Chapter 63: Lymphomas

INTRODUCTION

- *Lymphomas* are a heterogeneous group of malignancies that arise from malignant transformation of immune cells residing predominantly in lymphoid tissues. Differences in histology have led to the classification of Hodgkin and non-Hodgkin lymphoma (HL and NHL, respectively), which are addressed separately in this chapter.

HODGKIN LYMPHOMA: PATHOPHYSIOLOGY

- B-cell transcriptional processes are disrupted during malignant transformation, preventing expression of B-cell surface markers and production of immunoglobulin messenger RNA. Alterations in the normal apoptotic pathways favor cell survival and proliferation.
- Malignant Reed–Sternberg cells overexpress nuclear factor-κB, which is associated with cell proliferation and antiapoptotic signals. Infections with viral and bacterial pathogens upregulate nuclear factor-κB. Epstein–Barr virus is found in many, but not all, HL tumors.

CLINICAL PRESENTATION

- Most patients with HL present with a painless, rubbery, enlarged lymph node in the supradiaphragmatic area and commonly have mediastinal nodal involvement. Asymptomatic adenopathy of the inguinal and axillary regions may also be present.
- Constitutional, or “B,” symptoms (eg, fever, drenching night sweats, and weight loss) are present at diagnosis in approximately 25% of patients with HL.

DIAGNOSIS AND STAGING

- Diagnosis requires the presence of Reed–Sternberg cells in the lymph node biopsy.
- Staging is performed to provide prognostic information and to guide therapy. Clinical staging is based on noninvasive procedures such as history, physical examination, laboratory tests, and radiography, including positron emission tomography (PET). Pathologic staging is based on biopsy findings of strategic sites (eg, bone marrow, spleen, and abdominal nodes) using an invasive procedure (eg, laparoscopy).
- At diagnosis, approximately half of patients have localized disease (stages I, II, and II_E) and the others have advanced disease, of which 10%–15% is stage IV.
- Prognosis predominantly depends on age and amount of disease; patients older than 65–70 years have a lower cure rate than younger patients. Patients with limited stage disease (stages I and II) have a 90%–95% cure rate, whereas those with advanced disease (stages III and IV) have a 60%–80% cure rate.

TREATMENT

- Goals of Treatment: The goal is to maximize curability while minimizing short- and long-term treatment-related complications.
- Treatment options include radiation therapy (RT), chemotherapy, or both (combined-modality therapy). The therapeutic role of surgery is limited, regardless of stage.

- RT is an integral part of treatment and can be used alone for select patients with early-stage disease, although most patients will receive chemotherapy and radiation.
- Long-term complications of RT, chemotherapy, and chemoradiotherapy include gonadal dysfunction, secondary malignancies (eg, lung, breast, and GI tract, as well as leukemia), and cardiac disease.

Initial Chemotherapy

- Treat all stages and risk-groups of HL with 8–12 weeks of chemotherapy and then obtain a restaging PET-CT (**Table 63-1**). Most patients with unfavorable disease will require RT.

TABLE 63-1

Combination Chemotherapy Regimens for Hodgkin Lymphoma

Drug	Dosage (mg/m^2)	Route	Days
MOPP			
Mechlorethamine	6	IV	1, 8
Vincristine	1.4	IV	1, 8
Procarbazine	100	Oral	1–14
Prednisone	40	Oral	1–14
Repeat every 21 days			
ABVD			
Doxorubicin (Adriamycin)	25	IV	1, 15
Bleomycin	10	IV	1, 15
Vinblastine	6	IV	1, 15
Dacarbazine	375	IV	1, 15
Repeat every 28 days			
MOPP/ABVD			
Alternating months of MOPP and ABVD			
MOPP/ABV hybrid			

Mechlorethamine	6	IV	1
Vincristine	1.4	IV	1
Procarbazine	100	Oral	1–7
Prednisone	40	Oral	1–14
Doxorubicin	35	IV	8
Bleomycin	10	IV	8
Vinblastine	6	IV	8
Repeat every 28 days			
Stanford V			
Doxorubicin	25	IV	Weeks 1, 3, 5, 7, 9, 11
Vinblastine	6	IV	Weeks 1, 3, 5, 7, 9, 11
Mechlorethamine	6	IV	Weeks 1, 5, 9
Etoposide	60	IV	Weeks 3, 7, 11
Vincristine	1.4	IV	Weeks 2, 4, 6, 8, 10, 12
Bleomycin	5	IV	Weeks 2, 4, 6, 8
Prednisone	40	Oral	Every other day for 12 weeks; begin tapering at week 10
One course (12 weeks)			
BEACOPP (standard-dose)			
Bleomycin	10	IV	8
Etoposide	100	IV	1–3

Adriamycin (doxorubicin)	25	IV	1
Cyclophosphamide	650	IV	1
Oncovin (vincristine)	1.4[a]	IV	8
Procarbazine	100	Oral	1–7
Prednisone	40	Oral	1–14
Repeat every 21 days			
BEACOPP (escalated-dose)			
Bleomycin	10	IV	8
Etoposide	200	IV	1–3
Adriamycin (doxorubicin)	35	IV	1
Cyclophosphamide	1250	IV	1
Oncovin (vincristine)	1.4[a]	IV	8
Procarbazine	100	Oral	1–7
Prednisone	40	Oral	1–14
Granulocyte colony-stimulating factor		Subcutaneously	8+
Repeat every 21 days			
A-AVD			
Brentuximab vedotin	1.2 mg/kg	IV	1, 15
Doxorubicin	25	IV	1, 15
Vinblastine	6	IV	1, 15
Dacarbazine	375	IV	1, 15

[a]Vincristine dose capped at 2 mg.

Salvage Chemotherapy

- Response to salvage therapy depends on the extent and site of recurrence, previous therapy, and duration of first remission. Choice of salvage therapy should be guided by response to initial therapy and a patient's ability to tolerate therapy.
- Patients who relapse after an initial complete response can be treated with the same regimen, a non–cross-resistant regimen, RT, or high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT).
- Lack of complete remission after initial therapy or relapse within 1 year after completing initial therapy is associated with a poor prognosis. Patients with these prognostic factors are candidates for high-dose chemotherapy and HSCT.
- Immune checkpoint inhibitors, specifically PD-1 (programmed death 1 pathway) inhibitors (eg, **nivolumab** and **pembrolizumab**), are approved for relapsed HL.

NON-HODGKIN LYMPHOMA: PATHOPHYSIOLOGY

- NHLs are derived from monoclonal proliferation of malignant B or T lymphocytes and their precursors. Current classification schemes characterize NHLs according to cell of origin, clinical features, and morphologic features.
- The World Health Organization (WHO) classification uses *grade* to refer to histologic parameters such as cell and nuclear size, density of chromatin, and proliferation fraction, and *aggressiveness* to denote clinical behavior of a tumor.

CLINICAL PRESENTATION

- Patients present with a variety of symptoms, which depend on site of involvement and whether it is nodal or extranodal.
- Adenopathy can be localized or generalized. Involved nodes are painless, rubbery, and discrete and usually located in the cervical and supraclavicular regions. Mesenteric or GI involvement can cause nausea, vomiting, obstruction, abdominal pain, palpable abdominal mass, or GI bleeding. Bone marrow involvement can cause symptoms related to anemia, neutropenia, or thrombocytopenia.
- Forty percent of patients with NHL present with B symptoms—fever, drenching night sweats, and weight loss.

DIAGNOSIS AND STAGING

- Diagnosis is established by biopsy of an involved lymph node. Diagnostic workup of NHL is generally similar to that of HL.
- NHL classification systems continue to evolve. Slow-growing or indolent lymphomas are favorable (untreated survival measured in years), whereas rapid-growing or aggressive lymphomas are unfavorable (untreated survival measured in weeks to months).
- Prognosis depends on histologic subtype and clinical risk factors (eg, age >60 years, performance status of two or more, abnormal lactate dehydrogenase, extranodal involvement, and stage III or IV disease). These risk factors are used to calculate the International Prognostic Index (IPI) that is most useful in patients with aggressive lymphomas.
- A newer prognostic index for patients with indolent (follicular) lymphomas uses similar risk factors except that poor performance status is replaced with low hemoglobin (<12 g/dL [120 g/L; 7.45 mmol/L]). Current research is focused on prognostic importance of phenotypic and molecular characteristics of NHL.

TREATMENT

- Goals of Treatment: The goals are to relieve symptoms and, whenever possible, cure the patient of disease while minimizing the risk of serious toxicity.

General Principles

- Appropriate therapy for NHL depends on many factors, including patient age, histologic type, stage and site of disease, presence of adverse prognostic factors, and patient preference.
- Treatment is divided into two categories: limited disease (eg, localized disease; Ann Arbor stages I and II) and advanced disease (eg, Ann Arbor stage III or IV and stage II patients with poor prognostic features).
- Treatment options include RT, chemotherapy, and biologic agents. RT is used for remission induction with early stage, localized disease and, more commonly, as a palliative measure in advanced disease.
- Effective chemotherapy ranges from single-agent therapy for indolent (follicular) lymphomas to aggressive, complex combination regimens for aggressive disease.

Follicular Lymphomas

- Follicular lymphomas occur in older adults, with a majority having advanced disease that includes the chromosomal translocation t(14;18). Clinical course is generally indolent, with median survival of 8–10 years. The natural history of follicular lymphoma is unpredictable, with spontaneous regression of objective disease seen in 20%–30% of patients.

Localized Follicular Lymphoma

- Options for stages I and II follicular lymphoma include locoregional RT and immunotherapy (ie, **rituximab**) with or without chemotherapy or RT.
- RT is the standard treatment and is usually curative. Chemotherapy is not recommended, unless the patient has high-risk, stage II disease.

Advanced Follicular Lymphoma

- Management of stages II bulky, III, and IV indolent lymphoma is controversial because standard approaches are not curative. Median time to relapse is only 18–36 months. After relapse, response can be reinduced; however, response rates and durations decrease with each retreatment.
- Therapeutic options are diverse and include watchful waiting, RT, single-agent chemotherapy, combination chemotherapy, biologic therapy, radioimmunotherapy, and combined-modality therapy. Immediate aggressive therapy does not improve survival compared with conservative therapy (ie, watchful waiting followed by single-agent chemotherapy, rituximab, or RT, when treatment is needed).
- Oral alkylating agents **chlorambucil** or **cyclophosphamide**, used alone or in combination with **prednisone**, are the mainstay of treatment. These single agents are as effective as combination regimens and produce minimal toxicity, but secondary acute leukemia is a concern. **Bendamustine** is an IV alkylating agent approved for relapsed or refractory indolent NHL.
- **Fludarabine** is an adenosine analogue that produces high response rates in previously untreated and relapsed advanced follicular lymphoma. Fludarabine is associated with prolonged myelosuppression and profound immunosuppression, increasing the risk of opportunistic infections, such as fungal infections.
- Rituximab, a chimeric monoclonal antibody directed at the CD20 molecule on B cells, is one of the most widely used therapies for follicular lymphoma. It is approved for first-line therapy either alone or combined with chemotherapy and as maintenance therapy for patients with stable disease or with partial or complete response following induction chemotherapy.

  ✔ The most common chemotherapy regimen used with rituximab is the CHOP regimen (**Table 63-2**). Practice guidelines list rituximab maintenance for up to 2 years as an option in both first- and second-line therapy.

✔ Rituximab adverse effects are usually infusion related, especially after the first infusion, and consist of fever, chills, respiratory symptoms, fatigue, headache, pruritus, and angioedema. Pretreatment with oral acetaminophen, 650 mg, and diphenhydramine, 50 mg, 30 minutes before the infusion is recommended.

- A second anti-CD20 monoclonal antibody, **obinutuzumab**, is approved in combination with chemotherapy, as first-line, second-line, and subsequent therapy options for treatment of follicular lymphoma.
- **^{90}Y-ibritumomab tiuxetan** is an anti-CD20 radioimmunoconjugate, linking mouse antibodies to radioisotopes. Radiation is selectively delivered to tumor cells expressing the CD20 antigen and to adjacent tumor cells that do not express it.

  ✔ Radioimmunotherapy is generally well tolerated. Toxicities include infusion-related reactions, myelosuppression, and possibly myelodysplastic syndrome or acute myelogenous leukemia.

- Phosphatidylinositol-3-kinase (PI3K) inhibitors, **idealisib** and **copanlisib**, reduce a messenger that affects malignant B lymphocyte proliferation and survival. They are treatment options for second-line therapy with relapsed or refractory follicular lymphoma. Both agents are associated with serious adverse reactions including severe neutropenia, diarrhea, infection, and pneumonia.
- High-dose chemotherapy followed by HSCT is an option for relapsed follicular lymphoma. The recurrence rate is lower after allogeneic than after autologous HSCT, but the benefit is offset by increased treatment-related mortality.

TABLE 63-2

CHOP Regimen

Drug	Dose	Route	Treatment Days
Cyclophosphamide	750 mg/m^2	IV	1
Doxorubicin	50 mg/m^2	IV	1
Vincristine[a]	1.4 mg/m^2	IV	1
Prednisone	100 mg	Oral	1–5
One cycle is 21 days			

[a]Vincristine dose is typically capped at 2 mg.

Another name for doxorubicin is hydroxydaunorubicin.

Aggressive Lymphomas

- Diffuse large B-cell lymphomas (DLBCLs) are the most common lymphoma in patients of all ages but most commonly seen in the seventh decade. Extranodal disease is present at diagnosis in 30%–40% of patients. IPI score correlates with prognosis. Diffuse aggressive lymphomas are sensitive to chemotherapy, with cure achieved in some patients.

Treatment of Localized Disease

- Stage I and nonbulky stage II should be treated with three or four cycles of rituximab and CHOP (R-CHOP) followed by locoregional RT or six to eight cycles of R-CHOP with no RT.

- Patients with at least one adverse risk factor should receive six cycles of R-CHOP followed by locoregional RT.

Treatment of Advanced Disease

- Bulky stage II and stages III and IV lymphoma should be treated with R-CHOP or rituximab and CHOP-like chemotherapy until achieving complete response (usually 4–6 cycles). Maintenance therapy following a complete response does not improve survival.
- Consider high-dose chemotherapy with autologous HSCT in high-risk patients who respond to standard chemotherapy and meet HSCT criteria.
- Although historically elderly adults have lower complete response and survival rates than younger patients, full-dose R-CHOP is recommended as initial treatment for aggressive lymphoma in the elderly.

Treatment of Refractory or Relapsed Disease

- Approximately one-third of patients with aggressive lymphoma will require salvage therapy at some point. Salvage therapy is more likely to induce response if the response to initial chemotherapy was complete (chemosensitivity) than if it was primarily or partially resistant to chemotherapy.
- High-dose chemotherapy with autologous HSCT is the therapy of choice for younger patients with chemosensitive relapse.
- Salvage regimens incorporate drugs not used as initial therapy. Commonly used regimens include DHAP (**dexamethasone**, **cytarabine**, and **cisplatin**), ESHAP (**etoposide**, **methylprednisolone**, cytarabine, and cisplatin), and MINE (**mesna, ifosfamide, mitoxantrone,** and **etoposide**). None is clearly superior to the others.
- Rituximab is being evaluated in combination with many salvage regimens.

Non-Hodgkin Lymphoma in Acquired Immunodeficiency Syndrome

- Patients with AIDS have more than a 100-fold increased risk of developing NHL, which is usually aggressive (eg, Burkitt or DLBCL).
- Treatment of AIDS-related lymphoma is difficult because underlying immunodeficiency increases the risk of treatment-related myelosuppression.
- Standard combination regimens (eg, CHOP) yield disappointing results. Newer approaches, including dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), appear promising. The role of rituximab in the treatment of AIDS-related DLBCL is not clear.
- Prophylactic antibiotics should be continued during chemotherapy, but the optimal timing for highly active antiretroviral therapy (HAART) is not clear in patients with AIDS-related lymphoma.

EVALUATION OF THERAPEUTIC OUTCOMES

- The primary outcome to be identified is tumor response, which is based on physical examination, radiologic evidence, PET/computed tomography (CT) scanning, and other baseline findings.

See Chapter 149, Lymphomas, authored by Alexandre Chan, Chia Jie Tan, and Jolynn Sessions, for a more detailed discussion of this topic.