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The diagnosis of CLL, the role of prognostic factors in determining treatment goals, and new first- and second-line treatment strategies are reviewed.

Chronic Lymphocytic Leukemia: Putting New Treatment Options Into Perspective

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Chronic lymphocytic leukemia (CLL) is a monoclonal B-cell malignancy that afflicts mainly older individuals. Since many patients are diagnosed in the earliest stages, the course of the disease may be indolent and asymptomatic, requiring no therapy. For those who are diagnosed in advanced stages or whose disease becomes symptomatic, treatment is indicated. Advances in identifying prognostic factors, such as cytogenetics, IgHV mutational status, CD38, TP53, and ZAP-70, are helping physicians better predict who is more likely to have progressive disease and thus needs more frequent monitoring. Some of these prognostic factors are also helping to guide therapy choices as they can predict response to treatment and/or duration of response.

Recent advances in treatment options have moved beyond traditional management with alkylating agents and purine analogs into regimens combining these two chemotherapy classes with monoclonal antibodies targeting CD20. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) has become the most effective therapy option to date for CLL. Compared with fludarabine and cyclophosphamide, FCR has shown higher complete response rates and longer progression-free survival. Bendamustine, a unique alkylating agent with purine analog properties, has recently been approved by the FDA for treatment of CLL and provides a new alternative to existing therapies. Initial trials combining bendamustine with rituximab are showing promise for both untreated and relapsed/refractory disease. Other agents recently approved and/or being tested, such as ofatumumab, flavopiridol, and lenalidomide, are demonstrating activity in the relapsed setting.

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The authors disclose that this article discusses unlabeled/unapproved use of the drugs flavopiridol and lenalidomide for patients with chronic lymphocytic leukemia.

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Introduction

Chronic lymphocytic leukemia (CLL), a monoclonal B-cell malignancy with a low level of proliferation, is characterized by a progressive accumulation of mature-appearing but functionally incompetent, malignant B lymphocytes.¹ CLL is the most common form of leukemia diagnosed in Western countries.² It accounts for over 15,000 new diagnoses (almost 40% of all leukemias) and over 4,000 deaths per year in the United States.² The median age at diagnosis is 72 years, and the prevalence is higher among Caucasians and males.² Over half of CLL patients are diagnosed with early-stage disease (Rai stage 0).³

Though CLL has historically been considered an indolent and incurable disease, the clinical course is heterogeneous, with some patients progressing rapidly and

Table 1. — Signs and Symptoms of Symptomatic Chronic Lymphocytic Leukemia

Fatigue (due to anemia)
Infection
Lymphadenopathy
Splenomegaly
Hepatomegaly
“B” symptoms (rare) — fevers, weight loss, night sweats

succumbing within 2 years, while others live for over 20 years without developing symptoms or requiring therapy.^{1,4} As a disease of the elderly (more than two-thirds of patients are over 65 years of age), treatment of CLL needs to be tailored to each patient’s fitness level and must take into account patient comorbidities.

Historically, the approach to management of CLL focused on reducing tumor bulk and alleviating symptoms while maintaining a good quality of life. Treatment options included alkylating agents, purine analogs, or a combination of the two.⁴ More effective combination regimens, such as fludarabine, cyclophosphamide, and rituximab (Rituxan®, Genentech, Inc, South San Francisco, CA) (FCR), have recently been shown to prolong progression-free survival (PFS) and overall survival (OS), thereby changing the treatment paradigm to one with a goal of complete elimination of the disease in patients who are both younger and older but physically fit.⁵ Therefore, more aggressive management may be warranted for patients who can tolerate the additional toxicities.

Advances in the identification of new prognostic factors and in new treatments for CLL have been seen in recent years. In the future, identification of more sensitive prognostic markers may help physicians make treatment decisions by identifying those patients who may have more indolent or aggressive forms of CLL and by predicting treatment response and duration.³ Chemoimmunotherapy has claimed the title of most effective treatment strategy for initial management of CLL. This review examines the diagnosis of CLL, the role of prognostic factors in determining treatment goals, and new first- and second-line treatment strategies.

Clinical Presentation

Many CLL patients present without symptoms, but they are diagnosed as a result of routine blood testing.¹ Clinicians need to be aware of the mix of clinical signs and symptoms that may present with this malignancy (Table 1). Patients presenting with symptoms tend to be diagnosed with disease at a more advanced stage. B symptoms are not common and, if present, may represent Richter’s transformation to a more aggressive diffuse large B-cell lymphoma.¹

Diagnosis, Staging, and Risk Stratification

The diagnostic workup begins with a complete blood count, a peripheral blood smear examination, and a physical examination. B-cell lymphocytosis of greater than $5 \times 10^9/L$ in the peripheral blood for at least 6 months is diagnostic for CLL.⁶ Peripheral blood smear will show a majority of small, mature-appearing lymphocytes with a narrow border of cytoplasm and a dense nucleus. Bone marrow biopsy is not required for diagnosis of CLL. Flow cytometry can be performed on the peripheral blood to confirm clonality of B lymphocytes. The classic immunophenotyping of CLL shows expression of CD5, CD19, and CD23, with dim expression of CD20 and CD79b and IgG- κ or λ light chain restriction.⁶

Clinical staging proposed by Rai (in the United States) and Binet (in Europe) served as the first widely used staging systems for CLL and remain in use today (Table 2).^{3,6} They are based only on physical examination and complete blood count.^{7,8} The revised Rai staging system places patients in low-, intermediate-, and high-risk categories based on the presence or absence of lymphocytosis, enlarged lymph nodes, splenomegaly, hepatomegaly, anemia, and/or thrombocytopenia. These staging systems are simple to use and predict prognosis, but they do not identify who has indolent or progressive disease and do not predict response to treatment.⁹

Investigators at M.D. Anderson Cancer Center recently proposed and tested a prognostic index that combines six factors that are independently associated with survival: age, Rai stage, sex, absolute lymphocyte count, β 2-microglobulin, and number of involved lymph node regions.¹⁰ Compared with using clinical stage alone, use of this index was a better predictor of survival and has been validated in two subsequent tri-

Table 2. — Staging of Chronic Lymphocytic Leukemia

Modified Rai Classification	Criteria	Binet Stage	Criteria
Low risk (Rai stage 0)	Lymphocytosis alone	A	Enlarged lymph nodes (> 1 cm) or organomegaly in ≤ 2 specified areas
Intermediate risk (Rai stages I and II)	Lymphocytosis, enlarged lymph nodes, and splenomegaly and/or hepatomegaly	B	Enlarged lymph nodes (> 1 cm) or organomegaly in ≥ 3 specified areas
High risk (Rai stages III and IV)	Lymphocytosis and disease-related anemia (hemoglobin < 11 g/dL) and/or thrombocytopenia (platelet count < $100 \times 10^9/L$)	C	Hemoglobin < 10 g/dL and/or platelet count < $100 \times 10^9/L$

als to be applicable to Rai stage 0 patients and to predict time to treatment initiation.^{11,12}

In addition to clinical staging, traditional prognostic factors for stratifying risk of disease progression have included high serum levels of β 2-microglobulin and soluble CD23, diffuse bone marrow infiltration, and short lymphocyte doubling time.³ The identification and validation of new prognostic factors allow for the stratification of patients into high-, intermediate-, and low-risk categories for disease progression (Table 3).^{13,14}

The most meaningful predictors of disease progression at this time may be cytogenetic abnormalities identified by fluorescence in situ hybridization (FISH) analysis.³ This technique has identified chromosomal abnormalities in over 80% of CLL cases. Investigators identified deletion 13q as the most common cytogenetic abnormality (55%) and noted it to be associated with a favorable prognosis and the longest survival (133 months).¹⁴ In addition, deletion of 11q (18%) was associated with development of extensive lymphadenopathy and shorter survival (79 months), and deletion 17p13 (7%) correlated with shorter treatment-free intervals, shorter survival (32 months), and resistance to therapy.¹⁴

Other predictors of disease progression are the mutational status of immunoglobulin heavy chain (IgHV) and its surrogates, such as the expression of ZAP-70 and CD38.³ All of these markers have successfully predicted OS and the time to initiation of treatment in CLL patients.^{3,13} While IgHV status does not predict response to therapy, it can predict duration of response.^{13,15,16} All of these prognostic factors may help physicians to determine the most appropriate monitoring frequency during the “watch-and-wait” period and counsel patients about what they might expect in terms of anticipated treatment-free period and survival. At this time, with the exception of del(17p), these prognostic factors should not be used to individualize treatment selection outside the context of a clinical trial.

The detection of poor prognostic factors is not an indication for earlier treatment in asymptomatic patients.

Goals of Therapy

Historically, the goal for treatment of CLL has focused on reducing disease-related symptoms such as lymphadenopathy or splenomegaly. Today, improved treatment strategies make it possible to attain a complete response (CR) in a higher percentage of patients. Until recently, response criteria were based on the 1996 National Cancer Institute-sponsored Working Group criteria in which only peripheral blood and physical examination were required.¹⁷ Hallek et al⁶ updated the criteria for response after treatment to include assessments of bone marrow and CT scans (Table 4). Recent data from the use of chemoimmunotherapy regimens demonstrate a prolongation of PFS in patients who achieve a CR. However, physicians must select patients carefully when pursuing CR as their treatment goal. Risk of higher toxicity generally accompanies regimens that produce higher CR rates, making many patients poor candidates for more aggressive therapy.

First-Line Therapy

Single-Agent Chemotherapy

For decades traditional chemotherapy for CLL has included monotherapy with alkylating agents such as chlorambucil.¹⁸ Chlorambucil still plays a role in treating elderly CLL patient in the palliative setting because it is convenient as an oral agent, is relatively inexpensive, and has a low toxicity profile.¹⁸ Randomized phase III trials have since shown that monotherapy with purine analogs such as fludarabine, cladribine, and pentostatin results in superior overall response (OR) and CR rates compared with alkylating agents (Table 5).¹⁹⁻²³ No statistically significant differences in OS were identified in any of these trials, including the recently published German CLL Study Group (GCLLSG) CLL5 trial that failed to demonstrate superior PFS in the fludarabine arm.²⁴

Bendamustine

Bendamustine (Treanda[®], Cephalon, Inc, West Chester, PA), a derivative of mechlorethamine, is a bifunctional alkylating agent that contains a purine-like benzimidazole ring.²⁵ Like other alkylating agents, its cytostatic action is cell-cycle nonspecific.²⁵ However, bendamustine is unique in that it has additional mechanisms of action beyond causing single- and double-stranded DNA breaks.²⁶ It induces many proapoptotic genes, thereby restoring p53/tumor suppressor gene function and causing a strong activation of intrinsic apoptosis.²⁶ Bendamustine also inhibits mitotic checkpoints that are essential to delivering undamaged DNA for mitosis. When significantly damaged DNA is present during mitosis, mitotic catastrophe, a necrotic cell death pathway that is distinctly different from apoptosis, is trig-

Table 3. — Risk Categories for Selected Prognostic Factors

Risk Category	Prognostic Factor
High	del(17p)/TP53 gene mutation (p53 tumor suppressor gene locus) del(11q) (ataxia-telangiectasia-mutated gene locus) IgHV unmutated CD38 positive ZAP-70 positive lymphocyte doubling time < 6 mos β 2-microglobulin > 3.5 mg/L
Intermediate	trisomy 12
Low	del(13q) normal cytogenetics mutated IgHV

gered. This initiation of mitotic catastrophe by bendamustine may explain its clinical activity in drug-resistant CLL.²⁶

Bendamustine was recently compared to chlorambucil for treatment-naïve CLL in a phase III randomized trial.^{27,28} Given at 100 mg/m² on days 1 and 2 of a 28-day cycle, bendamustine had superior outcomes with OR rates of 67% compared with 30% with chlorambucil. CR rates were significantly higher with bendamustine (31% vs 2%), which translated to a significantly longer PFS of 22 months compared with 8 months with chlorambucil. Bendamustine is FDA-approved for front-line treatment of CLL.²⁵

Monoclonal Antibodies

The surface antigens CD20 and CD52 are expressed by CLL B cells and provide targets for therapy using the monoclonal antibodies rituximab and alemtuzumab (Campath®, Genzyme Corp, Cambridge, MA).

Rituximab

Rituximab, a chimeric monoclonal antibody targeting CD20, has only modest activity at standard doses.²⁹ Investigators have tested higher or more frequent dosing strategies, with seemingly better results. However, none of these strategies have been compared to standard dosing in a randomized trial; therefore, superiority remains to be proven.^{30,31} Despite only modest responses to single-agent rituximab, combinations of rituximab with chemotherapy have proven to be more effective for CLL, as discussed in the Chemoimmunotherapy section.

Alemtuzumab

Alemtuzumab, a humanized monoclonal antibody targeting CD52, has shown notable activity as monotherapy for CLL. After sufficient activity was shown in the relapsed/refractory setting, a randomized phase III trial was conducted comparing alemtuzumab to chlorambucil in treatment-naïve, progressive CLL.^{32,33} OR and CR rates were 83% and 24%, respectively, for alemtuzumab and 55% and 2% for chlorambucil (both *P* < .0001). Median PFS was also significantly longer in the alemtuzumab arm. Minimal residual disease (MRD) negativity was achieved in 7% of patients receiving alemtuzumab and in none of those receiving chlorambucil.³³ Alemtuzumab has also shown efficacy in treating patients with high-risk cytogenetics, such as del(11q), del(17p), and p53 mutations, making it a treatment option that can be considered for these patients with poor prognostic features.^{34,35} Alemtuzumab has been FDA-approved for front-line treatment of CLL; however, efficacy in the front-line setting has been established only relative to chlorambucil.

Combination Chemotherapy

Since fludarabine prevents repair of DNA interstrand crosslinks caused by alkylating agents, thereby reducing leukemia cell resistance, purine analogs and alkylating agents have been combined in an attempt to improve responses.⁴ The most extensively studied combination chemotherapy regimen for CLL is fludarabine plus cyclophosphamide (FC).¹⁸ Three randomized trials have compared fludarabine alone to the FC com-

Table 4. — Criteria for Response After Treatment for Chronic Lymphocytic Leukemia, According to the International Workshop on Chronic Lymphocytic Leukemia/NCI Working Group Guidelines

Parameter	Complete Remission (CR)*	Partial Remission (PR)*	Progressive Disease (PD)*
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4,000/μL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules; hypocellular marrow defines CRi	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	> 100,000/μL	> 100,000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline due to CLL
Hemoglobin	> 11 g/dL	11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline due to CLL
Neutrophils‡	> 1,500/μL	> 1,500/μL or > 50% improvement over baseline	

* CR: All criteria must be met and patient must be free of disease-related constitutional symptoms, PR: at least 2 criteria from group A plus one of the criteria from group B must be met, PD: At least one criteria from group A or B must be met, CRi = CR with incomplete marrow recovery.

† Sum of the products of multiple lymph nodes as seen on CT scan in clinical trials, or physical examination in clinical practice.

‡ Not relevant for all response categories.

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bination. All three trials demonstrated significantly higher OR, CR, and PFS rates for the combination regimen (Table 5).³⁶⁻³⁸ Of note, FC caused more grade 3/4 thrombocytopenia and neutropenia, despite the use of growth factor support in one trial. The incidence of serious infections, however, was not increased over fludarabine alone.^{36,37}

Chemoimmunotherapy

In vitro data suggested synergy between fludarabine and rituximab in a follicular cell line that was resistant to each drug alone.³⁹ This observation inspired the development of protocols combining chemotherapy with immunotherapy for treatment of CLL in several phase II trials. Schulz et al⁴⁰ examined the safety and efficacy of combining fludarabine and rituximab (FR) in 31 previously treated or untreated patients with CLL. The OR rate was 87%, the CR rate was 32%, and the median duration of response was 75 weeks. Investigators saw similar outcomes in the CALGB 9712 trial when FR was administered in either a sequential or concurrent manner to previously untreated CLL patients. Updated results after a median follow-up of 92 months demonstrated that OR and CR rates in the 104 patients randomized were higher in the concurrent administration arm (90% and 47% vs 77% and 28%). The median PFS was 37 months and median OS was 85 months.^{41,42} All patients from this trial were combined into one group and retrospectively compared to the fludarabine arm of the CALGB 9011 trial, which had the same inclusion criteria as CALGB 9712.⁴³ The FR group had higher OR (0.84 vs 0.63, $P = .0003$) and CR (0.38

vs 0.20, $P = .002$) compared with the group receiving fludarabine alone. Despite these trials being only phase II and retrospective, they have had a tremendous impact on clinical practice, with many physicians adopting the use of FR as front-line therapy for CLL.

Investigators have added rituximab to the FC regimen (FCR) in phase II and III trials. Keating et al⁴⁴ tested FCR in 300 previously untreated patients with CLL in a single-institution phase II trial with the goal of improving CR rates to above 50%. At a median follow-up of 6 years, the OR rate was 95%, the CR rate was 72%, and the 6-year OS and failure-free survival rates were 77% and 51%, respectively. Median time to progression (TTP) was 80 months. The CR rate was significantly higher for patients with β 2-microglobulin less than twice the upper limit of normal.⁴⁵

In response to these promising results, the GCLLSG compared FCR to FC in a multicenter, international phase III randomized trial.⁵ In a recent update (after a median observation time of 37.7 months), the group reported a higher OR rate with FCR compared to FC (95.1% vs 88.4%) and more CRs (44.1% vs 21.8%). FCR vs FC also produced a longer median PFS (51.8 months vs 32.8 months) and higher OS at 37.7 months (84.1% vs 79%) ($P = .01$), though the superiority in OS was observed only in patients with Binet stage A and B disease. Patients with del(17p) were the only prognostic subgroup to not achieve an improvement in PFS and OS. FCR had a higher rate of hematologic toxicity (especially neutropenia), but this did not translate to a higher infection rate. This is the first randomized trial to demonstrate a significant improvement in OS from a

Table 5. — Randomized Trials Comparing Alkylating Agent-Containing Regimens to Single-Agent Therapies for Previously Untreated Chronic Lymphocytic Leukemia

Trial (Year)	Study	No. of Patients	CR (%)	OR (%)	Median Response Duration (mos)	Median Survival
Rai et al ¹⁹ (2000) CALGB 9011	Fludarabine	170	20	63	25	66 mos
	Chlorambucil	181	4	37	14	56 mos
Johnson et al ²¹ (1996)	Fludarabine	52	23	71	NR	60% at 4 yrs
	CAP	48	17	60	6.9	60% at 4 yrs
Leporrier et al ²² (2001)	Fludarabine	341	40	71	32	69 mos
	CAP	240	15	58	28	70 mos
	CHOP	305	30	72	30	67 mos
Robak et al ²³ (2000)	Cladribine + prednisone	126	47	87	21	78% at 2 yrs
	Chlorambucil + prednisone	103	12	57	18	82% at 2 yrs
Eichhorst et al ²⁴ (2009) GCLLSG CLL5	Chlorambucil	100	4	37	14	64 mos
	Fludarabine	93	20	63	20	46 mos
Knauf et al ^{27,28} (2009), updated	Chlorambucil	157	2	31	8	65.4 mos
	Bendamustine	162	31	68	22	not reached
Hillmen et al ³³ (2007) CAM 307	Chlorambucil	148	2	55	12	84% at 2 yrs
	Alemtuzumab	149	24	83	15	84% at 2 yrs

CAP = cyclophosphamide + doxorubicin + prednisone, CHOP = cyclophosphamide + doxorubicin + vincristine + prednisone.

particular front-line therapy for CLL (Table 6). The FDA recently granted approval to rituximab, in combination with FC, for the treatment of therapy-naive and previously treated patients with CD20-positive CLL.

Investigators have substituted pentostatin for fludarabine in the FCR regimen in an attempt to reduce myelosuppression.^{46,47} Results with the combination of pentostatin, cyclophosphamide, and rituximab (PCR) suggest comparable efficacy with fewer infectious complications in phase II trials.^{46,47} More recently, PCR was compared with FCR in untreated CLL patients in a randomized, multicenter, community-based trial.⁴⁸ The OR rates in the two groups were similar (45% with PCR and 57.5% with FCR, $P = .13$), but the PCR combination produced a significantly lower CR rate (7% vs 15% with FCR, $P = .04$). Infectious complications, the primary endpoint, did not differ between PCR and FCR (33.7% vs 30.7%). The response rates seen in this phase III multicenter trial in the community setting were lower than those reported from previous phase II trials.

While FCR has demonstrated significant efficacy, patients with $\beta 2$ -microglobulin of 4 mg/L and higher were noted to have lower CR rates and shorter OS.⁴⁵ In an attempt to improve outcomes in this high-risk subset, Parikh et al⁴⁹ added alemtuzumab to FCR (CFAR) for front-line therapy in a phase II trial. Patients were younger than 70 years and had a $\beta 2$ -microglobulin level ≥ 4 mg/L. This combination achieved a 70% CR rate and a 92% OR rate. Grade 3/4 cytopenias and infection

rates were comparable to those seen in historical high-risk patients receiving FCR. Median OS has not been reached (49+ months), and TTP was 38 months. Investigators observed remarkable CR rates in patients with the high-risk features: del(17p) and unmutated IgHV (57% and 73%, respectively). However, these remissions were not durable, as these patients had significantly shorter TTP than patients without high-risk features. CFAR appears to be an active regimen for front-line therapy of CLL. The regimen needs further testing in a multicenter trial and should be compared to FCR in a randomized fashion. Further testing of CFAR is particularly important in light of the fact that a similar regimen, FC-CAM (fludarabine, cyclophosphamide, alemtuzumab), caused an excess number of deaths due to toxicity, resulting in the trial comparing FC-CAM to FCR to be closed prematurely.⁵⁰

Fischer et al⁵¹ tested the combination of bendamustine and rituximab (BR) in untreated CLL in a multicenter phase II trial. Bendamustine was administered at 90 mg/m² on days 1 and 2 plus rituximab at 375 mg/m² with the first cycle and 500 mg/m² for subsequent cycles. A total of six cycles were given every 28 days. The OR rate was 90.9% and the clinical CR rate was 32.7%. After 18 months, median PFS has not been reached, and 75.8% of patients are still in remission. Major infections and myelosuppression were infrequent. Due to the high response rates, the ability of BR to eradicate detectable MRD in some patients, and the

Table 6. — Combination Chemotherapy and Chemoimmunotherapy Trials for Previously Untreated Chronic Lymphocytic Leukemia

Trial (Year)	Study	No. of Patients	CR (%)	OR (%)	Median PFS (mos)	Overall Survival
Eichhorst et al ³⁷ (2006) GCLLSG CLL4	Fludarabine	182	7	83	20	80.7% at 3 yrs
	FC	180	24	94	48	80.3% at 3 yrs
Flinn et al ³⁶ (2007) ECOG E2997	Fludarabine	137	5	60	19	80% at 2 yrs
	FC	141	23	74	32	79% at 2 yrs
Catovsky et al ³⁸ (2007) LRF CLL4	Chlorambucil	366	7	72	20	59% at 5 yrs
	Fludarabine	181	15	80	23	52% at 5 yrs
	FC	182	38	94	43	54% at 5 yrs
Byrd et al ⁴¹ (2003), updated (phase II) CALGB 9712	Concurrent FR	51	47	90	32	84 mos (median)
	Sequential F→R	53	28	77	40	91 mos (median)
Byrd et al ⁴³ (2005) CALGB 9011 vs CALGB 9712	Fludarabine	179	20	63	45% at 2 yrs	81% at 2 yrs
	FR + F→R	104	38	84	67% at 2 yrs	93% at 2 yrs
Tam et al ⁴⁵ (2008) (phase II) MDACC	FCR	300	72	95	80	77% at 6 yrs
Hallek et al ¹⁸ (2009) GCLLSG CLL8	FC	408	22	88	33	79% at 38 mos
	FCR	409	44	95	52	84% at 38 mos
Fischer et al ⁵¹ (2009) (phase II) CLL2M	BR	117	33	91	Not reached	Not reached at 18 mos

FC = fludarabine + cyclophosphamide, FR = fludarabine + rituximab, FCR = fludarabine + cyclophosphamide + rituximab, BR = bendamustine + rituximab.

relatively low toxicity seen in this trial, the GCLLSG is currently conducting a phase III study comparing BR to FCR in untreated CLL patients.⁵¹

Second-Line Therapy

Once a patient relapses after initial treatment of CLL, treatment selection depends on the duration of the response to initial therapy, disease-related manifestations, type of prior therapy, and genetic abnormalities within the CLL cells. Options for fludarabine-refractory patients include alemtuzumab,³² bendamustine,⁵² high-dose corticosteroids with rituximab,⁵³ ofatumumab,⁵⁴ combination regimens, and investigational therapies.

Chemoimmunotherapy

In the REACH trial, Robak et al⁵⁵ compared rituximab, fludarabine, and cyclophosphamide (R-FC) to FC alone in 552 patients with relapsed or refractory CLL. Results from this international randomized phase III trial included a higher OR rate (70% vs 58%), a higher CR rate (24% vs 13%), and a significantly longer PFS (30.6 months vs 20.6 months; $P = .0002$) in the R-FC arm compared with FC, respectively. Median OS was 53 months for FC but was not reached for R-FC. Grade 3/4 adverse events were higher in the R-FC group with slightly more neutropenia, febrile neutropenia, and thrombocytopenia but the grade 3/4 infection rate was similar to that in the FC group. Fatal adverse events were slightly higher with R-FC (13% vs 10% with FC) and were mostly the result of infections, secondary neoplasms, or cardiac disorders. The results of this trial demonstrate that R-FC is an active regimen for treatment of relapsed or refractory CLL. However, R-FC is not without significant toxicity in this setting, and its use is most appropriate for fit patients in whom prolongation of PFS is a goal.

After obtaining encouraging results from the combination of pentostatin and cyclophosphamide in heavily pretreated patients with CLL, Lamanna et al⁴⁶ tested the PCR combination in 46 patients with previously treated CLL or other low-grade B-cell malignancies. The OR rate was 75% and CR rate was 25%. Myelosuppression was the most common side effect, with grade 3/4 infections developing in 28% of patients. PCR may be used as an alternative to FCR in relapsed and refractory CLL.

Alemtuzumab

Alemtuzumab monotherapy has resulted in OR rates of 33% to 53% and a median duration of response of 8.7 months to 15.4 months in patients with relapsed or refractory CLL.^{32,56,57} The drug has effectively eradicated disease from the blood, bone marrow, and spleen, but it has been relatively ineffective at treating bulky lymphadenopathy.⁵⁶ Alemtuzumab has also demonstrated notable efficacy in treating CLL with p53 deletions or mutations, possibly due to the fact that it is not

dependent on p53 for its antitumor activity.⁵⁸ However, this agent has been associated with significant infectious complications, including opportunistic infections with *Pneumocystis jirovecii* and cytomegalovirus (CMV).⁵⁸ Though investigators are testing alemtuzumab in combination with rituximab and other therapies and also as consolidation to eradicate MRD, at this time alemtuzumab should not be used in either manner outside of a well-designed clinical trial.

Bendamustine

A number of small studies have suggested that bendamustine has clinical activity in the treatment of alkylating agent-refractory CLL.^{52,59,60} While doses of 100 mg/m² for monotherapy and 90 mg/m² in combination with rituximab are used for treatment of newly diagnosed CLL, dose-escalation trials in the relapsed/refractory setting suggest that these doses cause significant myelosuppression. Therefore, a lower dose of 70 mg/m² should be used in pretreated patients, especially in those who have received fludarabine.⁵²

Fischer et al⁶¹ enrolled 81 patients into a phase II trial to evaluate the efficacy and toxicity of bendamustine plus rituximab in the treatment of relapsed or refractory CLL. The bendamustine dose was 70 mg/m² on days 1 and 2 of a 28-day cycle, combined with rituximab 375 mg/m² for the first cycle and 500 mg/m² for subsequent cycles. In the 62 patients who were included in the response assessment, the OR rate was 77.4% and the CR rate was 14.5%. The OR rate was 92.3% for the subset with del(11q), 100% for trisomy 12, 44.4% for del(17p), and 74.4% for unmutated IgHV. Major toxicities included myelosuppression and infections. The investigators concluded that bendamustine plus rituximab has significant activity in high-risk relapsed or refractory CLL. Bendamustine appears to be a good choice for second-line therapy based on its efficacy in pretreated CLL patients and its lack of significant cross-resistance with other alkylating agents or fludarabine.^{26,52,62}

Ofatumumab

Ofatumumab (Arzerra™, GlaxoSmithKline, Philadelphia, PA) is a fully humanized monoclonal antibody targeting CD20.⁶³ Complement-dependent cytotoxicity and antibody-dependent, cell-mediated cytotoxicity are possible mechanisms of B-cell lysis elicited by ofatumumab.⁶³ A slower off-rate and more stable binding of ofatumumab to CD20-expressing cells may explain the higher in vitro efficacy observed with ofatumumab compared with rituximab.⁶⁴ Ofatumumab binds to a different epitope on the CD20 antigen than rituximab does, and it activates complement-dependent cytotoxicity even in B cells with low-level expression of CD20.⁶⁵ Noting these characteristics, investigators evaluated the safety and efficacy of ofatumumab in the treatment of relapsed and refractory CLL.

Österborg et al⁵⁴ recently reported results from a planned interim analysis of an international, multicenter, phase II trial evaluating 138 patients with CLL refractory to both fludarabine and alemtuzumab (double refractory, DR) or refractory to fludarabine with bulky (> 5 cm) lymphadenopathy (bulky fludarabine refractory, BFR). The OR rate was 51% for the DR group and 44% for the BFR group. Median time to next treatment and OS were 9 months and 14 months, respectively, for the DR group and 8 months and 15 months, respectively, for the BFR group. The median OS of 14 months in the DR group was a significant improvement for patients who historically have a median OS of only 8 months.⁶⁶ Infusion-related reactions were common with the first dose (38% to 46%) but were less frequent with subsequent doses.⁵⁴ Infections, neutropenia, and anemia were the most common grade 3/4 adverse events. Ofatumumab has been FDA-approved for treatment of CLL that is refractory to fludarabine and alemtuzumab.

Emerging Therapies

Lumiliximab

CLL cells exhibit high expression of CD23, while non-CLL cells only minimally express this antigen. As such, CD23 has become a potential target for directed therapy. Lumiliximab is a macaque-human primatized anti-CD23 monoclonal antibody.⁶⁷ In a phase I trial, investigators found that lumiliximab was well tolerated, but its efficacy was limited to reduction of lymphadenopathy and lymphocytosis with no documented CRs or partial remissions (PRs).⁶⁷ Since preclinical data suggested an enhancement of antitumor effect when lumiliximab was combined with both rituximab and fludarabine, investigators tested the safety and efficacy of the combination of FCR with lumiliximab for treatment of relapsed CLL in a phase I/II trial.⁶⁸ Toxicity of the combination appeared to be no different from what has previously been reported with FCR in treatment of relapsed CLL. FCR plus lumiliximab resulted in an OR rate of 65% and a CR rate of 52%. Investigators have initiated a trial comparing FCR to FCR plus lumiliximab in relapsed CLL in hopes of determining if the addition of lumiliximab to FCR will provide a benefit over FCR alone.⁶⁹ A separate trial will evaluate the safety and efficacy of FCR with lumiliximab in previously untreated CLL.⁶⁹ At the time of this writing, the FDA has not approved lumiliximab, and therefore its use is limited to clinical trials.

Oblimersen

Bcl-2, an antiapoptotic protein, is overexpressed in CLL cells and results in resistance to chemotherapy. Oblimersen, an antisense oligonucleotide, downregulates the Bcl-2 protein and enhances the cytotoxic activity of agents such as fludarabine, rituximab, and alemtuzumab.⁷⁰ O'Brien et al⁷⁰ conducted a randomized phase III trial comparing FC to FC plus oblimersen in

241 patients with relapsed or refractory CLL. Twenty patients (17%) in the group receiving FC plus oblimersen and 8 patients (7%) in the FC-only group achieved a CR or nodular PR. TTP and survival were both prolonged in patients who achieved a CR or a nodular PR ($P < .0001$). Five-year follow-up of these patients demonstrated a significant survival benefit for patients who had fludarabine-sensitive disease or who achieved a CR or a PR with FC plus oblimersen.⁷¹ Adverse effects of oblimersen included nausea, thrombocytopenia, tumor lysis syndrome (rare), and cytokine release reactions (rare). Oblimersen remains an investigational drug at this time.

Flavopiridol

Flavopiridol (alvocidib), a cyclin-dependent kinase inhibitor, induces apoptosis of CLL cells in vitro and is not dependent on p53 for its activity. A phase II trial evaluating flavopiridol as treatment of relapsed CLL demonstrated an OR rate of 53%.⁷² Patients with genetically high-risk disease, including those with del(17p) and del(11q), also had significant OR rates (57% and 50%, respectively). Patients with bulky lymphadenopathy had an OR rate of 51%. Adverse effects included cytopenias, diarrhea, nausea and vomiting, transaminitis, acute tumor lysis syndrome, and cytokine release syndrome (fever, flushing, tachycardia, nausea). Flavopiridol has demonstrated activity in relapsed CLL with high-risk cytogenetics and bulky lymphadenopathy, but it remains investigational and requires further study to establish its ultimate role in treating CLL.

Lenalidomide

Lenalidomide (Revlimid®, Celgene Corp, Summit, NJ), an immunomodulator with multiple effects on the immune system, has demonstrated activity in CLL. In two phase II trials evaluating lenalidomide for treatment of relapsed and refractory CLL, the OR rates ranged from 32% to 53%, and the CR rates ranged from 7% to 18%.^{73,74} Median time to best response was 5.9 months in one trial.⁷³ Notable adverse effects included myelosuppression (dose-limiting), acute tumor lysis syndrome, and a tumor flare reaction (29% to 58%) that appeared to be disease-specific, unrelated to dose, and a possible result of tumor cell activation.⁷³⁻⁷⁶ Lenalidomide has not been approved by the FDA for the treatment of CLL.

Investigators have recently reported results from using the combination of lenalidomide and rituximab for treatment for relapsed CLL.^{77,78} The larger study reported an OR rate of 68% for the 60 patients enrolled, but there were no CRs.⁷⁷ Investigators concluded that lenalidomide plus rituximab was more effective than historically observed with single-agent lenalidomide, even though all patients had received prior rituximab therapy. Tumor flare was less frequent and less severe than that seen with single-agent lenalidomide.⁷⁷

Treatment Selection and Practical Considerations

The National Cancer Institute (NCI) Working Group guidelines are the gold standard for deciding when to initiate therapy in CLL patients.^{4,17} Treatment should not be initiated in asymptomatic patients with early-stage CLL outside of a clinical trial, regardless of how high the absolute lymphocyte count or if hypogammaglobulinemia is present. Indications for initiating treatment are listed in Table 7.⁶ For patients with early-stage disease who are asymptomatic, a watch-and-wait approach is recommended and may be the only approach needed if they are without poor prognostic markers and have an indolent, asymptomatic disease course.

For those who require treatment, the GCLLSG has recently proposed classifying patients into two categories, “go go” and “slow go,” in an attempt to aid in making treatment decisions.¹⁸ In order to determine which patients fall into the fit (“go go”) category, functional status can be determined using Eastern Cooperative Oncology Group (ECOG) performance status, and comorbidities can be measured using the Cumulative Illness Rating Scale-Geriatric (CIRS-G).⁷⁹ To qualify as “go go,” patients must have normal renal function (creatinine clearance > 70 mL/min) and a low score (≤ 6) on the CIRS-G.^{18,79} ECOG performance status should be 0 to 2. Patients in the “go go” category should be offered regimens proven to produce higher response rates and longer PFS and OS, such as FCR. Patients with del(11q), trisomy 12, and del(13q) had improved CR rates and PFS with the addition of an alkylating agent to fludarabine.³⁸ Therefore, physicians should consider including an alkylating agent in combination regimens used to treat patients with CLL displaying these cytogenetic abnormalities.

Though significant, the addition of cyclophosphamide to fludarabine in front-line therapy resulted in only a modest improvement in CR, suggesting the addition of rituximab to this combination is a major contributor to the increased CR rate seen with FCR.^{5,36-38,45} Whether the contribution of rituximab to FCR is enough to allow for the removal of cyclophosphamide

from the regimen without compromising efficacy remains to be determined. FR is frequently used to treat CLL in the United States, but its role is less well defined as it has not been compared to either FC or FCR in a randomized trial.

Patients who have significant comorbidities are categorized as “slow go” and should be offered a less toxic treatment for symptom management, such as chlorambucil, dose-reduced fludarabine-containing regimens, single-agent bendamustine, bendamustine plus rituximab, or alemtuzumab.¹⁸ In these more frail patients, the treatment goal should be to alleviate disease symptoms with minimal treatment-related toxicity, even if this treatment is less effective at achieving CR or prolonging survival.⁴ It is important to note, however, that age alone does not preclude the use of fludarabine and chemoimmunotherapy, as data suggest that response to therapy and quality of life are not age-dependent.³⁸ However, in an exploratory analysis of the CLL8 and REACH trials, the use of FCR in patients 70 years and older did not show a significant benefit over FC alone.⁸⁰

Regimens that result in more MRD negativity, such as FCR, may be ideal for the “go go” group of patients, as MRD negativity has been shown to correlate with a longer PFS and/or OS in some trials.^{81,82} MRD negativity refers to the eradication of leukemic cells assessed by four-color flow cytometry or allele-specific oligonucleotide PCR.^{81,82} Of note, consolidation therapy with alemtuzumab or lenalidomide until MRD eradication is currently under investigation, but it cannot be recommended for general clinical practice. Though alemtuzumab consolidation has improved PFS, exposing patients to additional therapy in order to achieve MRD negativity has resulted in significant, and sometimes fatal, toxicity.^{81,83-85} The role of consolidation therapy has yet to be clearly defined.

Several randomized prospective trials have demonstrated that patients with unfavorable prognostic factors respond poorly to or have a shorter duration of response from purine analogs.^{38,86-88} In particular, patients with del(17p) or p53 mutations have significantly worse outcomes than other risk categories. Until more effective treatment options can be developed, enrollment in a clinical trial is most appropriate for this subset of patients. However, if conventional therapies such as chemoimmunotherapy or alemtuzumab are used and result in a good response, consolidation with an allogeneic stem cell transplant should be considered.⁸⁹ Alternatively, the CFAR regimen combines alemtuzumab with a fludarabine-based regimen and has produced noteworthy response rates in high-risk patients.⁴⁹ Flavopiridol has also shown promise in this setting.⁷² In addition, patients with p53 mutation or deletion appear to respond better to high-dose methylprednisolone plus rituximab, though responses are generally of short duration if not fol-

Table 7. — Indications for Initiation of Treatment of Chronic Lymphocytic Leukemia

Progressive marrow failure
Autoimmune anemia and/or thrombocytopenia poorly responsive to standard therapy
Disease-related symptoms: fatigue, night sweats, weight loss, fever
Massive splenomegaly
Massive lymphadenopathy
Lymphocyte doubling time < 6 mos

Note: Transient localized lymphadenopathy due to infection and marked hypogammaglobulinemia are not reasons to treat.

lowed by an allogeneic stem cell transplant.^{53,89} Therefore, allogeneic transplant may be considered as front-line for younger, healthy patients with del(17p) in first CR or may be considered as salvage after failure to respond to front-line therapy or early relapse (within 12 to 24 months) following purine analog therapy.⁹⁰ In order to better define its role, allogeneic transplant should be performed in the setting of a clinical trial whenever possible. The Figure outlines proposed treatment options for therapy-naïve CLL.⁹¹

Patients who relapse after a disease-free period of over 1 year (or 2 years after chemoimmunotherapy) are considered to be fludarabine-sensitive and can receive the same regimen used for initial treatment.¹⁸ Those who relapse within 6 months of completing initial fludarabine-containing treatment or who progress during therapy are considered to be fludarabine-refractory.⁹² Options for refractory patients include alemtuzumab with or without rituximab (not for bulky lymphadenopathy), bendamustine with or without rituximab, high-dose corticosteroids with rituximab, ofatumumab, and combination regimens.

Alemtuzumab and high-dose corticosteroids are associated with significant toxicity and prolonged immunosuppression. Since CLL itself causes immune dysregulation, serious and life-threatening infections often occur after using such immunosuppressive agents. Guidelines for the use of alemtuzumab include mandated weekly polymerase chain reaction analysis

for cytomegalovirus (CMV) to check for reactivation of CMV, cotrimoxazole prophylaxis to prevent *Pneumocystis jirovecii* pneumonia, and acyclovir prophylaxis against herpes viruses.⁹³ If CMV infection is noted, preemptive therapy should be initiated with ganciclovir or foscarnet and treatment with alemtuzumab should be interrupted.⁹³

Conclusions

Identification of new prognostic markers for CLL has improved our understanding of the clinical behavior of the disease, although their role in directing therapy remains unclear. Purine analogs, novel alkylating agents, combination chemotherapy with monoclonal antibodies, and immunomodulators have made complete response a more attainable goal. Progression-free and overall survival can now be extended in these patients with an incurable disease.

As a disease of the elderly, treatment strategy should remain highly individualized. The watch-and-wait approach remains standard for asymptomatic patients. For patients who require treatment, FCR appears to be the most effective front-line therapy but is not a suitable option for unfit patients due to higher hematologic toxicity. More effective regimens tend to be more toxic regimens; therefore, it is important to assess the condition of the patient and define the goals of therapy before making treatment decisions. Bendamustine in combination with rituximab is an active regimen in the front-line setting, though lower doses should be used in the relapsed setting due to more severe myelosuppression in these patients. BR is currently being compared to FCR for front-line treatment in a phase III randomized trial in order to further define its role. Alemtuzumab has proven activity in treating del(17p) CLL, but it is relatively ineffective for treating bulky lymphadenopathy. Ofatumumab has activity in patients with CLL refractory to both fludarabine and alemtuzumab and is now approved for this indication. Other drugs, such as flavopiridol and lenalidomide, have shown activity in the relapsed setting, and clinical trials are still ongoing. Although MRD negativity has correlated with longer PFS, use of consolidation therapy in order to achieve MRD negativity remains investigational. Continued advances in the research of this condition and enrollment of patients in clinical trials will aid in the pursuit of a future cure for CLL.

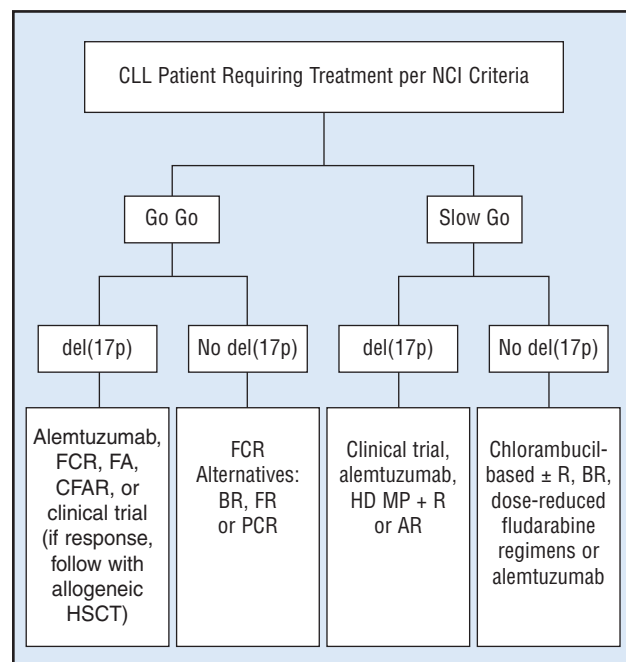


Figure. — Proposed algorithm for front-line treatment of chronic lymphocytic leukemia. HD MP = high-dose methylprednisolone, R = rituximab, B = bendamustine, F = fludarabine, A = alemtuzumab, C = cyclophosphamide, P = pentostatin, HSCT = hematopoietic stem cell transplantation, Go Go = patients with normal renal function (creatinine clearance > 70 mL/min) and a low score (≤ 6) on the CIRS-G, Slow Go = patients with significant comorbidities (do not qualify as Go Go).

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