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Management of relapsed chronic lymphocytic leukemia: applying guidelines to practice

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common hematologic malignancy in Western countries.¹ Despite improvements in care, CLL is incurable and patients usually relapse after initial treatment. Although mortality in the US has declined since 1993, 4580 individuals are expected to die of this disease in 2012.^{2,3} The most frequently used first-line chemoimmunotherapy regimen is the combination of fludarabine, cyclophosphamide, and rituximab (FCR). However, after treatment with FCR, approximately 6% of patients relapse within 6 to 12 months and a further 14% do so within 2 years.^{4,5}

Treatment of relapsed CLL often hinges on providing therapy that maximizes survival and disease control while minimizing toxicity with the overall goal of improving quality of life. Current data from the Connect™ CLL Disease Registry (n = 899) show that health-related quality of life (assessed using the Functional Assessment of Cancer Therapy-Leukemia, EuroQol 5-Dimensions, and Brief Fatigue Inventory questionnaires) in newly diagnosed and relapsed patients in routine clinical care decreased with worsening Eastern Cooperative Oncology Group (ECOG) performance status, and was lower in patients with fatigue.⁶ Performance status and the presence of comorbidities are therefore important factors in deciding the best treatment options for the patient. Because treatments can be associated with severe adverse events (AEs), the choice of appropriate therapy for patients with relapsed disease should account for performance status when defining the goal and role of treatment.

Other key factors to be considered when deciding treatment are the chronic nature of the disease, and the number and types of prior therapy. CLL has a variable course, but patients may remain stable and asymptomatic for years before progressing. Given that the median age at death for patients with leukemia is 79 years, and that the average life expectancy in the United States is approximately the same age, the decision of if and when to treat has to be carefully considered.^{3,7} As CLL is characterized by relapses, even after prolonged

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responses to therapy, many patients receive multiple lines of treatment. In this article we discuss treatment options for patients with CLL who have relapsed after at least 1 prior treatment.

How should a patient with relapsed CLL be evaluated?

A relapsed patient is defined as one who has previously achieved complete remission or partial remission, but who exhibits evidence of disease progression after a period of 6 months or more (Table 1).⁸ Relapse may occur after a prolonged complete remission following initial treatment, or within months following a partial remission to second- or third-line treatment.

In general, relapsed patients should be evaluated in the same way as newly diagnosed patients. Evidence of CLL at relapse should be confirmed by flow cytometry and a complete blood count demonstrating 5×10^9 B lymphocytes/L in the peripheral blood. Differential diagnoses include prolymphocytic leukemia and transformation to an aggressive lymphoma.^{1,8}

As described in the previous article, there are 2 widely accepted staging systems for CLL: the Rai system and the Binet system.⁹ Currently, both systems use physical examination and standard laboratory tests to stratify patients into 3 risk groups, which correlate with clinical outcome.^{10,11}

A history of previous treatment should always be taken. In this era of fludarabine-based therapy, it is important to note that patients refractory to fludarabine respond relatively poorly to subsequent fludarabine-based therapy.¹²

Cytogenetic tests should also be performed following each relapse, as genetic defects may develop over the course of the disease, and may be more common in patients with early relapse.⁴ Interphase fluorescence in situ hybridization (FISH) should be used to detect cytogenetic abnormalities, including specific deletions, trisomy, and translocations of chromosomal bands, which are key predictive markers for response to therapy and patient outcome.¹³

The presence of a deletion in the short arm of chromosome 17, del(17p), which frequently results in abnormalities in the key tumor suppressor gene *TP53*, is a marker of inferior prognosis. Patients bearing this mutation are poor responders to common treatments for CLL, including purine analogs, which are common and preferred treatments for relapsed disease in suitable, fit patients.^{12,14,15} The presence of del(11p) has been associated with extensive lymphadenopathy, progression, and shorter survival time.^{13,16} However, untreated patients bearing this abnormality do respond to treatments containing fludarabine and cyclophosphamide.^{17,18} The presence of del(13p) as the sole cytogenetic abnormality is favorable.¹³

International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines recommend the evaluation of cytogenetic markers when patients request prognostic information, but not to guide treatment.⁸ However, the more recent National Comprehensive Cancer Network (NCCN) guidelines state that cytogenetic information may be used to guide treatment choice, as discussed below.¹ The role of cytogenetic testing at relapse should be discussed with each patient to determine the optimal use of this test in clinical decision-making for each individual.

Other prognostic markers include the presence of an unmutated immunoglobulin heavy chain variable region (IgVH), as detected by DNA sequencing. This has been associated

with significantly shorter survival when compared with the presence of mutated IgVH.¹⁹ Increased expression of CD38 or zeta-chain-associated protein kinase 70 (ZAP-70) is also associated with poor outcome.^{20–26} IWCLL guidelines do not recommend testing for either of these markers in routine clinical practice.⁸ The NCCN guidelines, on the other hand, do recommend testing for these markers to provide prognostic information.¹ Minimal residual disease has recently received interest as a prognostic marker for progression-free survival (PFS), although this is not currently recognized by either the IWCLL or NCCN guidelines.^{1,8,27}

Bone marrow aspiration and biopsy may be useful to assess the cause of anemia or thrombocytopenia (eg, leukocyte infiltration of the bone marrow). A biopsy is recommended before restarting treatment to determine susceptibility to drug-induced cytopenias.^{1,8}

When should a patient with relapsed CLL be treated?

The timing of treatment is of utmost importance with regard to quality of life in patients with CLL, who are often elderly and frail, and who may present with comorbidities. On the one hand, chemotherapy—with an inherent risk of severe AEs—should not be introduced to a patient in whom disease is minimal and not progressing. On the other hand, treatment should not be left until the patient has a high disease burden and has become too weak to withstand optimum treatment. Carefully balancing these clinical factors requires skillful practice.

Progressive disease (PD; Table 1) or symptomatic disease should be evident before treatment is initiated in the relapsed setting. Although patients with CLL may present with an elevated leukocyte count, this alone should not trigger the start of re-treatment; the symptoms caused by leukocyte aggregates in acute leukemias are rarely observed in CLL.⁸ Likewise, hypogammaglobulinemia or paraproteinemia (monoclonal or oligoclonal) are not criteria for restarting treatment, although these laboratory abnormalities should be monitored once the patient is treated.⁸

What is the optimal treatment for relapsed CLL?

In general, the NCCN guidelines recommend re-treatment with the regimen used as first-line therapy if the first-line response was of long duration.¹ If the response to initial treatment was of short duration, other therapy options should be considered. In the Connect™ CLL Disease Registry, the most commonly recorded first-line regimens among patients treated predominantly in community-based practices in the United States were FCR (33%), bendamustine ± rituximab (19%), fludarabine ± rituximab (15%), or investigational therapies (15%). For patients who received second-line or later regimens, the most frequently recorded regimens were bendamustine ± rituximab (30%), FCR (23%), other fludarabine-based regimens (13%), or investigational therapies (8%). Although commonly employed in the past, the use of chlorambucil was infrequent. As noted above, ECOG performance status influenced treatment selection, but predominantly in older patients.⁵

The German CLL Study defined patient groups suitable for initial treatment: “go go” for patients in good physical condition; “slow go” for those with relevant comorbidities; and a group comprising those with symptomatic disease and del(17p)/p53 deletions.²⁸ These concepts can be extended to relapsed patients. The treatment options discussed below for these 3 patient groups are summarized in Figure 1.

“Go go” patients

In “go go” patients, preferred choices of treatment for the patient with relapsed CLL should include FCR. This combination therapy has been shown to be highly effective in untreated patients, and is frequently used in this setting.^{5,29} If the response duration with first-line FCR was ≥ 3 years, then FCR can also be considered as second-line treatment. In an initial phase II trial in relapsed and refractory patients (n = 177), FCR was associated with an overall response rate (ORR) of 73%, including complete remissions in 25% of patients.³⁰ A second phase II trial, in relapsed patients alone (n = 284), reported similar ORR and complete remission rates (74% and 30%, respectively). FCR remained effective in patients who received this combination therapy as initial treatment.¹² However, patients who were refractory to fludarabine (ORR 56%; $P < .001$) or with chromosome 17 abnormalities (ORR 35%; $P < .001$) responded relatively poorly. Follow-up data from a phase III trial showed that FCR was a common treatment following relapse >24 months after initial treatment with fludarabine and cyclophosphamide (FC) ± rituximab, and that it was the most effective second-line treatment studied in patients initially treated with FC.³¹

The benefit of FCR over FC in patients with relapsed CLL was shown in the international, randomized phase III Rituximab in the Study of Relapsed Chronic Lymphocytic Leukemia (REACH) trial.³² In this study, 276 patients were randomized to receive fludarabine (25 mg/m²/d IV) and cyclophosphamide (250 mg/m²/d), each for 3 days, repeated every 28 days, for 6 cycles. A further 276 patients were randomized to receive rituximab on Day 1 of each cycle (375 mg/m² in Cycle 1, and 500 mg/m² in subsequent cycles) in addition to FC. Patients had Binet stage A (10%), B (59%), or C (31%) disease. After a median follow-up of 25 months, PFS (the primary endpoint) was significantly longer in the FCR group than in the FC group (30.6 months vs 20.6 months; hazard ratio, 0.65; $P < .001$). FCR was generally well tolerated and did not substantially alter quality of life.

The benefit of FCR was maintained in patient subgroups with high-risk features, including those with unmutated IgVH, the chromosomal abnormality del(11q), and increased ZAP-70 expression. However, in this study, no PFS benefit for FCR over FC was observed in patients previously treated with FC ± rituximab, alkylator-refractory patients, those diagnosed ≥ 10 years beforehand, female or nonwhite patients, patients aged ≥ 65 years, those with ECOG performance status ≥ 1, patients with B symptoms, patients with a diffuse/nodular pattern of bone marrow involvement, and those with the chromosomal abnormalities trisomy 12 or del(17p).³² Although the benefits of the addition of rituximab can be debated for these subgroups of relapsed patients, it is commonly incorporated into therapy for most patients as the above data were derived from unconfirmed exploratory analyses, and the immunotherapy adds minimal toxicity to the regimen.

Resistance to fludarabine is an important consideration when choosing treatment. As stated above, patients with fludarabine-resistant disease commonly respond poorly to FCR. Moreover, many of these patients will have previously been exposed to and have become resistant to alkylating agents. However, as noted above, NCCN guidelines recommend re-treatment with the regimen used as first-line therapy if the response to that first-line therapy was of long duration.¹

On-label options suggested by the NCCN for patients with fludarabine-resistant disease who would be regarded as being in the “go go” category include monotherapy with alemtuzumab or ofatumumab.¹ Alemtuzumab is a humanized anti-CD53 monoclonal antibody shown in a series of studies to be active as monotherapy in relapsed/refractory patients (including those who had previously received fludarabine, or who had p53 or del(17p) abnormalities). The ORRs were 13% to 54% in patients with fludarabine-refractory disease.^{33–39}

Ofatumumab is a human anti-CD20 monoclonal antibody. Its activity in patients with relapsed/refractory leukemia was reported in a phase I/II study in 2008.⁴⁰ It has since been approved for use in patients with CLL refractory to fludarabine and alemtuzumab on the basis of data from a phase II study.⁴¹ In this study (n = 138), ORRs were 58% and 47% in patients refractory to alemtuzumab or fludarabine, respectively. A post-hoc analysis showed that ofatumumab was effective irrespective of prior rituximab treatment.⁴²

Off-label treatments recommended by the NCCN include bendamustine plus rituximab (BR; rituximab is currently indicated for use only in combination with FC in patients with previously treated CLL), fludarabine plus alemtuzumab, and several rituximab-containing combination therapies: rituximab plus high-dose methylprednisolone (R-HDMP); pentostatin, cyclophosphamide, and rituximab (PCR); oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR), and alemtuzumab plus rituximab. Lymphoma regimens such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), rituximab plus cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (R-hyperCVAD), and dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) plus rituximab can also be used in certain instances.¹

Bendamustine is approved in the United States for the treatment of CLL. Although an alkylating agent, it has incomplete cross-resistance with other such agents.⁴³ Bendamustine monotherapy was initially shown to have activity in relapsed/refractory patients and an acceptable safety profile in a number of small trials.^{44–46} Interim data from a larger, randomized study comparing fludarabine and bendamustine (n = 96) revealed ORRs of 65% and 78%, respectively, including complete remissions in 10% and 29% of patients, respectively.⁴⁷ Clinical data support the use of bendamustine following relapse with FCR and the use of BR following relapse with other therapies.^{32,48}

Allogeneic hematopoietic stem cell transplantation is a viable option for some patients without significant comorbidities with short responses to chemoimmunotherapy, but is more generally suitable following reestablishment of remission.¹

“Slow go” patients

Reduced-dose FCR should be considered in patients aged ≥70 years or in younger patients with comorbidities (ie, “slow go” patients).¹ Data in predominantly younger patients suggest that this can be effective in the first-line setting, but limited data exist on the use of dose-reduced FCR in the relapsed setting.⁴⁹ Other on-label treatment options recommended by the NCCN for this patient population include monotherapy with bendamustine, ofatumumab, or alemtuzumab. Off-label treatments recommended by the NCCN include rituximab-based treatments, such as reduced-dose PCR, BR, R-HDMP, alemtuzumab plus rituximab, and dose-dense rituximab.¹

Patients with chromosomal abnormalities and/or symptomatic disease

The NCCN guidelines provide further guidance for patients with chromosomal abnormalities. For patients with del(17p), enrollment in clinical trial is highly recommended. If this is not possible, FCR, ofatumumab or alemtuzumab monotherapy, and high-dose methylprednisolone are other on-label options. Off-label options include: alemtuzumab plus rituximab; R-CHOP; cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR); R-HDMP; R-hyperCVAD; and OFAR.¹

For those with del(11p), enrollment in a clinical trial is again a preferred option. If the patient progressed following a complete remission, first-line therapy may be repeated depending on the duration of the response. FCR can be used in patients aged <70 years or in

older patients without comorbidities. Other on-label options for all patients with this abnormality include ofatumumab or alemtuzumab monotherapy. Off-label options include PCR, BR, FR, R-CHOP, R-hyperCVAD, dose-adjusted EPOCH plus rituximab, OFAR, alemtuzumab plus rituximab, and R-HDMP. Reduced-dose FCR and bendamustine monotherapy are approved in those aged ≥ 70 years. Off-label treatments include reduced-dose PCR, BR, R-HDMP, alemtuzumab plus rituximab, and dose-dense rituximab.¹

It is important that treatment is not withheld from older and less fit patients with PD if it would increase their quality of life. New treatments are constantly being developed. If it is not certain that a patient will respond to standard treatment, then the option of a clinical trial should be explored.

While detailed discussion of compounds in development is beyond the scope of this article, there are several promising agents being assessed in clinical trials as single agents and in combination with other agents. One such agent is ibrutinib (PCI-32765), an oral Bruton tyrosine kinase inhibitor.⁵⁰ Interim data from a phase I/IIb study suggest it may be highly active (ORR, 73%) in elderly patients with untreated CLL.⁵¹ Another promising agent is CAL-101, a phosphatidylinositol 3-kinase-delta inhibitor.⁵² Early data from phase I studies showed this agent to have promising activity and acceptable safety profiles in patients previously treated for CLL, either as monotherapy or combined with anti-CD20 monoclonal antibody therapy and/or bendamustine.^{53,54} Recent data from a phase I/II study show that, in combination with ofatumumab, CAL-101 was associated with marked and rapid reductions in lymphadenopathy.⁵⁵ However, the effect that these agents will ultimately have on the management of patients with relapsed CLL remains to be seen.

A case history

A 67-year-old man was diagnosed 5 years ago with CLL. His leukemia cells expressed unmutated IgVH and increased expression of ZAP-70 (both poor prognostic features). FISH studies revealed no abnormalities. He was initially observed without treatment (ie, 'watch and wait') as he was asymptomatic with a low disease burden. Eighteen months later he developed progressive and symptomatic CLL and began treatment with FCR; after 6 cycles he attained a partial remission. In the last month of treatment he began experiencing progressive fatigue and increasing lymphadenopathy. At the last assessment, the patient had multiple cervical, supraclavicular, and axillary lymph nodes 4 to 5 cm in size, and his spleen was palpable 10 cm below the left costal margin. Laboratory assessments demonstrated a white blood cell count of 33,900/ μ L (14% neutrophils, 84% lymphocytes), a platelet count of 129,000/ μ L, and a hemoglobin level of 124 g/L. His serum beta-2 microglobulin level was 4 mg/L, and his lactate dehydrogenase level was 240 U/L. Bone marrow biopsy revealed a hypercellular marrow mostly comprising well-differentiated lymphocytes, with tri-lineage hematopoiesis, a reduced level of megakaryocytes, and no dysplasia. Flow cytometry testing confirmed that the lymphocytes had the phenotype of CLL cells. Abnormal karyotype and FISH data demonstrated the presence of del(11q) (a poor prognostic factor). The patient had few, well-compensated comorbidities, and his ECOG performance status was 1. After discussion of available clinical trials and the standard therapies discussed, the patient has initiated treatment with BR. Although not interested in a clinical trial at this juncture, the patient did express interest in pursuing treatment in a clinical trial at his next relapse.

Conclusions

Assessment of the patient with relapsed/refractory CLL requires as much attention as evaluation of patients at initial presentation. Treatment of relapsed CLL is highly

personalized due to the typical age of the patient population, the risk of severe AEs, and the often chronic nature of this disease. Patients with asymptomatic, stable disease should be monitored without treatment. Patients with documented PD should be treated when it is most likely to benefit the patient. Numerous treatment options exist for less fit patients with relevant comorbidities, fludarabine resistance, or chromosomal abnormalities. Treatment should be tailored based on patient characteristics and should aim to maximize survival, minimize toxicity, and improve overall quality of life.

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FIGURE 1.

Treatment options for patients with relapsed chronic lymphocytic leukemia.¹

Abbreviations: BR, bendamustine and rituximab; CFAR, cyclophosphamide, fludarabine, alemtuzumab, and rituximab; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; FCR, fludarabine, cyclophosphamide, and rituximab; FR, fludarabine and rituximab; HDMP, high-dose methylprednisolone; HSCT, hematopoietic stem cell transplantation; OFAR, oxaliplatin, fludarabine, cytarabine, and rituximab; PCR, pentostatin, cyclophosphamide, and rituximab; R-CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab; R-HDMP, high-dose methylprednisolone plus rituximab; R-hyperCVAD: cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine plus rituximab

^aOff label.

^bIn patients with short response to prior treatment, without comorbidities, and following re-establishment of remission.

TABLE 1

Response definitions for chronic lymphocytic leukemia

Response	IWCLL guidelines ⁸	NCCN guidelines ¹	
		Group A ^a	Group B ^b
Complete remission	Blood lymphocytes ^c $<4 \times 10^9/L$; no significant lymphadenopathy (lymph node diameter <1.5 cm) ^d ; no hepato/splenomegaly ^d ; no constitutional symptoms; neutrophils ^e $>1.5 \times 10^9/L$; platelets ^e $>100 \times 10^9/L$; Hb >110 g/L without transfusions/erythropoietin	Peripheral blood lymphocytes $<4 \times 10^9/L$; no lymph nodes >1.5 cm; no spleno/hepatomegaly; bone marrow normocellular and no B-lymphoid nodules; $<30\%$ lymphocytes in bone marrow	Platelets ^e $>100 \times 10^9/L$; Hb >110 g/L without transfusions/growth factors; neutrophils ^e $>1.5 \times 10^9/L$
Partial remission	Blood lymphocyte decrease of $\geq 50\%$ from baseline; reduction in lymphadenopathy ^f ; neutrophils ^e $>1.5 \times 10^9/L$; platelets ^e $>100 \times 10^9/L$ or $\geq 50\%$ increase from baseline; Hb >110 g/L or $\geq 50\%$ increase from baseline without transfusions/erythropoietin	Blood lymphocyte decrease of $\geq 50\%$ from baseline; decrease in summed products of lymph nodes by $\geq 50\%$; decrease in spleno/hepatomegaly by $\geq 50\%$; $\geq 50\%$ reduction in marrow infiltrate or B-lymphoid nodules	Neutrophils ^e $>1.5 \times 10^9/L$ or $\geq 50\%$ increase from baseline; platelets ^e $>100 \times 10^9/L$ or $\geq 50\%$ increase from baseline; Hb >110 g/L or $\geq 50\%$ increase from baseline without transfusions/growth factors
Progressive disease	Any new lesion: enlarged lymph nodes (>1.5 cm), increase in enlarged liver/spleen by $>50\%$ or de novo spleno/hepatomegaly (or other organ infiltrates); blood lymphocyte increase of $\geq 50\%$ (with ≥ 5000 B lymphocytes/ μL); transformation to more aggressive histology; cytopenia attributable to CLL	Blood lymphocyte increase of $\geq 50\%$ from baseline; increase in summed products of lymph nodes by $\geq 50\%$; increase in spleno/hepatomegaly by $\geq 50\%$	Platelets decreased by $\geq 50\%$ from baseline secondary to CLL; Hb decreased by >20 g/L from baseline secondary to CLL

Abbreviations: CLL, chronic lymphocytic leukemia; Hb, hemoglobin; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; NCCN, National Comprehensive Cancer Network.

^aGroup A criteria define the tumor load;

^bGroup B criteria define hematopoietic system (or marrow) function;

^cBy blood and differential count;

^dBy physical examination;

^eWithout growth factor support;

^fDecreased lymph node size by $\geq 50\%$ in sum products of ≤ 6 nodes (or largest diameter of enlarged nodes) relative to baseline, and no increase in any node, and no new enlarged nodes (except increases of $<25\%$ in nodes <2 cm wide).