Review

Chronic Lymphocytic Leukemia
A Clinical Review

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IMPORTANCE The most common leukemia is chronic lymphocytic leukemia (CLL). Every year, there are 15 000 new diagnoses and 5000 CLL deaths in the United States. Although therapeutic choices were once limited, treatment of this disease has vastly improved in the last decade.

OBJECTIVE Evidence-based review of the diagnosis, staging, and treatment of CLL.

EVIDENCE REVIEW PubMed, Cochrane Library, Scopus, and Google Scholar databases were searched through August 28, 2014. English-language peer-reviewed articles published between 2000-2014 were found using the keywords *chronic lymphocytic leukemia*, *upfront therapy*, *upfront therapies*, *upfront therapeutic*, *upfront therapeutics*, *upfront treatment*, *front-line treatment*, *first-line treatment*, *front-line treatments*, *first-line treatments*, *front-line therapy*, *front-line therapies*, *randomized*, *randomized studies*, *randomized study*, *clinical trial*, *clinical trials*, *phase 3*, and *phase 3 clinical trial*. Abstracts and presentations at scientific meetings were excluded. A total of 277 articles were retrieved, of which 24 met our predefined selection criteria; treatment recommendations were based on subsequent analysis of these 24 articles.

FINDINGS The Rai and Binet systems for staging CLL were established in 1975 and 1977, respectively. However, they do not account for new disease categories such as monoclonal B-cell lymphocytosis (peripheral blood clonal lymphocytosis that does not meet other criteria for CLL). Two subsets of CLL are now recognized based on risk stratification involving molecular and cytogenetic analyses. Outcomes are improved by the addition of immunotherapy to combination chemotherapy for initial treatment in all subsets of treated patients. Overall response rates between 75% and 90% and complete responses between 22% and 45% are expected in the current era, with more than 80% of treated patients alive at 3 years. Overall, 5-year survival has increased to 66% from 60% ($P < .001$) in the past 10 years.

CONCLUSIONS AND RELEVANCE Chemoimmunotherapy is the standard first-line option approach for CLL, the most common leukemia observed in adults. Treatment is initiated when the disease becomes symptomatic, and survival is high following treatment.

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With more than 15 000 cases recognized annually, chronic lymphocytic leukemia (CLL) is the most common leukemia diagnosed in the Western world, resulting in almost 5000 cancer-related deaths yearly in the United States.[1] Molecular diagnostics and improved understanding of the biology of the disease have facilitated characterization of variations in the disease's clinical course, resulting in better risk stratification.[2] Consequently, more precise targeting of therapy is possible, capitalizing on knowing CLL clonal evolution. For example, CD-20 is a phosphoprotein expressed on the surface of B cells. Targeting this molecule with immunotherapy has improved CLL survival when added to conventional chemotherapy.[3] We review the diagnosis, staging, and treatment for CLL.

Literature Search and Results

PubMed, Cochrane Library, Scopus, and Google Scholar databases were searched through August 28, 2014, to identify English-language articles published from 2000-2014. Keywords searched included *chronic lymphocytic leukemia*, *upfront therapy*, *upfront therapies*, *upfront therapeutic*, *upfront therapeutics*, *upfront treatment*, *front-line treatment*, *first-line treatment*, *front-line treatments*, *first-line treatments*, *front-line therapy*, *front-line therapies*,

randomized, *randomized studies*, *randomized study*, *clinical trial*, *clinical trials*, *phase 3*, and *phase 3 clinical trial*.

We identified a total of 277 articles. We excluded noninterventional studies, meta-analyses, review articles, and studies reporting on other than first-line treatments (ie, stem cell transplantation, maintenance strategies, and treatment of relapsed disease or second-line therapies). Articles reporting updated analyses on previously published studies were included. We included all prospective phase 3 studies addressing front-line therapy and select phase 2 studies that enrolled 100 or more patients with CLL. We limited our search to articles published in peer-reviewed journals and excluded reports having only abstracts or presentations at scientific meetings. The bibliography of each article was reviewed to find any studies missed using our search strategy.

Our search and inclusion criteria yielded 24 articles (eFigure in the Supplement). Where appropriate, the level of evidence for therapeutic recommendations is presented as previously described (level I: randomized trials with low false-positive rates; level II: randomized trials with high false-positive or high false-negative rates; level III: nonrandomized concurrent cohort comparisons; level IV: nonrandomized historical cohort comparisons; level V: case series without controls).[4]

Diagnosis and Risk Stratification of CLL

Features related to the initial presentation and diagnosis of CLL are reported in **Box 1**. The disease is characterized by the progressive accumulation of phenotypically mature malignant B lymphocytes, primarily in the peripheral blood, bone marrow, and lymph nodes. These cells are small, with a narrow border of cytoplasm, a dense nucleus without nucleoli, and aggregated chromatin. The characteristic presence of smudge cells that result from lymphocyte debris as the peripheral smear is being prepared has been a pathognomonic feature of CLL (**Figure**).

The National Cancer Institute (NCI)–sponsored working group guidelines for the diagnosis of CLL require an absolute clonal lymphocyte count of 5000 cells/mm^3 or more and a characteristic phenotype combining the presence of CD19, the T-cell antigen CD5, and CD23. The expression of CD20 is generally weak, and the malignant cells are either κ or λ light chain restricted (Figure).[5] This immunophenotype is essential to differentiate CLL from other lymphoproliferative disorders, for which management might be fundamentally different. Small lymphocytic lymphoma occurs when CLL cells spare the peripheral blood and the bone marrow but infiltrate the lymph nodes and other tissues. Small lymphocytic lymphoma occurs in 5% of patients with CLL; management is the same as that for conventional CLL.[6] The majority of patients are asymptomatic at the time of presentation, and the diagnosis is often made when coincidental leukocytosis and lymphocytosis are noted on routine laboratory examination. Histologic confirmation by a lymph node biopsy is not routinely needed when the diagnosis is confirmed using flow cytometry of the peripheral blood and is reserved for cases in which different or transformed lymphoid malignancy are thought to coexist with CLL. Monoclonal B lymphocytosis (MBL) occurs in otherwise healthy adults having peripheral blood clonal B lymphocytes but fewer than the minimum of 5000 cells/mm^3 required to diagnose CLL. These patients lack other features of CLL such as adenopathy or constitutional symptoms, and 1% to 2% cases of MBL progress to CLL per year.[7] Monoclonal B lymphocytosis occurs in 5.1% of all people with normal complete blood cell counts and 13.9% of patients with lymphocytosis. It is not known if MBL and CLL have similar molecular features or cytogenetic abnormalities, but recent reports suggest that most patients with CLL have a preceding MBL phase and that advancing age, along with high initial lymphocyte counts, predispose to faster progression to CLL.[8]

Box 1. Initial Presentation and Diagnosis of Chronic Lymphocytic Leukemia (CLL)

Clinical Presentation

- Majority of patients are asymptomatic at diagnosis. Referral is generated when elevated white blood cell counts, lymphocyte counts, or both are noted on routine blood cell counts
- Ten percent of patients present with B symptoms (unexplained fevers, unintentional >10% body weight loss in the preceding 6 months, or drenching night sweats)
- Most patients have enlarged and palpable lymph nodes on examination
- Hepatosplenomegaly may be noted on physical examination in 20% to 50% of patients at presentation

Laboratory Abnormalities

- Absolute lymphocytosis defined as more than 5000 cells/μL
- Autoimmune hemolytic anemia may be present at diagnosis in 1% to 11% of cases
- Autoimmune thrombocytopenia present at diagnosis in less than 2% of cases
- Levels of low-density lipoprotein cholesterol and β2 microglobulin are variably elevated
- Hypogammaglobulinemia is present in 8% to 10% of patients at diagnosis

Establishing the Diagnosis

- Flow cytometry and immunophenotyping of the peripheral blood to establish clonality of circulating lymphocytes
- Lymphocytes usually express CD19, CD20, CD23, and CD5
- Imaging studies are not required to establish a diagnosis of CLL
- Bone marrow biopsy and aspirate is not routinely required to establish a diagnosis but might be indicated to investigate causes of cytopenias should they exist
- Lymph node biopsy is not routinely needed to diagnose CLL; biopsy might be clinically indicated if transformation or a concurrent alternate lymphoid malignancy exists

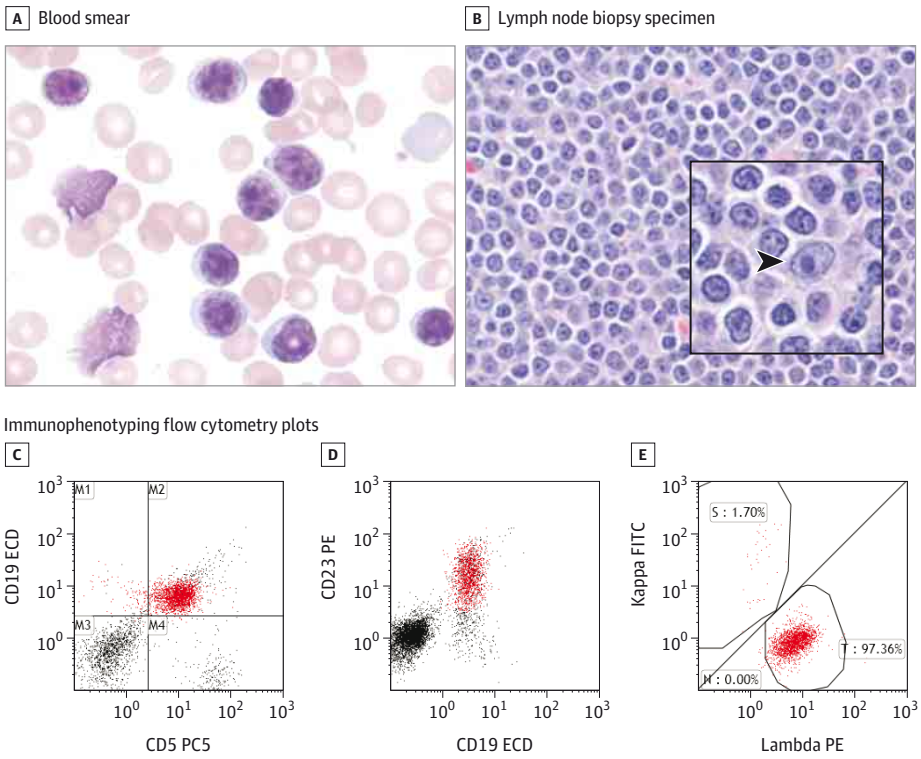
The Rai and Binet CLL staging systems are used to classify patients with CLL, although both systems are not very effective for predicting early disease progression (**Table 1**).[9,10] Although routine imaging is not recommended for staging of patients with CLL, visceral adenopathy may occur in early-stage disease and might predict disease progression.[11] It is not known if the presence of visceral adenopathy warrants any specific change in therapy.

Chronic lymphocytic leukemia does not require treatment until symptoms develop or the disease progresses, causing severe cytopenia.[5] Routine imaging studies are not recommended in initial staging or as interim assessments unless dictated by clinical trials.[5] Numerous clinical and molecular features are predictive of the course of CLL and can be used for risk stratification (**Box 2**).[12,13]

CLL Upfront Therapy

Historically, CLL was treated with alkylating agent and purine analogue chemotherapies. Recently, the addition of anti CD-20

Figure. Characteristic Histologic Features and Immunophenotype of Chronic Lymphocytic Leukemia



A, Peripheral blood smear from a patient with chronic lymphocytic leukemia (CLL) that shows scattered smudge cells and small lymphoid cells with clumped chromatin typical of CLL (Wright-Giemsa, original magnification ×200). B, Histology of lymph node biopsy tissue from the same patient showing diffuse proliferation of small lymphoid cells with occasional pale areas corresponding to proliferation centers (hematoxylin-eosin, original magnification ×100). Inset shows a paraimmunoblast (large cell with prominent nucleoli) within 1 proliferation center (arrowhead) (hematoxylin-eosin, original magnification ×400). Flow cytometry plot (from a different patient with CLL) depicting CLL population in red expressing (C) CD19 (B-cell marker) and CD5, in addition to (D) CD23 with (E) lambda light chain restriction; nearly all CLL cells shown in red express uniform lambda light chain as depicted on the x-axis. All antigens are tagged with the depicted fluorochromes. The axis scales represent fluorescence intensity. FITC indicates fluorescein isothiocyanate; PE, phycoerythrin; ECD, electron coupled dye; PC5, phycoerythrin-cyanine 5. Figure courtesy of Girish Venkataraman, MD, Department of Pathology, University of Chicago.

Table 1. Rai and Binet Staging Systems for Chronic Lymphocytic Leukemia

Stage	Risk	Clinical Features	Overall Survival, y[a]
Rai			
0	Low	Lymphocytosis in peripheral blood and bone marrow only	>10
I/II	Intermediate	Lymphadenopathy ± hepatosplenomegaly	7
III/IV	High	Anemia ± thrombocytopenia	<4
Binet			
A	Low	<3 areas of lymphadenopathy[b]	12
B	Intermediate	>3 areas of lymphadenopathy	7
C	High	Anemia, thrombocytopenia, or both	2-4

[a] Durations are of historical importance as these are changing with newer and targeted therapies.

[b] Nodal areas: cervical, axillary, inguinal (one side or both), spleen, and liver.

immunotherapy to chemotherapeutic treatment of CLL has improved survival, resulting in front-line treatment now recommended as combined immunochemotherapy (**Box 3**). Treatment is not initiated until CLL is symptomatic or the disease progresses (**Box 4**). High-risk patients should be enrolled into clinical trials that explore novel therapy, early therapy, or both before symptoms develop.

Although randomized studies have not shown an overall survival benefit for purine analogues relative to alkylating agents for front-line CLL treatment, purine analogues have better overall and complete response rates and better progression-free survival. Consequently, purine analogues are now the preferred chemotherapeutic agents for front-line CLL treatment.[14] Long-term follow-up of the original study comparing the purine analogue fludarabine with the alkylating agent chlorambucil suggests a survival advantage in favor of fludarabine.[15,16] Although definitive evidence showing superiority of one purine analogue over another is lacking, extensive familiarity and expertise with fludarabine has resulted in this agent becoming an essential component of current CLL treatment regimens.[17,18]

Box 2. Selected Adverse Clinical and Novel Prognostic Factors in Chronic Lymphocytic Leukemia (CLL)

Adverse Clinical/Laboratory Prognostic Factors

1. Advanced age[a]
2. Advanced stage (Rai III/IV or Binet C)
3. Poor performance status
4. Short lymphocyte doubling time (<12 mo)
5. Diffuse bone marrow infiltration pattern
6. Increased percentage of prolymphocytes
7. Male sex
8. High lactate dehydrogenase level[b]
9. High β2-microglobulin level[c]
10. Increased levels of soluble CD23
11. Advanced stage (Rai III/IV or Binet C)

Novel/Molecular Adverse Prognostic Factors

1. 17p and 11q deletions by fluorescence in situ hybridization
2. CD38 overexpression (>30%)
3. Zap-70 greater than 20%
4. Unmutated *IgVH*
5. NOTCH-1 mutations
6. High lipoprotein lipase expression
7. Variance expressions of specific micro-RNAs (ie, down-regulation of miR-15a and miR-16-1 is associated with good prognosis, whereas down-regulation of miR-29 family is associated with poor prognosis)

Abbreviations: *IgVH*, immunoglobulin variable heavy chain gene; ZAP-70, zeta-associated protein-70.

[a] The older the patient is, the worse the disease can be, without an actual age cutoff.

[b] Level above the upper limit of normal.

[c] Abnormal β2-microglobulin and specifically if the levels are above 4 μg/mL.

Box 3. Categories of Selected Drug Therapy for Chronic Lymphocytic Leukemia (CLL)

Alkylating Agents (Targeting and Causing DNA Damage in Cancer Cells)

Chlorambucil

Bendamustine

Cyclophosphamide

Purine Analogues

Fludarabine (inhibits function of DNA polymerase, primase)

Pentostatin (inhibits enzyme adenosine deaminase, affecting DNA processing)

Cladribine (inhibits adenosine deaminase)

Immunotherapy and Monoclonal Antibodies

Rituximab (anti-CD20)

Alemtuzumab (anti-CD52)

Ofatumumab (anti-CD20)

Obinutuzumab (anti-CD20)

Lenalidomide (immunomodulatory agent with multiple targets)

B-Cell Receptor Pathway and Tyrosine Kinase Inhibitors

Ibrutinib (targets bruton tyrosine kinase)

Idelalisib (targets phosphoinositide 3-kinase delta)

Combination Regimens

Alkylating agents work by inducing DNA interstrand crosslinks, damaging cancer cells. Purine analogues such as fludarabine inhibit repair of this defect, enhancing the cancer-killing effect of alkylating agents. Indeed, combined therapy with alkylating agents and purine analogues resulted in better overall response rate, complete response, and progression-free survival (but not overall survival in 3 prospective, randomized clinical trials) (**Table 2**).[19-21] These trials provided high quality evidence that the combination of fludarabine and cyclophosphamide results in better outcomes than fludarabine alone, resulting in fludarabine and cyclophosphamide becoming the new standard to which other chemotherapy combinations are compared.

Chemoimmunotherapy

Monotherapy using rituximab, a chimeric anti-CD20 monoclonal antibody, is very effective as a treatment for indolent lymphomas[22,23] but not for CLL. The safety of this antibody, coupled with its predictable pharmacokinetics and half-life, makes it an attractive anticancer drug. Consequently, studies were performed to explore its utility for treating CLL as part of a combination chemoimmunotherapy program.

Byrd et al[24] reported on a randomized phase 2 trial that compared concurrent fludarabine and rituximab vs sequential therapy of both agents. Patients in the concurrent treatment group achieved higher complete response and overall response rate, although survival remained similar between both groups. Subsequently, a comparative retrospective analysis conducted using data from patients with similar disease characteristics who received fludarabine alone vs those who were treated with concurrent fludarabine + rituximab in the above-mentioned study[25] showed that the chemoimmunotherapy group provided patients with improved overall and progression-free survival.

When fludarabine + cyclophosphamide was combined with rituximab in the front-line setting, overall response rate was 95% and complete response was 70%, as described by Keating et al,[26] who also reported that fludarabine + cyclophosphamide + rituximab induced molecular remission in some patients. However, this regimen was deemed more toxic in patients older than 65 years, who were more likely to prematurely discontinue treatment.[26] This issue, along with the suggested, yet controversial, increase in the incidence of secondary leukemias and myelodysplasias[27] associated with this regimen, led to limiting the use of fludarabine + cyclophosphamide + rituximab to fit and young patients with CLL and adequate renal function.[28] The significant activity noted with fludarabine + cyclophosphamide + rituximab led to the conduct of a prospective phase 3 randomized trial comparing fludarabine + cyclophosphamide + rituximab with fludarabine + cyclophosphamide. In that study, 817 previously untreated, fit patients with CLL and with a median age of 61 years were randomized to either 6 cycles of fludarabine + cyclophosphamide + rituximab or fludarabine + cyclophosphamide. Although fludarabine + cyclophosphamide + rituximab was associated with more toxicity, it also demonstrated better efficacy (overall response rate, 93% vs 85%; complete response, 44.5% vs 23%; $P < .001$).[3] Importantly, this study was the first to show level I evidence on survival advantage for any combination program in CLL. With a median follow-up that approached 6

Box 4. Treatment Indications and Response Criteria for Chronic Lymphocytic Leukemia

Indications to Start Therapy for Chronic Lymphocytic Leukemia

1. Evidence of progressive bone marrow failure as evidenced by anemia, thrombocytopenia, or both
2. Massive (>6 cm below the left costal margin), symptomatic, or progressive splenomegaly
3. Massive (≥10 cm) adenopathy or progressive symptomatic adenopathy
4. Progressive lymphocytosis: >50% increase in 2 months or lymphocyte doubling time less than 6 months[a]
5. Autoimmune anemia or thrombocytopenia not responsive to standard therapies
6. Constitutional symptoms: unintentional weight loss greater than 10% over the preceding 6 months, unexplained night sweats for more than 1 month, unexplained fevers (>38.1°C [100.5°F]) for 2 weeks

Complete Response[b]

All of the below must be met:
- Absence of clonal lymphocytosis
- Absence of palpable adenopathy
- No hepatosplenomegaly
- No constitutional symptoms
- Absolute neutrophil counts ≥1500/μL
- Hemoglobin ≥11 g/dL
- Platelets ≥100 000/μL

Complete Response With Incomplete Marrow Recovery

Similar to complete response but with persistent cytopenia in 1 or more lineage

Partial Response

Any 2 of the below must be met:
- Decrease >50% in clonal lymphocytes
- Decrease >50% in lymph node size in the sum product of up to 6 nodes
- No new adenopathy
- No increase in any preexisting lymph node size
- Decrease >50% in hepatosplenomegaly

Plus 1 of the following:
- Absolute neutrophil counts ≥1500/μL or improved >50% from baseline
- Hemoglobin ≥11 g/dL or improved >50% from baseline
- Platelets ≥100 000/μL or improved >50% from baseline

[a] Should not be used as a single parameter as an indication of when white blood cell counts are less than 30 000 cells/μL. Also, all factors that might be contributing to lymphocytosis, such as infections, should be excluded.

[b] In some clinical trials, complete response requires the bone marrow to be also free of clonal lymphocytes.

years, more patients receiving fludarabine + cyclophosphamide + rituximab were alive compared with those receiving fludarabine + cyclophosphamide (69.4% vs 62.3%, $P = .001$), which corresponded to a median survival of "not reached" in the group receiving fludarabine + cyclophosphamide + rituximab vs 86 months in the group receiving fludarabine + cyclophosphamide.

Other regimens followed as additional chemotherapeutic agents either alone or in combinations were combined with monoclonal antibodies. Universally, these regimens produced higher overall response rates, complete response, and improvements in progression-free survival as compared with chemotherapy (**Table 3**). Another chemoimmunotherapy program combined bendamustine with rituximab and provided patients with an overall response rate that approached 90%.[29] This led to a prospective randomized study comparing bendamustine + rituximab with fludarabine + cyclophosphamide + rituximab. Partial results of this study have been presented in an abstract format, but a final analysis has not been published.[30]

Alemtuzumab, a humanized monoclonal antibody targeting CD52 ubiquitously present on the surface of the malignant lymphocytes, has also been incorporated into chemotherapy combinations. The fludarabine + cyclophosphamide + rituximab regimen was compared with the fludarabine + cyclophosphamide + alemtuzumab combination, but this study was closed prematurely because of increased toxicity in the alemtuzumab group, solidifying fludarabine + cyclophosphamide + rituximab as the better and safer chemoimmunotherapy regimen.[31]

Collectively, the above data support that chemoimmunotherapy should be considered a standard front-line approach in patients with CLL in need of therapy.[32,33] Fludarabine + cyclophosphamide + rituximab appears to be the most effective, with a proven overall survival advantage when used in fit patients with normal renal function. It is plausible to assume that these more effective therapies, coupled with improvements in supportive measures and better understanding of disease biology, have led to incremental survival improvements in patients treated in the contemporary era. A retrospective analysis of Surveillance, Epidemiology, and End Results data has shown that 5-year overall survival for all patients with CLL treated between 2001 and 2009 was significantly better than that for patients treated between 1992 and 2000 (66% vs 60%, $P < .001$).[34]

Emerging Therapies

The B-cell receptor is crucial for the evolution and progression of CLL. Therapies targeted to this receptor and its downstream proteins have been developed. These include the bruton tyrosine kinase inhibitor ibrutinib[35] and the phosphatidylinositol 3-kinase (PI3K) inhibitor idelalisib.[36] Other newly studied agents include drugs targeting the antiapoptotic protein BCL-2[32] and anti-CD20 antibodies that are modified and engineered differently to provide better cell killing.[37,38]

Current Guidelines

As treatment strategies have become more complex, various international societies have issued CLL treatment guidelines (**Table 4**). All of these guidelines emphasize the importance of accurate diagnosis and underscore that initial observation without active treatment for patients with CLL is the standard approach for all asymptomatic patients, regardless of their risk category. The National Comprehensive Cancer Network recommends stratifying patients with CLL by cytogenetic analysis and fluorescence in-situ hybridization because some high-risk patients, such as those carrying the 17p deletion, could benefit from early allogeneic bone marrow transplantation (discussed below). All of the guidelines also recommend the use of chemoimmunotherapy in the upfront setting (patients receiving treatment for the first time once they require therapy). A variety of drug combinations are available to use. Selection between the various chemoimmunotherapeutic regimens are

Table 2. Prospective Chemotherapy-Only Randomized Trials for Upfront Therapy in Chronic Lymphocytic Leukemia[a]

Source	Therapy Comparators	No. of Patients	Overall Response Rate, %	Complete Response, %	Survival		Comments
					Progression-free, mo	Overall	
Rai et al,[16] 2000	Chlorambucil	181	37	4	14	56 mo	Overall response rate, complete response, and progression-free survival were significant in favor of fludarabine ($P < .001$); overall survival was not significant
	Fludarabine	170	63	20	20	66 mo	
Robak et al,[69] 2000	Cladribine + prednisone	126	87	47	21	Not reached	$P = .01$ for progression-free survival
	Chlorambucil + prednisone	103	57	12	18		$P = .60$ for overall survival
Leporrier et al,[17] 2001	Fludarabine	341	71.1	40.1	31.7	69 mo	$P < .0001$ for overall response rate in favor of ChOP and fludarabine and $P = .003$ for complete response in favor of the same
	CAP	240	58.2	15.2	27.7	70 mo	
	ChOP	357	71.5	29.6	29.5	67 mo	
Mabed et al,[70] 2004	Chlorambucil	109	34.9	Not reported	30	55 mo	$P = .371$ for overall survival
	Chlorambucil + theophylline	101	35.7		44	56 mo	$P = .006$ for progression-free survival
Eichhorst et al,[19] 2006	Fludarabine	180	83	7	20	80% alive at 3 y in both groups	All patients were <66 y. $P < .001$ in favor of fludarabine + cyclophosphamide for overall response rate and complete response; $P = .001$ for progression-free survival in favor of fludarabine + cyclophosphamide
	Fludarabine + cyclophosphamide	182	94	24	48		
Robak et al,[71] 2006	Cladribine	166	78	21	23.5	51.2 mo	CMC had better complete response than 2-CDA ($P = .004$), but all other comparisons were not significant
	Cladribine + cyclophosphamide	162	83	29	22.4	Not reported	
	Cladribine + mitoxantrone + cyclophosphamide	151	80	36	23.6	Not reported	
Flinn et al,[20] 2007	Fludarabine	137	59.5	4.6	19.2	79% alive at 2 y ($P = .69$)	$P < .01$ for overall response rate, <.001 for complete response, and <.0001 for progression-free survival in favor of fludarabine + cyclophosphamide
	Fludarabine + cyclophosphamide	141	74.3	23.4	31.6		
Catovsky et al,[72] 2007	Chlorambucil	387	72	7	20	59%	$P < .001$ for overall response rate and complete response in favor of fludarabine + cyclophosphamide vs fludarabine, that was superior to chlorambucil; progression-free survival was better in fludarabine + cyclophosphamide group ($P < .001$) vs both
	Fludarabine	194	80	15	23	52%	
	Fludarabine + cyclophosphamide	196	92	38	43	54% at 5 y (not significant)	
Eichhorst et al,[60] 2009	Chlorambucil	100	51	0	18	64 mo	All patients >65 y (median, 70 y); $P = .003$ and $P = .01$ for overall response rate and complete response respectively, favoring fludarabine. Progression-free survival was not significant
	Fludarabine	93	72	7	19	46 mo ($P = .15$)	
Knauf et al,[73,74] 2009 and 2012	Chlorambucil	157	31	10.8	8.8	Not significant (median follow-up, 54 mo)	Overall response rate, complete response, and progression-free survival were superior with bendamustine ($P < .001$)
	Bendamustine	162	68	21	21.2		
Robak et al,[75] 2010	Fludarabine + cyclophosphamide	212	82	46	27.2	Not significant	Overall response rate, complete response, and progression-free survival were all not significant
	Cladribine + cyclophosphamide	211	88	47	28.08		
Mulligan et al,[76] 2014	Chlorambucil	77	59	8	9	91 mo	$P = .001$ favoring cladribine; not significant for overall survival among the 3 treatment groups
	Cladribine	72	70	12	25	96 mo	
	Fludarabine	74	67	7	10	82 mo	

Abbreviations: CAP, cyclophosphamide + doxorubicin + prednisone; ChOP, cyclophosphamide + vincristine + doxorubicin + prednisone.

[a] *Upfront* indicates that patients receive treatment for the first time once they require therapy.

Table 3. Prospective Phase 3 Randomized and Select Phase 2 Trials that Included Immunotherapy or Chemoimmunotherapy for Upfront Chronic Lymphocytic Leukemia Therapy[a]

Source	Therapy Comparisons	No. of Patients	Overall Response Rate, %	Complete Response, %	Survival		Comments
					Progression-free	Overall	
Hillmen et al,[77] 2007	Chlorambucil	148	55	2	11.7	84% alive in both groups at a median follow-up of 24.6 mo	Overall rersponse rate, complete response, and progression-free survival all favored alemtuzumab (P < .0001)
	Alemtuzumab	149	83	24	14.6		
Hallek et al,[3] 2010	Fludarabine + cyclophosphamide	409	85	23	32.8	83%	P < .0001 favoring fludarabine + cyclophosphamide + rituximab for progression-free survival and <0.001 for overall survival
	Fludarabine + cyclophophamide + rituximab	408	93	44.5	51.8	87% alive at 3 y	
Lepretre et al,[31] 2012[b]	Fludarabine + cyclophophamide + rituximab	82	90	33.7	83%	90.1%	Median follow-up, 38 mo; progression-free and overall survival were not significant between groups
	Fludarabine + cyclophosphamide + campath (alemtuzumab)	83	91	19.2	72.5% progression-free at 3 y	86.4% alive at 3 y	
Fischer et al,[29] 2012	Bendamustine + rituximab	117	88	23.1	Event-free survival, 33.9%	90.5% alive	Phase 2; median follow-up, 27 mo
Goede et al,[37] 2014	Chlorambucil	118	31.4	0	11.1	Not significant (median not reported)[c]	Overall response rate, complete response, and progression-free survival were all in favor of combination groups vs chlorambucil; progression-free survival favored chlorambucil + obintuzumab vs chlorambucil + rituximab (P < .001)
	Chlorambucil + rituximab	233	65.7	7.3	16.3		
	Clorambucil + obintuzumab	238	77.3	22.3	26.7		
Geisler et al,[78] 2014	Fludarabine + cyclophosphamide	139	78	43	37% vs 53% at 3 y	Not significant[d]	Included high-risk patients defined as unmutated *IgVH*, 17p or 11q, or trisomy 12 Post hoc analysis showed that overall survival improved in patients <65 years receiving fludarabine + cyclophosphamide + alemtuzumab (85% vs 76%, P = .035).
	Fludarabine + cyclophosphamide + subcutaneous alemtuzumab	133	88	64			
Hillmen et al,[79] 2014	Chlorambucil + rituximab	100	84	10	23.5	Not reached	Phase 2; median follow-up, 30 mo

Abbreviation: *IgVH*, immunoglobulin variable heavy chain gene.

[a] *Upfront* indicates that patients receive treatment for the first time once they require therapy.

[b] Recruitment was halted prematurely because of excess toxicity in the fludarabine + cyclophosphamide + alemtuzumab group (8 deaths, 5 from infection)

[c] Twenty percent died in the chlorambucil group, 15% in the chlorambucil + rituximab group, and 9% in the chlorambucil + obintuzumab group. P = .002 for chlorambucil/obintuzumab vs chlorambucil but not significant between chlorambucil/obintuzumab and chlorambucil/rituximab.

[d] Overall survival was better in patients younger than 65 years receiving Fludarabine + cyclophosphamide + subcutaneous alemtuzumab (85% vs 76%, P = .03).

generally dependent on patients' performance status and comorbidities. The German CLL Study Group classifies patients as fit or unfit based on their renal function (unfit when the glomerular filtration rate is <70 mL/min) and their scores on the cumulative illness rating scale (unfit when the combined score is ≥6). Treatment regimens are then adjusted based on fitness level (Table 4).[32] As new molecular targets become more integrated into current therapies, these guidelines are likely to be further revised and refined.

Critical Questions in CLL

1. Treating Richter Syndrome

Richter syndrome occurs at a rate of 0.5% to 1% per year in patients with CLL and represents the transformation of CLL into an aggressive lymphoma.[39] Patients with Richter syndrome experience a change in their clinical course and disease behavior, with rapid progression of adenopathy, elevated serum tumor marker levels, and development of B symptoms.[40] The majority of these transformations are compatible with diffuse large B-cell lymphoma histologically, although lower-grade lymphomas and Hodgkin transformation have been described. Although molecular predisposition to Richter syndrome continues to be refined,[41] advanced-stage disease and enlarged lymph nodes (>3 cm on clinical examination) have been proposed as predictors for higher risk of transformation.[41] The contribution of prior CLL therapy to the development of Richter syndrome remains unknown.[42,43] The prognosis of the syndrome is poor. Richter syndrome prognostic scores rely on performance status, prior

Table 4. National Comprehensive Cancer Network Upfront Treatment Guidelines for Chronic Lymphocytic Leukemia

Factor	Guidelines
National Comprehensive Cancer Network	
Diagnosis and staging	Exclude monoclonal B-lymphocytosis Performing a lymph node biopsy is recommended if diagnosis cannot be established by immunophenotyping on the peripheral blood Computed tomography scans are recommended only in the context of clinical trials Bone marrow biopsy is performed if clinically indicated but not required
Prognostic factors	Chromosomal analysis by FISH to detect 17p and/or 11q deletions. ZAP-70 and mutational analyses of the *IgVH* are recommended in clinical trials. Assessment of minimal residual disease is recommended in prospective clinical trials.
Upfront treatment[a]	
Rai stage 0, 1, 2	Observe unless there are indications to treat (Box 4)
Rai stage 3 or 4 or early stages with indications to treat:	
Frail patients	Anti-CD20 antibody + chlorambucil[b] Chlorambucil Rituximab Steroids
Fit patients	
17p deletion	Clinical trial Chemoummunotherapy[c] Ibrutinib Combination antibodies Rituximab plus high-dose steroids (consider allogeneic HSCT in responding patients)
11q deletion	Clinical trial Chemoimmunotherapy tailored in dose and intensity based on age and comorbidity[b] (consider allogeneic HSCT in patients who achieve less than complete remission)
No 17p or 11q deletion	
Age <70 y	Chemoimmunotherapy (various regimens)[b]
Age ≥70 y	Chemoimmunotherapy[b] Antibody-only therapy Chemotherapy alone[d]
European Leukemia Network	
Diagnosis and staging	Exclude monoclonal B-lymphocytosis Computed tomography scans are recommended only in the context of clinical trials Bone marrow biopsy is desirable but not required for diagnosis
Prognostic factors	Chromosomal analyses and FISH for 17p and 11q deletions are desirable but other prognostic analyses are recommended in the context of prospective clinical trials Assessment of minimal residual disease is recommended in prospective clinical trials
Upfront treatment	
Early-stage asymptomatic disease	Observe
Advanced-stage disease or early-stage symptomatic disease	
Younger (<65 y)	Purine analogue–based therapy in combination with anti-CD20 antibodies
Older, less fit (≥65 y)	Chlorambucil as monotherapy or with anti-CD20 antibodies
German CLL Study Group	
Diagnosis, staging, and prognostic	Similar to above guidelines
Upfront treatment	
Early-stage asymptomatic disease	Observation
Symptomatic early-stage or advanced-stage disease	
Fitness level[e]	
Go-go	
No 17p or Tp53 deletion or mutation	Fludarabine + cyclophosphamide + rituximab
17p deletion, Tp53 mutation, or both	Allogeneic HSCT after induction if complete or partial response achieved
Slow-go	
No 17p or Tp53 deletion or mutation	Chlorambucil plus anti-CD20 antibody
17p deletion, Tp53 mutation, or both	Alemtuzumab, ofatumumab, or rituximab plus high-dose steroids

Abbreviations: FISH, fluorosence in-situ hybridization; HSCT, hematopoietic stem cell transplantation; *IgVH*, immunoglobulin variable heavy chain gene; ZAP-70, zeta-associated protein-70.

[a] *Upfront* indicates that patients receive treatment for the first time once they require therapy.

[b] Rituximab or obinutuzumab.

[c] Various chemoimmunotherapy regimens combining rituximab with a variety of combination chemotherapeutic programs.

[d] Variety of chemotherapeutic agents: alkylators or purine analogues.

[e] Fitness level is assessed based on serum creatinine level and glomerular filtration rate (<70 mL/min) or geriatric assessment using the Cumulative Illness Rating Scale, with patients scoring higher than 6 on that scale considered unfit. *Slow go* indicates that patients did not fulfill either criterion (glomerular filtration rate or Cumulative Illness Rating Scale).

therapies, response to prior interventions, elevated low-density lipoprotein cholesterol levels, thrombocytopenia, and enlarged lymph nodes.[40,44] Parikh et al[41] proposed that for the 20% of patients with Richter syndrome who have a clone unrelated to the underlying CLL, standard therapy for large-cell lymphoma should be pursued. For the bulk of remaining patients, clinical trials are favored, because standard therapies have provided suboptimal results. Outside of clinical trials, it is appropriate to induce patients with Richter syndrome into the best remission possible using intensive chemoimmunotherapy regimens followed by allogeneic transplantation in suitable individuals.

2. Treating Hemolytic Anemia and Immune-Mediated Thrombocytopenia

Autoimmune hemolytic anemia (AIHA) is a well-known complication of CLL. Mauro et al[45] reported that the incidence of AIHA was 1.3% among 1203 patients with CLL treated at a single institution, but in other case series up to 11% of cases have been reported. Risk factors to developing AIHA have varied, but male sex, older age, and higher white blood cell counts have been reported to increase risk. It has been recommended that a Coombs test be performed for any anemic patient with CLL to differentiate AIHA from progressive disease.[46] Historically, steroids have been the first line of treatment. However, some patients do not respond, while others are unable to tolerate high doses of systemic steroids. Some patients with steroid failure have used cyclosporine or mycophenolate with moderate success.[46] The combination of rituximab + cyclophosphamide + dexamethasone to treat refractory AIHA in patients with CLL has proven effective.[46] In the absence of other clear indications to treat the underlying CLL, single-agent rituximab appears to be a reasonable choice, but rituximab + cyclophosphamide + dexamethasone can be considered. In patients with refractory disease, treating the underlying CLL is appropriate. Also, while some observers have suggested that purine analogues could induce AIHA, Dearden et al[47] reported a beneficial effect for the fludarabine + cyclophosphamide combination, because patients receiving that combination had lower incidence of AIHA compared with others receiving chlorambucil.

Immune-mediated thrombocytopenia occurs in 2% to 3% of patients with CLL. The diagnosis is made on clinical grounds by ruling out other causes of thrombocytopenia, which might require performing a bone marrow biopsy to exclude progressive disease infiltration.[6] Evans syndrome is defined when patients have immune-mediated thrombocytopenia and AIHA at the same time. Treatment is similar to that for AIHA, although some observers have recommended splenectomy for patients with refractory nonresponding disease.

3. The Role of Minimal Residual Disease

Approximately 25% of patients who demonstrate a complete response by standard response criteria could harbor residual disease detected molecularly or by flow cytometry.[48] Although it remains uncertain if there is a benefit from treating CLL when residual clones are present as opposed to when a true hematologic and clinical relapse occur, several lines of evidence have supported the notion that the presence of minimal residual disease (MRD) after cytotoxic chemotherapy predicts inferior overall survival.[48,49] Several strategies have been proposed to achieve MRD negativity, most of which have incorporated induction with chemoimmunotherapy,[27,50] immunotherapy,[49] consolidation immunotherapy postinduction,[51-53] or consolidation autologous stem cell transplantation.[54-56] The International Working Group for CLL recommends the incorporation of MRD detection as an exploratory end point in prospective clinical trials and not to initiate therapy based solely on the fact that MRD is detected.[5] At present, there is no level I evidence to support eradicating MRD in patients achieving major responses using standard first-line therapies.

4. Treating Older Patients With CLL

The median age at diagnosis for patients with CLL is more than 70 years. Most clinical trials of CLL therapy enrolled significantly younger patients. Understanding how to best treat older patients with CLL is critical. Older patients who received fludarabine + cyclophosphamide + rituximab had lower response rates and did not benefit from treatment as much as did their younger counterparts.[57,58] Shanafelt et al[59] proposed that replacing fludarabine with pentostatin, the less myelosuppressive purine analogue, is better tolerated by older patients with CLL and does not compromise responses. Notably, patients older than 70 years can have coexisting morbidities that could preclude administration of aggressive chemoimmunotherapy programs. Eichhorst et al[60] conducted a multicenter phase 3 trial in patients with CLL older than 65 years comparing first-line therapy with fludarabine vs chlorambucil. A total of 193 patients with a median age of 70 years were randomized. Although fludarabine produced a higher overall response rate and complete response rate, there was no between-group difference in progression-free survival (19 months with fludarabine, 18 months with chlorambucil; $P = .70$). Moreover, fludarabine did not improve overall survival (46 months vs 64 months in the chlorambucil group; $P = .15$).

These results and other phase 2 studies argued that chlorambucil is a viable option for older patients with CLL. Accordingly, the German CLL Study Group conducted a prospective phase 3 randomized trial comparing chlorambucil alone with chlorambucil plus either rituximab or obinutuzumab in patients with CLL who had coexisting morbidities defined as either reduced glomerular filtration rate (<70 mL/min) or cumulative score of 6 or more on the Cumulative Illness Rating Scale.[37] Most enrolled patients were older than 70 years and had coexisting medical conditions. The combination of chlorambucil + obinutuzumab proved safe and more effective than the comparator groups. Specifically, overall and progression-free survival favored obinutuzumab + chlorambucil compared with chlorambucil alone ($P < .001$). Progression-free survival, but not overall survival, favored the obinutuzumab group when compared with rituximab ($P < .001$). This study was the first specifically designed for patients with CLL and comorbidities and has provided level I evidence on the survival superiority of chemoimmunotherapy over standard chemotherapy.

Other studies have explored immunomodulatory agents such as lenalidomide in this patient population. Strati et al[61] reported the long-term outcomes of 60 patients with CLL older than 65 years who received lenalidomide monotherapy on an escalated dosing schedule. At a median follow-up of 4 years, overall survival was 82%, and time to treatment failure was not reached. Although the definition of elderly varied among studies, future studies in this patient population are starting to incorporate geriatric and comorbidity assessments as opposed to chronological age.[6]

5. Infections in CLL

The defective immune system in CLL, coupled with the use of therapies that deplete T cells and B cells, predisposes affected individuals to infectious complications that have been a major source of morbidity and mortality in patients with CLL. Griffiths et al[62] reported that the incidence and severity of infectious complications were less in patients with CLL who received intravenous gamma globulin prophylactic therapy. To that end, this approach is recommended for patients with CLL who have had repeated infectious episodes that can be attributed to hypogammaglobulinemia. Molica et al[63] conducted a crossover study of 42 patients with CLL who received either low-dose gamma globulin prophylaxis every 4 weeks for 6 months or no treatment. A protective effect for gamma globulin was clearly demonstrated. Of importance is the recognition of some unique infectious complications and pathogens that occur when specific therapy is instituted. Cytomegalovirus reactivation occurs in up to 25% of patients receiving alemtuzumab.[64] Prolonged, depressed immune surveillance associated with purine analogues might lead to Listeria or Pneumocystis infections.[65] Although high-quality evidence is lacking, it is reasonable to consider giving prophylactic antiPneumocystis and antiviral prophylaxis to patients with CLL while they are receiving antineoplastic therapy. This recommendation is based on the observation that all contemporary CLL clinical trials used this approach.

6. Role of Transplantation in CLL

Current evidence supports discussing allogeneic hematopoietic stem cell transplantation (HSCT) in patients with poor risk disease, specifically those who harbor the 17p mutation, P53 mutation, or both, even in their first remission.[66] Despite the fact that patients with CLL are diagnosed at an older age, advances in supportive measures, the utilization of reduced-intensity conditioning programs, and successful HSCT from unrelated donors or from those who are less than a complete match have all led to some patients attaining long-term disease control and possible cure.[67] In fact, Sorror et al[68] reported a 2-year overall survival of 60% among 64 patients with advanced CLL who have undergone reduced-intensity conditioning–based allogeneic HSCT. Patients who received a transplant from an unrelated donor fared better than their counterparts, suggesting a beneficial graft vs leukemia effect. Based on the National Comprehensive Cancer Network recommendations,[33] early referral of patients with high-risk CLL to a transplantation center to better coordinate care and plan the induction regime is advised.

Conclusions

Chronic lymphocytic leukemia is a heterogenous disease with variable clinical course that has become more predictable with better understanding of disease biology and newer prognostic factors. Chemoimmunotherapy—specifically, fludarabine + cyclophosphamide + rituximab—has become the default standard in young, fit patients with good renal function, because it was the only combination program to improve overall survival in a randomized phase 3 setting in this patient population. Other regimens are more applicable to older and frailer patients who are unlikely to tolerate fludarabine + cyclophosphamide + rituximab. In fact, the combination of chlorambucil and obinutuzumab has improved survival in older patients with CLL who have comorbidities. Novel targeted therapies mainly directed at disrupting the B cell receptor pathway have emerged as valuable tools in the armamentarium for treating CLL. Whether these biologic agents will replace standard chemotherapy remains to be seen and will certainly be the subject of future prospective clinical trials.

Clinical Bottom Line

- Improvements in response rates, durations of response, progression-free survival, and overall survival have been achieved in patients with CLL.
- Chemoimmunotherapy, the addition of anti-CD20 antibodies to combination chemotherapy, is now the standard approach for patients with CLL receiving treatment for the first time once they require therapy. Despite recent advances in CLL risk stratification, there are no indications to initiate therapy in asymptomatic patients unless in the context of clinical trials.

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Drafting of the manuscript: Nabhan, Rosen.
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