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Review Based Book Chapter

AN OVERVIEW OF LYMPHOMAS AND LEUKEMIAS FOR THE INTERNIST

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REVIEW BASED BOOK CHAPTER

AN OVERVIEW OF LYMPHOMAS AND LEUKEMIAS FOR THE INTERNIST

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Abstract

Lymphoid and myeloid malignancies, including lymphomas and leukemias, represent a significant portion of hematologic cancers globally, with distinct pathophysiology, prognosis, and therapeutic approaches. Non-Hodgkin lymphomas (NHL), notably diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL), demonstrate variable clinical behaviors and treatment paradigms shaped by molecular classification and emerging targeted therapies. Acute leukemias, particularly acute promyelocytic leukemia (APL), have seen remarkable improvements in survival with the advent of differentiation therapies. Chronic leukemias—chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML)—are now highly controllable chronic diseases in many cases, with tyrosine kinase inhibitors revolutionizing CML outcomes. This chapter provides an updated, concise review of these malignancies tailored for the practicing internist, emphasizing recent advances that influence diagnosis, risk stratification, and initial management.

Keywords
Hodgkin Lymphomas, Non-Hodgkin Lymphomas, Chronic Leukemia, Acute Promyelocytic Leukemia

Introduction

Hematologic malignancies, including lymphomas and leukemias, account for approximately 10% of new cancer diagnoses globally [1]. Internists play a critical role in the early recognition, initial workup, and coordination of care for these complex diseases. Non-Hodgkin lymphomas (NHL), such as diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL), exhibit distinct

molecular and clinical profiles with evolving therapeutic standards [2]. Similarly, leukemia management, including acute leukemias like acute promyelocytic leukemia (APL) and chronic leukemias such as CML and CLL, has dramatically changed due to targeted treatments [3, 4].

Internists must remain current with evolving diagnostic criteria, risk stratification tools (e.g., revised International Prognostic Index for DLBCL), and indications for urgent hematology referral, especially in suspected APL—a medical emergency.

Hematologic malignancies are remarkably heterogeneous, with diverse pathophysiological mechanisms involving genetic mutations, chromosomal abnormalities, and dysregulated signaling pathways that drive malignant transformation and disease progression. The discovery of molecular markers such as BCL2 and BCL6 rearrangements in lymphomas and BCR-ABL1 fusion in chronic myeloid leukemia has not only improved diagnostic accuracy but also enabled the development of highly specific targeted therapies [3]. These advancements underscore the importance of understanding the underlying biology of these malignancies to inform personalized treatment strategies and improve patient outcomes.

In addition to therapeutic innovations, the landscape of supportive care in hematologic cancers has evolved substantially. The management of complications such as tumor lysis syndrome, neutropenic infections, cytopenias, and bleeding diathesis requires vigilance from both hematologists and internists. Moreover, survivorship care—including monitoring for therapy-related secondary malignancies, cardiovascular risks associated with certain chemotherapeutic agents, and psychosocial support—has become an integral component of comprehensive cancer management. As survival rates improve, internists are increasingly called upon to address these long-term health considerations in collaboration with oncology teams.

1. Hodgkin Lymphoma

1.1. Overview of Hodgkin's Lymphoma

Hodgkin's lymphoma (HL) is a relatively uncommon cancer of B-cell origin, comprising about 10% of all lymphoma cases in the United States. It exhibits a characteristic bimodal age distribution, with incidence peaks in young adults and

again in individuals aged 50 to 70. The disease is broadly categorized into two distinct forms: classical Hodgkin lymphoma (cHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), the latter being the less frequent subtype [5, 6].

1.2. Subtypes and Pathogenesis

Classical Hodgkin lymphoma encompasses several histologic variants: nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted [5, 6]. These are all unified by the presence of Reed-Sternberg cells, abnormal large B cells typically identified by immunohistochemical markers such as CD30+ and CD15+, with frequent absence of CD20 and CD45 [6]. The disease was first described in the 19th century by Thomas Hodgkin, and many cases today still present with systemic symptoms such as enlarged lymph nodes, unexplained fever, and weight loss [7].

Approximately 25–40% of cHL cases are associated with Epstein-Barr virus (EBV), especially among individuals with prior immune compromise, autoimmune disease, or HIV infection. Some cHL cases may also develop from pre-existing low-grade B-cell malignancies, such as chronic lymphocytic leukemia (CLL), particularly in older adults [8].

1.3. Diagnosis and Staging

Diagnosis requires an excisional lymph node biopsy, which is necessary to observe Reed-Sternberg cells in the context of a reactive inflammatory background [6]. Variations in both the quantity of Reed-Sternberg cells and the makeup of the surrounding inflammatory environment give rise to different pathological subtypes, such as nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted forms [7, 9]. The Ann Arbor staging system, supported by PET/CT imaging, guides both initial classification and treatment response assessment [6]. Routine bone marrow biopsy is generally reserved for cases with unexplained hematologic abnormalities [10].

1.4. Treatment Strategies

Treatment is tailored according to disease stage and risk profile. For patients with early-stage, favorable disease, abbreviated chemotherapy—most commonly ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine)—followed by involved-site radiation therapy (ISRT) is standard. Some patients may achieve remission with as few as two cycles of chemotherapy and ISRT [5, 6]. In those with a strong response on early PET

imaging, four to six cycles of chemotherapy alone may be sufficient, potentially avoiding the long-term risks of radiation [11].

For advanced-stage HL, longer chemotherapy courses are required, often without radiation. Up to 25% of patients may experience bleomycin-induced lung toxicity, prompting the use of alternative regimens. One such approach replaces bleomycin with brentuximab vedotin, a CD30-directed antibody-drug conjugate, which shows improved outcomes and reduced pulmonary risk [6, 12, 13]. A complete response shown on PET imaging after two to three cycles of chemotherapy is a strong predictor of treatment outcome [10, 14-18].

1.5. Novel Therapies and Relapse Management

Patients with relapsed or refractory HL are typically treated with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). For those unresponsive to ASCT, newer options include brentuximab vedotin, immune checkpoint inhibitors (such as nivolumab and pembrolizumab), non-myeloablative allogeneic transplantation, or clinical trials [5, 19].

1.6. Prognosis and Survivorship

Early PET scan response after 2–3 cycles of therapy is a key prognostic indicator and guides further treatment [15, 20-22]. Long-term follow-up is essential due to the elevated risk of secondary cancers, cardiovascular disease, and other late complications of therapy [5, 6]. Modern regimens are generally less toxic than earlier protocols and have a more favorable profile for fertility preservation [13, 23, 24].

1.7. Nodular Lymphocyte-Predominant HL

NLPHL differs significantly from cHL in both its pathology and clinical presentation. It accounts for about 10% of HL cases and is often diagnosed at an early, localized stage [25]. Although typically indolent, late relapses are common [26, 27]. Treatment may involve radiation therapy alone for localized disease, while more extensive or recurrent disease may be managed with rituximab, either alone or in combination with chemotherapy [28, 29].

2. Non-Hodgkin Lymphoma

2.1. Diffuse Large B-Cell Lymphoma (DLBCL)

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common subtype of Non-Hodgkin lymphoma (NHL), accounting for nearly 30-40% of cases worldwide [30]. It is a clinically aggressive disease but potentially curable with appropriate therapy. Understanding its molecular heterogeneity is essential for optimal management [31].

DLBCL primarily affects older adults with a median age of diagnosis around 65 years, although it can occur at any age. Risk factors include immunosuppression (e.g., HIV/AIDS, post-transplantation), autoimmune diseases (e.g., rheumatoid arthritis), and certain infections (e.g., EBV in endemic regions) [30].

DLBCL arises from mature B lymphocytes and displays molecular heterogeneity classified into two main subtypes via gene expression profiling: Germinal Center B-cell-like (GCB) subtype, associated with a better prognosis, and Activated B-cell-like (ABC) subtype, linked to worse prognosis due to NF-kB pathway activation [31]. In addition, double-hit and triple-hit lymphomas harbor rearrangements involving MYC, BCL2, and/or BCL6 and are associated with an aggressive clinical course [31].

Recent advancements in genetic and molecular testing, including next-generation sequencing (NGS), have enhanced our ability to personalize treatment strategies for DLBCL patients. NGS allows for the comprehensive assessment of genetic mutations, translocations, and copy number variations, providing insights into disease pathogenesis and therapeutic targets. For example, mutations in genes such as MYD88, CD79B, and EZH2 can inform prognosis and guide the selection of targeted therapies like ibrutinib for ABC-DLBCL or EZH2 inhibitors for GCB-DLBCL. Additionally, cell-of-origin determination using molecular assays refines risk stratification beyond traditional immunohistochemistry-based methods, offering a more precise therapeutic approach [31].

Patients typically present with rapidly enlarging lymphadenopathy, often accompanied by B-symptoms such as fever, night sweats, and weight loss. Extranodal involvement is seen in up to 40% of cases, affecting the gastrointestinal tract, bone marrow, and central nervous system [30].

Diagnosis relies on excisional lymph node biopsy, which remains the gold standard. Immunohistochemistry shows positivity for CD19, CD20, BCL6, with subtype markers aiding further classification [30]. PET-CT imaging is essential for staging and response assessment. Laboratory tests such as LDH levels, beta-2 microglobulin, and hepatitis/HIV screening are critical. The International Prognostic Index (IPI) guides risk stratification [30].

R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) remains the frontline therapy [30]. High-risk or refractory disease options include CAR T-cell therapies (axicabtagene ciloleucel, lisocabtagene maraleucel) and bispecific antibodies (glofitamab), which show significant efficacy [32]. Targeted therapies such as lenalidomide, ibrutinib, and checkpoint inhibitors are promising in ABC-DLBCL [31].

The five-year overall survival is 60-70% for limited-stage disease. Poor prognostic factors include advanced stage, elevated LDH, poor performance status, and unfavorable molecular features [30].

2.2. Mantle Cell Lymphoma (MCL)

Mantle Cell Lymphoma (MCL) is a rare but distinct B-cell malignancy, accounting for 6-8% of NHL cases [30]. It exhibits an intermediate clinical behavior—more aggressive than indolent lymphomas but less responsive to curative-intent therapies compared to DLBCL [30].

MCL predominantly affects older men (median age ~68 years). Its hallmark molecular feature is the t(11;14)(q13;q32) translocation, resulting in cyclin D1 overexpression, a driver of cell cycle dysregulation. SOX11 expression distinguishes classical MCL from its rare, leukemic non-nodal form [30].

MCL often presents with advanced-stage disease, widespread lymphadenopathy, hepatosplenomegaly, bone marrow involvement, and gastrointestinal tract infiltration (lymphomatous polyposis). B-symptoms are less common at presentation [30].

Diagnosis involves biopsy and immunohistochemistry, showing positivity for CD20, CD5, cyclin D1, and SOX11. FISH analysis confirms t(11;14) [5]. PET-CT imaging is used for staging. The Mantle Cell Lymphoma International Prognostic Index (MIPI) incorporates age, performance status, LDH, and WBC count [30].

For fit, younger patients, intensive immunochemotherapy such as R-hyperCVAD or R-DHAP, followed by autologous stem cell transplantation (ASCT), can induce long remissions. Elderly or unfit patients benefit from less intensive regimens such as bendamustine-rituximab [33]. BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) have revolutionized care for relapsed/refractory disease. CAR T-cell therapy and bispecific antibodies are under clinical investigation [34].

Minimal residual disease (MRD) monitoring has emerged as an important prognostic and predictive tool in MCL management. MRD assessment using sensitive techniques such as polymerase chain reaction (PCR) or next-generation sequencing (NGS) enables the detection of subclinical disease burden, which correlates with patient outcomes. Achieving MRD negativity after induction therapy or autologous stem cell transplantation has been associated with prolonged progression-free and overall survival. Moreover, MRD status is increasingly being used to tailor therapeutic strategies, potentially guiding decisions regarding maintenance therapy or the intensity of consolidation treatments. As MRD monitoring becomes integrated into clinical practice, it promises to refine risk-adapted management and improve personalized care in MCL [34].

MCL remains incurable with standard therapy. Median survival has improved to 6-8 years with modern approaches, especially in low-MIPI risk patients [33].

2.3. Follicular Lymphoma (FL)

Follicular Lymphoma (FL) is the most common indolent NHL, representing approximately 20% of cases [5]. Despite its indolence, FL has potential for transformation into aggressive lymphoma such as DLBCL [30].

The median age at diagnosis is 60 years. The genetic hallmark is t(14;18)(q32;q21), leading to BCL2 overexpression and resistance to apoptosis. Secondary mutations in epigenetic regulators (e.g., EZH2, CREBBP) contribute to disease progression [30].

Painless, slowly progressive lymphadenopathy is typical. B-symptoms and extranodal disease are uncommon initially. Bone marrow involvement occurs in 40-70% of cases [30].

Diagnosis relies on histology grading (1-3B), immunophenotyping positive for CD10, CD20, BCL6, BCL2, and PET-CT imaging to detect high metabolic activity suggestive of transformation [30].

Asymptomatic, low-tumor burden patients are managed with watchful waiting. Advanced or symptomatic disease is treated with bendamustine-rituximab or obinutuzumab-based regimens. Rituximab maintenance prolongs progression-free survival but not overall survival [30]. Relapsed disease options include PI3K inhibitors (copanlisib), EZH2 inhibitors (tazemetostat), and bispecific antibodies (mosunetuzumab) [35].

Recently, bispecific T-cell engagers (BiTEs) have emerged as a promising therapeutic option in relapsed/refractory FL. These agents, such as mosunetuzumab and glofitamab, simultaneously target CD20 on malignant B cells and CD3 on T cells, redirecting the patient's own immune system to attack lymphoma cells. Clinical trials have demonstrated high overall response rates and manageable toxicity profiles, even in heavily pretreated populations [35]. BiTEs offer an off-the-shelf, readily available alternative to personalized cell therapies like CAR T-cells, and ongoing studies are evaluating their role in earlier lines of therapy and in combination regimens. These developments underscore the expanding therapeutic landscape for FL, aiming to improve outcomes while minimizing treatment-related morbidity.

The median overall survival exceeds 15 years. The transformation risk is 2-3% per year, drastically worsening prognosis if transformation occurs [30].

3. Acute Leukemias

Acute leukemias represent a heterogeneous group of hematologic malignancies characterized by the clonal proliferation of immature hematopoietic precursors in the bone marrow and peripheral blood. They are broadly classified into acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and rare subtypes such as mixed phenotype acute leukemia (MPAL), which co-express myeloid and lymphoid markers and present significant diagnostic and therapeutic challenges. AML predominantly affects adults, while ALL is more common in children but also occurs in adults [36, 37].

The pathogenesis of acute leukemia involves genetic mutations, chromosomal translocations, and epigenetic alterations that disrupt normal hematopoiesis, leading to

the accumulation of blasts. Key genetic abnormalities in AML include mutations in NPM1, FLT3-ITD, IDH1/2, and DNMT3A, which have prognostic and therapeutic implications [38]. In ALL, the Philadelphia chromosome (t(9;22)(q34;q11.2)) is a significant marker associated with poor prognosis, although tyrosine kinase inhibitors have improved outcomes in these patients [39]. MPAL is characterized by complex karyotypes and poor prognosis, requiring individualized treatment approaches often combining AML and ALL protocols [40].

Diagnosis relies on peripheral blood smear, bone marrow aspiration and biopsy, flow cytometry, cytogenetics, and molecular studies. Immunophenotyping distinguishes AML (CD13, CD33, MPO positivity) from ALL (CD19, CD22, TdT for B-ALL; CD3, CD7 for T-ALL) [37]. MPAL diagnosis requires expression of lineage-defining markers from both myeloid and lymphoid cells [40]. Next-generation sequencing (NGS) panels are increasingly used to detect mutations relevant for risk stratification and targeted therapy decisions [38].

Standard induction therapy for AML includes the "7+3" regimen (cytarabine for seven days with an anthracycline for three days). Recently, CPX-351 (liposomal cytarabine-daunorubicin) showed superior outcomes in therapy-related and secondary AML [41]. Targeted agents like FLT3 inhibitors (midostaurin, gilteritinib), IDH inhibitors (ivosidenib, enasidenib), and BCL-2 inhibitor venetoclax combined with hypomethylating agents have transformed treatment paradigms [42]. Immunotherapies such as gemtuzumab ozogamicin and bispecific T-cell engagers (BiTEs) like blinatumomab for ALL have demonstrated efficacy and are integrated into modern treatment protocols [43]. CAR-T cell therapies, particularly in relapsed/refractory B-ALL, have shown remarkable success and are FDA-approved [44]. Allogeneic stem cell transplantation remains the cornerstone for high-risk patients achieving remission [45].

3.1. Acute Promyelocytic Leukemia (APL)

Acute Promyelocytic Leukemia (APL), a distinct AML subtype (FAB M3), is characterized by the t(15;17)(q24;q21) translocation, resulting in the PML-RARA fusion gene. APL is notable for its coagulopathy, with a high risk of disseminated intravascular coagulation (DIC) and life-threatening hemorrhage at presentation [43].

Clinically, patients with APL may present with fatigue, easy bruising, mucosal bleeding, petechiae, and, less frequently, bone pain or fever. Laboratory findings include pancytopenia or leukocytosis, prolonged prothrombin time, elevated D-dimer, and hypofibrinogenemia. The hallmark of APL is the presence of abnormal promyelocytes containing multiple Auer rods, commonly referred to as "faggot cells" on peripheral smear and bone marrow aspirate [43].

The pathogenesis involves the PML-RARA fusion protein, which disrupts the function of retinoic acid receptors, blocking differentiation at the promyelocyte stage. This leads to the accumulation of malignant promyelocytes and subsequent coagulopathy driven by the release of procoagulant granules [33]. Risk factors for APL include prior chemotherapy or radiation therapy (therapy-related APL) and exposure to environmental toxins, though most cases are de novo without identifiable risk factors [43].

The introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) has revolutionized APL treatment, transforming this once highly fatal disease into the most curable adult leukemia [43]. Risk-adapted therapy based on leukocyte count stratifies patients into low- or high-risk categories. Low-risk patients (WBC <10,000/μL) are treated with ATRA and ATO alone, while high-risk patients receive additional anthracyclines or gemtuzumab ozogamicin. Molecular monitoring of minimal residual disease (MRD) via RT-PCR for PML-RARA transcripts guides post-remission management [44].

Early initiation of ATRA upon clinical suspicion is critical to prevent coagulopathy-related mortality. Supportive care with transfusions to maintain platelets >30,000/μL and fibrinogen >150 mg/dL is essential during induction therapy. Recent studies emphasize the role of oral arsenic formulations, which may offer outpatient management options and improved quality of life compared to intravenous regimens [44].

Additionally, novel agents such as tamibarotene, a synthetic retinoid, are under investigation in relapsed APL, showing promising differentiation effects with potentially reduced toxicity profiles. Updated recommendations also highlight the importance of prophylactic corticosteroids during induction to mitigate differentiation syndrome, a potentially fatal complication of ATRA/ATO therapy [44].

For patients relapsing after ATRA/ATO therapy, allogeneic hematopoietic stem cell transplantation remains a consideration, though newer salvage regimens incorporating arsenic and novel differentiating agents are being evaluated in clinical trials. Emerging data also suggest potential roles for immune-based therapies and small molecule inhibitors targeting the PML-RARA interaction or downstream pathways, although these remain investigational [44].

4. Chronic Leukemias

Chronic leukemias are clonal hematologic malignancies characterized by the proliferation of mature or maturing hematopoietic cells. These disorders primarily include Chronic Myeloid Leukemia (CML) and Chronic Lymphocytic Leukemia (CLL), each with distinct pathogenesis, clinical manifestations, and therapeutic approaches.

4.1. Chronic Lymphocytic Leukemia

Chronic Lymphocytic Leukemia (CLL) represents the most common leukemia in adults in Western countries, with a median age at diagnosis of approximately 70 years and a higher incidence in males. The markedly lower frequency of CLL in Asian populations suggests that both genetic and environmental factors contribute to its pathogenesis. Established risk factors for CLL include older age, male gender, a family history of hematologic malignancies, and certain genetic polymorphisms. The disease is characterized by the clonal proliferation and accumulation of mature CD5-positive B lymphocytes that exhibit defective apoptosis, leading to immune dysregulation and progressive lymphocytosis [46-48].

CLL is frequently diagnosed incidentally during routine complete blood counts, revealing a persistent absolute lymphocytosis ($\geq 5 \times 10^9$/L). Clinical manifestations vary widely, ranging from asymptomatic cases to presentations involving lymphadenopathy, splenomegaly, fatigue, and increased susceptibility to infections due to hypogammaglobulinemia. Autoimmune cytopenias, such as autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), may also occur at any disease stage. Laboratory evaluation typically demonstrates isolated lymphocytosis, reduced serum immunoglobulin levels, and elevated beta-2 microglobulin, the latter serving as a prognostic marker. Peripheral blood smear analysis reveals small, mature lymphocytes with the presence of "smudge cells," indicative of lymphocyte fragility.

Immunophenotyping by flow cytometry remains the gold standard for diagnosis, characteristically demonstrating a CD5+, CD19+, CD23+ B-cell population with dim surface immunoglobulin and low expression of CD20, CD22, and CD79b [49].

The pathogenesis of CLL involves multiple molecular and genetic abnormalities that influence prognosis and therapeutic response. Common cytogenetic alterations include deletions in chromosomes 13q, 11q, and 17p, as well as trisomy 12. Among these, deletion 17p and TP53 mutations are associated with poor outcomes and resistance to conventional chemoimmunotherapy, necessitating the use of targeted therapies. Additional mutations in genes such as NOTCH1 and SF3B1 have been implicated in disease progression and treatment resistance. The dysregulation of B-cell receptor (BCR) signaling and overexpression of the anti-apoptotic protein BCL2 are central mechanisms driving CLL pathobiology, resulting in prolonged cell survival and expansion within the peripheral blood, bone marrow, and lymphoid tissues [50-51].

CLL shares its biology with small lymphocytic lymphoma (SLL); the distinction lies in the predominant site of disease—blood/marrow for CLL and lymph nodes for SLL. Clinically and therapeutically, they are managed as one disease entity [51].

Staging systems such as the **Rai system** (more common in the U.S.) or the **Binet system** (used in Europe) are employed to stratify patients based on clinical parameters, including lymphadenopathy, organomegaly, anemia, and thrombocytopenia. These systems help stratify patients based on clinical findings like lymphadenopathy, organomegaly, anemia, and thrombocytopenia. However, in modern practice, molecular markers provide critical prognostic information. The mutation status of the immunoglobulin heavy chain variable region (IGHV) gene is particularly informative; unmutated IGHV is associated with a more aggressive disease course, whereas mutated IGHV suggests a more indolent disease [49].

For most patients, the clinical course of CLL is heterogeneous—many patients remain asymptomatic for years and are managed with active surveillance, while others develop progressive disease requiring intervention. Surveillance may involve periodic blood counts and physical exams [49, 52-53].

The therapeutic landscape of CLL has undergone a remarkable transformation with the advent of targeted agents. Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib,

acalabrutinib, and zanubrutinib are now integral to frontline therapy, especially for patients with high-risk cytogenetic features like del(17p) or TP53 mutations [49, 50]. These agents disrupt BCR signaling pathways critical for CLL cell survival and proliferation. Venetoclax, a BCL-2 inhibitor, is another pivotal agent, particularly in fixed-duration regimens combined with anti-CD20 monoclonal antibodies such as obinutuzumab or rituximab. This approach offers the advantage of time-limited therapy with deep and durable remissions. Importantly, these therapies have largely supplanted traditional chemoimmunotherapy in most clinical settings due to superior efficacy and tolerability [54-57].

Minimal residual disease (MRD) assessment using sensitive flow cytometry or next-generation sequencing has emerged as a valuable tool for evaluating treatment response and guiding therapeutic decisions, including treatment discontinuation in cases of sustained MRD negativity. Ongoing clinical trials, such as CAPTIVATE and GLOW, have demonstrated the efficacy of combining venetoclax with BTK inhibitors, achieving high MRD negativity rates and reshaping frontline management strategies. These regimens offer the potential for chemotherapy-free, fixed-duration treatment courses with excellent patient outcomes [58].

Though allogeneic stem cells are available in refractory cases, it is rarely used in older adults due to comorbidities and treatment-related risks [59].

Internists should also be alert to complications such as:

- **Infections**, particularly in those with hypogammaglobulinemia or those receiving immunosuppressive therapy. IVIG replacement may be considered for patients with recurrent infections [60].
- **Autoimmune cytopenias**, such as autoimmune hemolytic anemia or immune thrombocytopenia, which can occur at any disease stage [61-64].
- **Richter transformation**, the evolution of CLL into an aggressive large B-cell lymphoma, occurring in about 5% of patients and associated with a poor prognosis [49, 65].

The prognosis of CLL varies widely depending on disease biology and patient-specific factors. With modern targeted therapies, four-year survival rates now range between 78% and 94%, even among high-risk groups, marking a substantial

improvement over historical outcomes [49, 66-69]. Internists play a critical role in the initial detection of CLL, longitudinal monitoring for disease progression or complications, and coordination with hematology specialists for the timely initiation of therapy when indicated.

4.2. Chronic Myelogenous Leukemia

Chronic myeloid leukemia (CML) is a hematologic malignancy characterized by uncontrolled proliferation of granulocytic lineage cells, typically with preserved maturation. It arises from a clonal hematopoietic stem cell abnormality and accounts for approximately 15% of adult leukemias [70-72]. The incidence is about 1–2 per 100,000 adults annually, with a median age at diagnosis of 67 years, though it can present at any age [70, 71].

The defining molecular hallmark of CML is the **Philadelphia chromosome**, resulting from a reciprocal translocation between chromosomes 9 and 22: t(9;22)(q34;q11.2). This genetic rearrangement fuses the **BCR** and **ABL1** genes, producing the **BCR::ABL1 fusion protein**, a constitutively active tyrosine kinase [73, 74]. This oncoprotein drives unchecked myeloid proliferation, inhibits apoptosis, and leads to the clinical manifestations of the disease [70, 71].

Most patients are diagnosed during the **chronic phase (CP)**, which is defined by less than 10% blasts in the peripheral blood or bone marrow. Without treatment, CML naturally progresses through an **accelerated phase (AP)** and eventually transforms into **blast phase (BP)**, which resembles acute leukemia [75]. Disease staging relies primarily on blast percentage and clinical features: CP (<10% blasts), AP (10–19% blasts or specific cytogenetic/morphologic findings), and BP (≥20% blasts per WHO criteria; some guidelines use a 30% threshold) [71, 76].

Clinically, many patients are asymptomatic at diagnosis, with incidental detection during routine blood testing. However, symptoms such as fatigue, weight loss, early satiety due to splenomegaly, and low-grade fever may occur. Hematologic findings typically include leukocytosis with a left shift (presence of myelocytes, metamyelocytes, promyelocytes, and occasional blasts), along with thrombocytosis and a normocytic anemia [77]. Basophilia or eosinophilia in the absence of a reactive cause should raise suspicion for CML [71].

Treatment is initiated promptly upon diagnosis in all patients. The cornerstone of therapy is **tyrosine kinase inhibitors (TKIs)** that target BCR::ABL1. First-line options include imatinib (first-generation), or more potent second- and third-generation agents such as dasatinib, nilotinib, bosutinib, and asciminib. The choice of agent is individualized based on patient comorbidities, drug tolerability, and presence of resistance mutations (e.g., T315I, which may necessitate ponatinib or asciminib) [70, 71, 78]. Allogeneic hematopoietic stem cell transplantation is generally reserved for patients with advanced-phase disease or resistance to multiple TKIs [71, 78].

Long-term management typically involves continuous TKI therapy. However, select patients who achieve a deep and sustained molecular response may be considered for **treatment-free remission (TFR)** under close monitoring protocols. TFR is an emerging goal of therapy in stable chronic-phase patients and represents a paradigm shift in CML management [70, 79].

Conclusions

In conclusion, hematologic malignancies, including lymphomas and leukemias, encompass a wide range of diseases with unique biological features and treatment needs. The evolution of diagnostic techniques, including advanced molecular and genetic profiling, has enabled more precise classification, risk stratification, and personalized treatment approaches across these conditions. Significant advancements have been made in the treatment of Non-Hodgkin lymphomas, including DLBCL, MCL, and FL, through targeted therapies, CAR T-cell therapy, and bispecific antibodies, leading to improved outcomes even in challenging cases. Hodgkin lymphoma, particularly the classical type, now benefits from personalized, risk-adapted approaches and novel agents like brentuximab vedotin and checkpoint inhibitors. Acute leukemias, especially APL, have become highly curable with differentiation therapy, while AML and ALL are increasingly managed with molecular and immune-based treatments. Chronic leukemias such as CML and CLL now have effective oral therapies that provide long-term disease control and the potential for treatment-free remission.

Internists must remain vigilant in the early detection and appropriate referral of patients with suspected hematologic malignancies. Mastery of evolving diagnostic

algorithms, familiarity with emergent therapeutic modalities, and an understanding of disease-specific urgency—especially in cases like APL—are essential to optimizing patient outcomes. As treatment paradigms continue to advance, a multidisciplinary and individualized approach remains paramount in the management of these complex diseases.

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Conflicts of interest

The authors do not have conflict of interest.

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