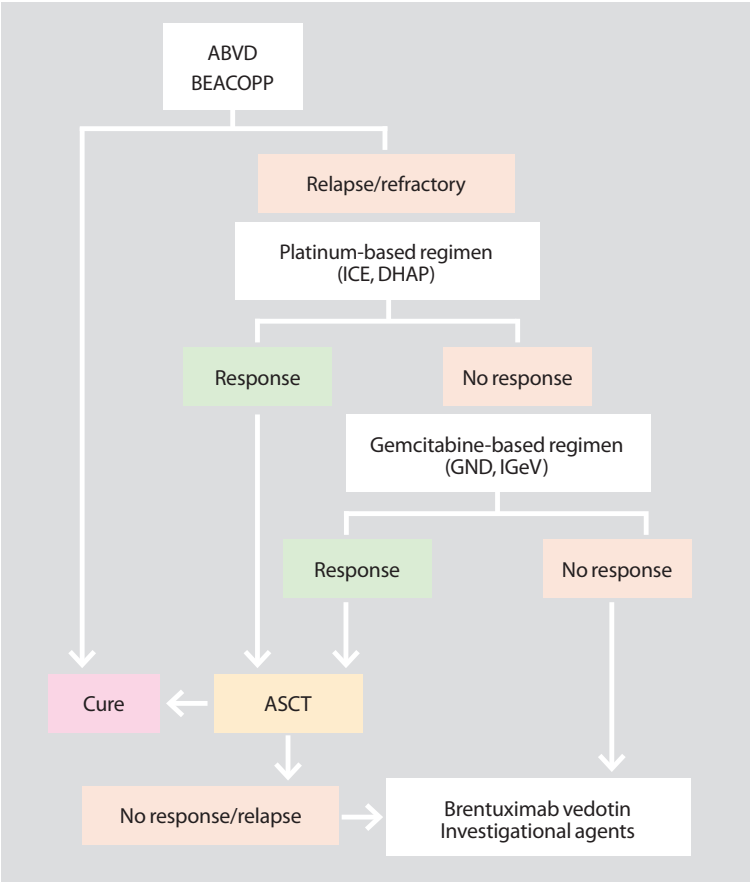

Figure 8.1 Algorithm for the management of patients with advanced stage and relapsed Hodgkin lymphoma. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT, autologous stem cell transplantation.

and Drug Administration (FDA) and the European Medicines Agency (EMA) for this indication.

Brentuximab vedotin

CD30 is an attractive target for monoclonal antibody therapy in patients with HL, as its expression is highly restricted to the malignant HRS cells. Initial attempts to develop naked anti-CD30 antibody therapy failed to produce meaningful clinical responses. In contrast, major clinical responses were achieved by conjugating the naked anti CD30 antibody SGN30 to anti-tubulin monomethyl auristatin E (MMAE), to generate the antibody drug-conjugate (ADC) brentuximab vedotin [33,34].

Brentuximab vedotin was approved by the FDA for the treatment of patients with relapsed and refractory HL based on a pivotal large Phase II study in 102 patients after receiving ASCT. Patients were treated with

Regimen/drug	Dose	Route	Schedule (day)	Cycle length (days)
DHAP				
Cisplatin	100 mg/m^2	IV	1	14–21
Cytarabine	2000 mg/m^2	IV	Day 2, Q12 h × 2 doses	
Prednisone	40 mg	IV	1–4	
ICE				
Ifosfamide	5000 mg/m^2	IV	2	14
Carboplatin	AUC-5	IV	2	
Etoposide	100 mg/m^2	IV	1–3	
MESNA	5000 mg/m^2	IV	2	
GVD				
Gemcitabine	1000 mg/m^2	IV	1, 8	21
Vinorelbine	20 mg/m^2	IV	1, 8	
Liposomal doxorubicin	15 mg/m^2	IV	1, 8	
IGEV				
Vinorelbine	20 mg/m^2	IV	1	21
Gemcitabine	800 mg/m^2	IV	1, 4	
Ifosfamide	2000 mg/m^2	IV	1–4	
Prednisone	100 mg	PO	1–4	
MESNA	1200 mg/m^2	IV	1–4, 30 min prior then at 4 and 8 h	

Table 8.3 Common front-line regimens for the treatment of patients with Hodgkin lymphoma. IV, intravenous; PO, oral.

1.8 mg/kg brentuximab vedotin given by intravenous infusions every 3 weeks. The overall response rate was 75%, and the complete remissions (CRs) rate was 34% [35]. The most common treatment-related side effects were peripheral neuropathy (42%), nausea (35%), and fatigue (34%). Current strategies are aiming at incorporating brentuximab vedotin in front-line regimens, and in pre-transplant salvage regimens, but this approach remains investigational [36–38].

Immune checkpoint inhibitors

Programmed death 1 (PD-1) pathway serves as a checkpoint to limit T-cell-mediated immune responses and to prevent autoimmunity. PD-1 is predominantly expressed by T cells. The ligands for PD-1, PD-L1, and PDL2 are expressed by antigen-presenting cells but are also frequently expressed by a variety of cancer cells, including HRS cells [39,40]. Recent clinical data from patients with solid tumors indicated that activation of autologous T cells by blocking PD-1, PD-L1, and PD-L2 interaction can induce clinical responses. In Hodgkin lymphoma (HL), two anti-PD1 antibodies (nivolumab and pembrolizumab) have recently demonstrated an impressive single agent activity in multiply pre-treated patients, including those who were previously treated with brentuximab vedotin [41,42].

Nivolumab, a fully human monoclonal IgG4 antibody directed against PD-1, was tested in 26 heavily pre-treated patients with HL. The overall response rate was 87% (17% CRs). Drug-related adverse events were reported in 78%, with the most common being rash (22%) and thrombocytopenia (17%). Drug-related grade 3 adverse events were observed in 22%. There were no drug-related grade 4 or 5 adverse events [41].

Pembrolizumab is a humanized IgG4 antibody targeting PD-1. It produced an overall response rate of 66% (21% CR) in 29 heavily pretreated patients with relapsed HL [42]. The toxicity profile is somewhat similar to nivolumab. Ongoing pivotal trials are being carried out with the intention that approval will be sought for both agents from the US FDA.

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Chapter 9

Management of human immunodeficiency virus-associated lymphomas

Connie Batlevi

Introduction

Human immunodeficiency virus (HIV) infection is associated with a variety of malignancies including acquired immune deficiency syndrome (AIDS)-defining and non-AIDS-defining lymphomas. Collectively, they may be referred to as HIV-associated lymphomas. AIDS-defining non-Hodgkin lymphomas (NHL) include diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma, primary central nervous system (CNS) lymphoma, and less commonly primary effusion lymphoma and plasmablastic lymphoma. Approximately 10% of HIV patients will develop a NHL. Non-AIDS-defining lymphomas, which have an increased prevalence in HIV-infected individuals, include Hodgkin lymphoma (HL). The risk of developing a HIV-associated lymphoma correlates directly with the degree of immune dysfunction.

Management of HIV-associated lymphomas has evolved over the years. Widespread use of antiretroviral therapy has reduced the incidence of HIV-associated lymphomas and improved the outcome of these patients. Often, HIV lymphomas have an aggressive presentation. Treatment balances the goal of achieving a complete response (CR) while managing the risk of opportunistic infections.

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Antiretroviral and supportive therapy

Concurrent use of antiretroviral therapy is associated with improved CR rates [1]. Large studies of antiretroviral therapy in patients without lymphoma show that continuous antiretroviral therapy is superior to episodic antiretroviral therapy based on reduced risk of opportunistic infection [2]. Therefore, antiretrovial therapy should be initiated or continued during chemotherapy. Drug interactions may arise from the potential of highly active antiretroviral therapies (HAART) to either inhibit or induce the cytochrome p450 system. While interactions between antiretroviral agents and chemotherapy may occur, the added benefit of an improved immune system and reduced risk of infection warrants the addition of antiretroviral therapy.

Opportunistic infection prophylaxis and use of granulocyte-colony stimulating factor (G-CSF) support for febrile neutropenia are mandatory with all rituximab-based chemotherapy regimens in HIV-associated DLBCL. Patients should be screened for hepatitis B infection and antiviral prophylaxis initiated as appropriate.

Systemic human immunodeficiency virus-associated non-Hodgkin lymphoma

In the past, HIV associated with NHL generally had a poorer prognosis. However, with the development of antiretroviral therapy, treatment outcomes and prognosis have improved significantly to be more in line with non-HIV-associated NHL. Factors that are associated with poor prognosis in patients with HIV-associated NHL include the lack of achievement of a complete remission, the presence of a high International Prognostic Index (IPI) score, and Burkitt subtype [3].

Indolent HIV-associated NHL is relatively less common. This entity can sometimes be managed by initiating antiretroviral therapy. The majority of HIV-associated NHLs are aggressive and treated depending on the histological subtype. Prior to the development of antiretroviral therapy, low-dose chemotherapy was believed to be superior to standard-dose chemotherapy because of increased toxicity with the standard dose therapy. In a large randomized trial, 198 patients with HIV-associated NHL were randomized to receive standard dose methotrexate, bleomycin,

doxorubicin, cyclophosphamide, vincristine, and dexamethasone, with folinic acid and GM-CSF to stimulate white cell production (mBACOD), compared with low-dose mBACOD. Standard-dose mBACOD was found to be as efficacious as low-dose mBACOD, with slightly higher hematologic toxicity in patients undergoing standard-dose mBACOD. These patients had a median CD4 count of 100 cells/ul with 75–80% having CD4 count less than 200 [4]. The tolerance of chemotherapy may have improved with effective antiretroviral therapy. We will comment on the management of DLBCL, Burkitt's lymphoma, and primary effusion lymphoma.

Diffuse large B-cell lymphoma

Prior to antiretroviral therapy, DLBCL was the most common subtype of HIV-associated lymphoma. In the post-HAART era, DLBCL accounts for 25–30% of HIV-associated lymphomas. These lymphomas tend to be aggressive in presentation with involvement of extranodal sites. Often they are of germinal center B-cell biology expressing CD10 and Bcl 6, which are markers of germinal center differentiation. The activated B-cell subtype of DLBCL expresses Bcl2 and MUM1. Cellular immunity may be associated with different DLBCL subtypes. The germinal center subtype of DLBCL is typically encountered in HIV patients with preserved CD4 counts while the ABC subtype is associated with CD4 counts <100/ul. Myc gene overexpression is seen in ~20% of HIV-associated DLBCL.

While there is no standard of care for HIV-associated DLBCL, the literature has supported the use of combined modality chemoimmunotherapy while balancing toxicities from immune suppression (Table 9.1). Rituximab was first thought to be contraindicated in patients with HIV-associated NHL based on a randomized study comparing rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (RCHOP) with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) alone. In the rituximab arm, treatment-related infection occurred in 13 of 99 patients (14%) compared with 2 out of 51 (2%) patients treated with CHOP alone [5]. Most deaths resulted from bacterial infections and occurred early during treatment, after the first or second cycle of chemotherapy, and were higher in patients with CD4 counts <50 [5].

Chemotherapy	Phase	Sample size	ORR	CR	OS	Infection rate	HAART
DR-COP	II	40: DLBCL N=39 Other N=1	67.5%	47.5%	67.5% 47.5%	40%	Yes
DA-R-EPOCH	II	48: DLBCL N=35 BL N=16	88%	73%	70% at 2 yr	27%	PRN
SC-EPOCH-RR	II	33: DLBCL N=33	94%	91%	68% at 5 yr		
R-CHOP	II	52: DLBCL N=36 BL N=9 Other=7	89%	77%	75% at 2 yr	Na	Yes
R-CDE	II	74: DLBCL N=52 BL N=21	75%	70%	64% at 2 yr	37%	Yes

Table 9.1 Common chemotherapy for human immunodeficiency virus-associated diffuse large B-cell lymphoma. BL, Burkitt's lymphoma; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; HAART, highly active antiretroviral therapy; IV, intravenous; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PO, oral; PRN, as needed. Data from [6–10].

Chemotherapy regimen	Ref
Rituximab 375 mg/m^2, IV, day 1	[9]
Pegylated liposomal doxorubicin 40 mg/m^2, IV, day 1	
Cyclophosphamide 750 mg/m^2, IV, day 1	
Vincristine 1.4 mg/m^2, capped at 2 mg, IV, day 1	
Prednisone 100 mg, PO, day 1–5	
Every 3 weeks x 6	
Rituximab 375 mg/m^2, IV, day 1	[7]
Etoposide 50 mg/m^2/day, CI, day 1–4	
Doxorubicin 10 mg/m^2/day, CI, day 1–4	
Vincristine 0.4 mg/m^2/day, no cap, CI, day 1–4	
Cyclophosphamide 750 mg/m^2, IV, day 5	
Prednisone 60 mg/m^2/day, PO, day 1–5	
Dose adjustment based on hematologic and neurotoxicity	
Every 3 weeks x 6	
Rituximab 375 mg/m^2, IV, day 1 and day 5	[10]
Etoposide 50 mg/m^2/day, CI, day 1–5	
Doxorubicin 10 mg/m^2/day, CI, day 1–5	
Vincristine 0.4 mg/m^2/day, CI, day 1–5	
Cyclophosphamide 750 mg/m^2, IV, day 5	
Prednisone 60 mg/m^2/day, PO, day 1–5	
Dose adjustment based on hematologic and neurotoxicity	
Every 3 weeks, 2 cycles then interim PET. If PET negative, total 3 cycles. If PET positive, total 6 cycles	
Rituximab 375 mg/m^2, IV, day 1	[6]
Doxorubicin 50 mg/m^2, IV, day 1	
Vincristine 1.4 mg/m^2, capped at 2 mg, IV, day 1	
Cyclophosphamide 750 mg/m^2, IV, day	
Prednisone 40 mg/m^2/day, PO, day 1–5	
Every 3 weeks x 6	
Rituximab 375 mg/m^2, IV, day 1	[8]
Doxorubicin 12.5 mg/m^2/day, CI, day 1–5	
Etoposide 60 mg/m^2/day, CI, day 1–5	
Cyclophosphamide 187.5–200 mg/m^2/d, CI , day 1–5	
Prednisone 60mg/m^2, PO, day 1–5	
Every 4 weeks x 6	

Several trials have since supported the safety and tolerability of rituximab in this population. Rituximab plus chemotherapy was well tolerated with a reported 70% CR across multiple studies and 2-year OS of 60–70% [5–8]. A randomized Phase II study AMC-034 of dose-adjusted etoposide, doxorubicin, cyclophosphamide with vincristine, and prednisone, in combination with rituximab (DA-EPOCH-R) either concurrently or weekly for 6 weeks demonstrated the importance of concurrent rituximab. The concurrent arm demonstrated a 73% CR versus 55% CR in the sequential arm [7]. Infusional cyclophosphamide, doxorubicin, and etoposide (iCDE) with rituximab showed similarly high CR and 2-year OS rates (70% and 64%, respectively) [8]. Substitution of doxorubicin with liposomal doxorubicin did not improve outcomes [9]. A meta-analysis of 19 prospective trials demonstrated that the addition of rituximab primarily benefits patients with CD4 counts >50 [1]. In patients with CD4 counts <50, rituximab may be held until CD4 counts improve with HAART therapy.

Positron emission tomography (PET) direct approaches are being explored in HIV-associated DLBCL. Short course EPOCH-R therapy, based on a PET-directed approach where PET negativity after two cycles results in a limit of the total chemotherapy cycles to three rather than the conventional six cycles, was studied. The 5-year OS was 68% in this population [10].

The addition of radiotherapy has not been evaluated in HIV-associated DLBCL. Practically, DLBCL is a radiosensitive disease therefore radiotherapy to sites of primary bulky disease can be considered.

The overall data support concurrent rituximab with EPOCH or conventional chemotherapy in the HAART era. Dose reductions are undertaken for CD4 counts <200 and rituximab may be held if CD4 count is <50. An ongoing AIDS Malignancy Consortium (AMC) trial is investigating the additional benefit of vorinostat to the R-EPOCH backbone.

Central nervous system prophylaxis

Prospective studies on the use of CNS prophylaxis in HIV-associated DLBCL is not available. In the HIV-negative population, the risk of CNS relapse ranges from 1 to 10%. In patients >60 years of age, the risk of

CNS relapse is increased if lactate dehydrogenase (LDH) is elevated, Eastern Cooperative Oncology Group (ECOG) performance status is >1, and there is a >1 extranodal site of disease involvement [11]. In particular, kidney and adrenal involvement is an associated with a heightened risk of CNS relapse [11,12]. In patients <60 years of age, the frequency of CNS relapse approached 5–10% with age-adjusted IPI (aaIPI) of 2 or 3 [13]. Based on this data, CNS prophylaxis may be offered to patients with testicular, kidney or adrenal involvement, or patients with elevated LDH, ECOG performance status >1, and >1 extranodal site of disease.

Human immunodeficiency virus-associated Burkitt's lymphoma

Burkitt's lymphoma is an aggressive lymphoma representing 30% of HIV-associated lymphomas; Epstein Barr virus (EBV) is positive in 30% of these cases. The majority of HIV-associated Burkitt's lymphomas have plasmacytoid differentiation characterized by medium-sized cells with abundant basophilic cytoplasm, eccentric nucleus, and often a centrally located prominent nucleolus.

Intensive chemotherapy regimens have been investigated in HIV-associated Burkitt's lymphoma (Table 9.2). The LMB86 regimen was evaluated in 63 patients who all had stage IV disease with CNS or bone marrow involvement [14]. The study demonstrated a 2-year OS and disease-free survival (DFS) of 47% and 68%, respectively [14]. Seven (11%) treatment-related deaths occurred. Low CD4 count <200 and ECOG performance >2 were identified as poor prognostic factors [14]. Patients with low-risk factors had good outcomes with 2-year OS of 60% versus 2-year OS of 12% in patients who had two or more risk factors [14]. The combination of cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide, and cytarabine (CODOX-M/IVAC) demonstrates a CR rate of 70% and 3-year OS and DFS of 52% and 75%, respectively [15,16]; adding rituximab to this regimen (R-CODOX-M/IVAC) was also studied in a Phase II trial. Preliminary results from 22 patients with 17 months of follow-up showed a 1-year OS of 86% with four patients (14%) taken off the study for toxicity or progression. In a trial conducted in parallel in Spain and Germany involving 81 patients, an intensive regimen B-ALL/

Chemotherapy	Phase	Sample size	ORR	CR	OS	Infection rate	HAART
LMB86	II	63: BL = 63		70%	41% at 2 yr	18%	Yes

Table 9.2 Common chemotherapy for human immunodeficiency virus-associated Burkitt's lymphoma (continues overleaf).

Chemotherapy regimen	Ref
Cytoreductive = COP	[14]
Vincristine 2 mg, IV, day 1	
Cyclophosphamide 300 mg/m^2, IV, day 1	
Prednisome 60 mg/m^2, PO, day 1–7	
Induction	
COPADM1	
Vincristine 2 mg, IV, day 1	
Methotrexate 8 g/m^2, IV, day 1	
Cyclophosphamide 500 mg/m^2, IV, day 2–4	
Doxorubicin 60 mg/m^2, IV, day 2	
Prednisone 60 mg/m^2, PO, day 1–7	
COPADM2	
IDEM with vincristine 2 mg, IV, day 1, day 6	
Cyclophosphamide 1000 mg/m^2, IV, day 2–4	
Prednisone 60 mg/m^2, PO, day 1–7	
Consolidation = CYVE x 2	
Etoposide 200 mg/m^2, IV, day 2–5	
Cytarabine 50 mg/m^2, IV, day 1–4, 12 hours before high-dose cytarabine	
Cytarabine 3 g/m^2, IV, day 2–5	
Maintenance – 4 cycles	
Sequence 1	
Vincristine 2 mg, IV, day 1	
Methotrexate 8 g/m^2, IV, day 1	
Cyclophosphamide 500 mg/m^2, IV, day 2–3	
Doxorubicin 60 mg/m^2, IV, day 3	
Prednisone 60 mg/m^2, PO, day 1–5	
Sequence 2 and 4	
Etoposide 150 mg/m^2, day 1–3	
Cytarabine 100 mg/m^2, SC, day 1–5	
Sequence 3	
Vincristine 2 mg, IV, day 1	
Cyclophosphamide 500 mg/m^2, IV, day 223	
Doxorubicin 60 mg/m^2, IV, day 3	
Prednisone 60 mg/m^2, PO, day 125	

Chemotherapy	Phase	Sample size	ORR	CR	OS	Infection rate	HAART
R-CODOX-M/ IVAC	II	81: BL N=81	90%	80%	72% at 4 yr	32% cycle A 13% cycle B *11% mortality in induction	Yes
DA-R-EPOCH	II	19: BL N=19			100% at 6 yr	NA	No

Table 9.2 Common chemotherapy for human immunodeficiency virus-associated Burkitt's lymphoma (continues overleaf).

Chemotherapy regimen	Ref
Prephase	[17]
Cyclophosphamide, 200 mg/m^2, IV, day 1–5	
Prednisone, 60 m/m^2, IV, day 1–5	
Cycle A	
Rituximab 375 mg/m^2, IV, day 7	
Vincristine 2 mg, IV, day 8	
Methotrexate 1500 mg/m^2, CI, day 8	
Ifosfamide 800 mg/m^2, IV, day 8–12	
Dexamethasone 10 mg/m^2, IV, day 8–12	
Teniposide 100mg/m^2, IV, day 11–12	
Cytarabine 150mg/m^2, IV q 12 hour, day 11–12	
Cycle B	
Rituximab 375 mg/m^2, IV, day 28	
Vincristine 2 mg, IV, day 29	
Methotrexate 1500 mg/m^2, CI, day 29	
Cyclophosphamide, 200 mg/m^2, IV, day 29–33	
Dexamethasone 10 mg/m^2, IV, day 29–33	
Doxorubicin 25 mg/m^2/day, IV, day 32–33	
Cycle C	
Rituximab 375 mg/m^2, IV, day 49	
Vindesine 3 mg/m^2, no cap, IV, day 50	
Methotrexate 1500 mg/m^2, CI, day 50	
Dexamethasone 10 mg/m^2, IV, day 50–54	
Etoposide 250 mg/m^2/day, CI, day 53–54	
Cytarabine 2000 mg/m^2, IV q 12 hour, day 54	
<55 yo A/B/C x 2, ≥A/B x 3	
Rituximab 375 mg/m^2, IV, day 1	[18]
Etoposide 50 mg/m^2/day, CI, day 1–4	
Doxorubicin 10 mg/m^2/day, CI, day 1–4	
Vincristine 0.4 mg/m^2/day, no cap, CI, day 1–4	
Cyclophosphamide 750 mg/m^2, IV, day 5	
Prednisone 60 mg/m^2/day, PO, day 1–5	
Dose adjustment based on hematologic and neurotoxicity	
Every 3 weeks x 6	

SC-EPOCH-RR	II	11: BL N=11	90% at 6 yr	NA	No

Table 9.2 Common chemotherapy for human immunodeficiency virus-associated Burkitt's lymphoma (continued). BL, Burkitt's lymphoma; CI, confidence interval; CR, complete response; HAART, highly active antiretroviral therapy; IV, intravenous; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PO, oral. Data from [14,17,18].

NHL2002 resulted in a CR rate of 80%, with 9% treatment failures, 11% deaths during induction, and 7% deaths in remission [17]. The 4-year OS was 72% [17]. Bone marrow involvement and CD4 count <200 were prognostic for OS and PFS [17]. ECOG performance of >1 was the only parameter influencing death during induction. Contrary to other experiences, age was not a prognostic factor for death during induction, CR, OS, PFS, or DFS [17]. In 11 patients with Burkitt's lymphoma and HIV infection treated at the National Institutes of Health (NIH) with a short course EPOCH and double-dose rituximab (SC-EPOCH-RR), the OS and PFS were 90% and 100%, respectively at 73 months of follow-up [18].

Primary effusion lymphoma

Primary effusion lymphoma is a rare B-cell neoplasm presenting as serous effusions in the pleural, peritoneal. or pericardial cavity without detectable tumor masses and universally associated with human herpesvirus-8 (HHV-8). Sometimes, secondary solid tumor masses can be seen in the pleura. Most cases are co-infected with EBV. The disease is extremely aggressive with median survival of 6 months and 1-year OS of ~40%. In a retrospective analysis of 28 patients, the median survival was 6.2 months after treatment with chemotherapy regimens, which included CHOP, high-dose methotrexate and iCDE [19]. Poor performance status and lack of antiretroviral therapy at diagnosis were predictors for poor survival [19]. Primary effusion lymphomas often have CD30 expression.

Rituximab 375 mg/m^2, IV, day 1 and day 5	[18]
Etoposide 50 mg/m^2/day, CI, day 1–5	
Doxorubicin 10 mg/m^2/day, CI, day 1–5	
Vincristine 0.4 mg/m^2/day, CI, day 1–5	
Cyclophosphamide 750 mg/m^2, IV, day 5	
Prednisone 60 mg/m^2/day, PO, day 1–5	
Dose adjustment based on hematologic and neurotoxicity	
Every 3 weeks. 2 cycles then interim PET. If PET negative, total 3 cycles. If PET positive, total 6 cycles	

In vitro experiments using primary effusion lymphoma cell lines and primary tumors demonstrate the ability of brentuximab vedotin, an anti-CD30 monoclonal conjugated antibody, to decrease cell proliferation, induce cell cycle arrest, and trigger apoptosis [20].

Case reports of patients treated with high-dose therapy and ASCT, allogeneic stem cell transplant (ALSCT), and adjunctive antiviral therapy are variable [21–23]. One patient managed with a reduced intensity conditioning with melphalan and fludarabine plus ALSCT from a matched HIV-negative sibling achieved a sustained remission for 31 months post-transplant [21]. In contrast, another patient managed with an ASCT relapse post-transplant [22]. Another case report describes the use of ganciclovir in conjunction with chemotherapy with a 2-year ongoing complete remission [23]. In the absence of prospective trials or large retrospective review, EPOCH- or CHOP-like regimens may be used.

Stem cell transplant in relapsed or refractory human immunodeficiency virus-related lymphoma

HIV patients with relapsed NHL can also benefit from high-dose chemotherapy followed by stem cell transplantation. The use of ASCT for HIV-related lymphoma was first published in a case report in 1996. The experience was notable for an increased risk of opportunistic infections. Since HAART development, feasibility of ASCT for HIV-associated NHL and HL has improved with demonstrated efficacy in early-stage and

chemosensitive disease. Across several trials, stem cell mobilization was effective [24–27]. A retrospective analysis from the European Group for Blood and Marrow Transplantation (EBMT) Lymphoma Working party of 68 patients with relapsed lymphoma showed a non-relapse mortality of 7.5% at 12 months [28]. Not achieving complete remission or having chemotherapy-resistant disease at ASCT was associated with worse PFS and OS. A subsequent EBMT study reporting matched case control study of HL and NHL patients undergoing ASCT stratified by HIV status showed similar relapse rates, PFS, and OS. There was a slight increase in non-relapse mortality at 1-year in HIV-positive patients versus HIV-negative patients (8% versus 2%, respectively) that did not reach statistical significance [29].

Primary central nervous system lymphoma

Primary central nervous system lymphoma (PCNSL) represents 15% of HIV-associated NHL. Comparatively, PCNSL occurs in 1% of all NHL. PCNSL is an AIDS-defining illness and commonly CD4 count is <200/ul at diagnosis [30]. In patients with AIDS, 20–30% of the CNS lesions are found to be primary CNS lymphoma with toxoplasmosis and progressive multifocal leukoencephalopathy accounting for many of the remaining cases. EBV has a pathogenetic role in these lymphomas and can be a reliable diagnostic marker [31]. Diagnosis is made through a combination of imaging by computed tomography (CT) or magnetic resonance imaging (MRI), toxoplasmosis serologic testing with an empiric trial of antibiotics, evaluation of EBV DNA in the cerebrospinal fluid (CSF), CSF cytology, or early brain biopsy.

PCNSL has an aggressive clinical course with a median survival of less than 2 months. Optimal therapy for PCNSL is unknown. CNS-penetrating regimens containing high-dose methotrexate, steroids, and antiretroviral therapy are recommended. In a small series of 15 patients treated with high-dose methotrexate intravenously at a dose of 3 g/m^2 every 14 days with leucovorin rescue, 47% of patient showed a CR with a median survival of 19 months [32]. Radiation therapy has historically been incorporated into the treatment. In a retrospective analysis of 111 patients with HIV-related PCNSL, those who received whole brain

radiation therapy had improved outcomes [33]. Since PCNSL occurs in the context of significant immunosuppression, patients can succumb to opportunistic infections. Monitoring the efficacy of the antiretroviral regimen is needed in the hope that enhancing the immune system may augment the response to therapy.

Other types of non-Hodgkin lymphoma

Rare cases of indolent lymphomas such as follicular lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma have been observed in patients with HIV infection. Rare cases of peripheral T-cell and NK T-cell lymphoma have also been described in case reports.

Human immunodeficiency virus-associated Hodgkin lymphoma

The relative risk of HIV patients to develop HL is higher than in the general population. In contrast to HL of the general population, HIV-associated HL is associated with EBV in 80–100% of cases. The IPS for a patient with advanced HIV-associated HL defined the following adverse risk factors: age over 45, male gender, stage IV disease, low albumin, anemia, lymphopenia, and leukocytosis. In patients with HIV-associated classical HL (cHL) 80% present with advanced stage disease and 70–96% present with B symptoms, defined by fevers over 100.4°F/38°C for 3 consecutive days, weight loss >10% body weight in 6 months, and drenching night sweats. These risks factors are similar for non-HIV-associated cHL.

In the post-HAART era, several chemotherapy regimens have been studied including ABVD, Stanford V, and BEACOPP [34–37]. However, the OS rates for Stanford V and BEACOPP did not compare well to ABVD despite inclusion of earlier stages in those studies. In a series of 62 patients with HIV and advanced stage HL treated with six to eight cycles of ABVD and HAART, 87% of patients achieved a CR and 5-year OS rate of 76% [37]. A large retrospective study of 224 patients demonstrated that HIV status did not influence OS and PFS for HL [38]. While BEACOPP demonstrated an improved CR compared to ABVD, only 66% of the BEACOPP-treated patients completed therapy compared with 82% in the ABVD trial [35,37]. In addition, 25% of the BEACOPP-treated patients died during

chemotherapy [35]. However, the use of a risk-adapted strategy for HL was reported with excellent results. In this study of 108 patients, early favorable patients received ABVD and 30 Gy of involved field radiation, early unfavorable patients received four cycles of BEACOPP or ABVD and 30 Gy IFRT, and advanced stage patient received six to eight cycles of BEACOPP. Patients with advanced HIV infection received ABVD. The CR rates for patients with early favorable, early unfavorable, and advanced stage HL were 96, 100, and 86%, respectively. The 2-year OS was 90.7% with no significant difference between early favorable (95.7%), early unfavorable (100%), and advanced HL (86.8%) [39]. As the use of 20 Gy and 30 Gy doses of RT proved equally effective in HIV-negative early stage HL, the lower dose of 20 Gy RT should be given in early stage HIV-associated HL [40].

Two cycles of ABVD followed by 20 Gy IFRT can be regarded as standard treatment for early favorable HL. In early stage unfavorable HL, four cycles of ABVD followed by 30 Gy IFRT is considered the standard of care. Patients with advanced stage HL should receive six cycles of ABVD [39].

Incorporation of novel agents such as brentuximab vedotin are being investigated in HIV-associated cHL. Results of the frontline use of brentuximab vedotin and AVD in HIV-negative and HIV-associated HL are highly anticipated.

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