

# Chronic Lymphocytic Leukemia

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## Comprehensive Management of the CLL Patient: A Holistic Approach

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**The current management of B-chronic lymphocytic leukemia (CLL) is no longer straightforward for the practicing hematologist. Rapid advances in diagnostic precision, methods of predicting prognosis, understanding of natural history of CLL, recognition of clinical complications, clarification of the quality of life**

**(QOL) issues facing the CLL patient, and the exciting array of novel treatment approaches have made the care of the CLL patient more demanding. This review is focused on summarizing these advances in order to provide a framework for integrating this knowledge into routine hematologic practice.**

### Introduction

The comprehensive approach to patients with B-chronic lymphocytic leukemia (CLL) now requires risk stratification for newly diagnosed patients, adherence to supportive care guidelines, attention to quality-of-life (QOL) issues specific to patients with CLL, and consideration of age, comorbidity, and QOL in selection of therapy and disease management. For this review we will emphasize how to translate the numerous recent advances in prognostic parameters, supportive care, and treatment into the care of individual patients with CLL.

### Initial Evaluation of Newly Diagnosed Patients with CLL: Diagnosis and Staging

CLL remains one of the most commonly diagnosed lymphoid malignancies in Western countries.<sup>1</sup> The widespread use of automated blood counters has led to the more frequent incidental discovery of asymptomatic lymphocytosis. The accurate diagnosis of CLL is made possible by flow cytometry detection of clonal blood B cells that also exhibit CD19, CD20, CD5, CD23 and CD79b in individuals with an absolute lymphocyte count (ALC) higher than 5000/ $\mu$ L. These technologic advances have led to the diagnosis of CLL being made more frequently at an earlier disease stage in relatively young individuals who will now have a long time to deal with the medical and psychological implications of their disease. Before counseling patients, it is critical for the hematologist to be certain of the diagnosis and to distinguish CLL from other entities such

as mantle cell lymphoma (MCL), splenic marginal zone lymphoma, nodal marginal zone B-cell lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, follicular lymphoma (FL), hairy cell leukemia, lymphoplasmacytic lymphoma (including Waldenström macroglobulinemia), and B-cell prolymphocytic leukemia (PLL).<sup>2</sup> We routinely perform fluorescent *in situ* hybridization (FISH) analysis for the t(11;14) as a component of our FISH panel to exclude the leukemic phase of MCL in all patients with newly diagnosed CLL.<sup>3</sup>

Historically, CLL has been considered an indolent disease in which patients are placed under “watchful waiting” until the disease progresses. More recent studies suggest that at least 50% of patients, including those diagnosed with an asymptomatic lymphocytosis, are at risk of disease progression. Once the diagnosis is evident, the patient should be accurately staged to determine if they are in a low (lymphocytosis only), intermediate (presence of lymphadenopathy and/or hepatosplenomegaly), or high (presence of anemia [Hgb < 11 g/dL] or thrombocytopenia [platelets < 100  $\times$  10<sup>9</sup>/L]) Rai risk category.<sup>4</sup> Although computed tomography (CT) scans have not been part of the traditional disease staging, recent studies suggest they may provide useful information in selected patients.<sup>5</sup>

### Prognostic Tools: Predicting Natural History

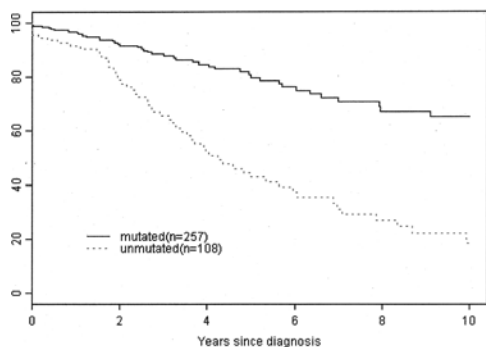
While patients in the high Rai risk category require immediate initiation of therapy, 80% to 90% of patients are now diagnosed while in the low or intermediate Rai risk cat-

egory. The clinical course of patients in these latter groups is highly variable, with 40% to 50% of patients experiencing more accelerated disease progression. Such early-stage patients should be subclassified as being at low, intermediate, or high risk for disease progression using modern prognostic markers. An array of molecular and biologic features of the leukemic cell, including IgVH gene mutation status (IgVH), cytogenetic analysis by FISH, and expression of ZAP-70 and CD38 protein can be very useful in predicting the patient's risk of progression (Figure 1)<sup>6</sup> and appear to be more useful than "traditional" tests such as beta-2 microglobulin and lymphocyte doubling time. With the exception of FISH defects, these parameters are relatively stable through time.<sup>7</sup> The intralaboratory reproducibility of the ZAP-70 assay performed by reference laboratories remains a significant problem, and at present, this parameter is best assessed only by well-established academic laboratories where correlation with patients' actual clinical outcome has been demonstrated. Although studies have begun to assess which assay has the greatest predictive power and to determine how to integrate the results of all assays into a single prognostic index, how best to combine these assays

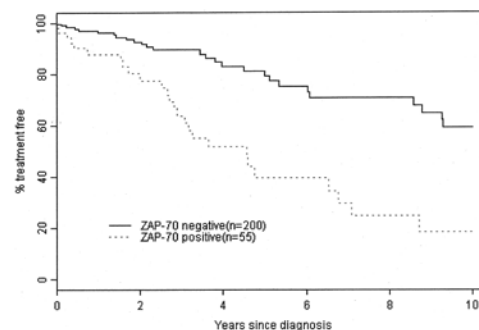
is not yet defined. Our current approach for using these assays to classify a patient's risk of progression is shown in Figure 2. Reliable information from these assays can allow patients to plan their lives, guide the frequency of follow-up with their physician, and identify those patients at greatest risk for early progression/premature death who may be candidates for clinical trials evaluating the role of early treatment (Table 1).<sup>2</sup> Asymptomatic patients should never be treated based solely on the results of prognostic parameters outside of clinical trials, as there is no evidence to support this approach. While low Rai-risk patients who have more favorable risk parameters can be reassured, it remains important to educate such patients about disease-related complications.

### Disease-Related Complications

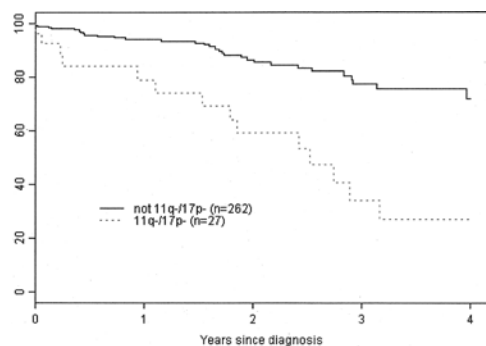
In addition to the potential for disease progression, patients with CLL are at risk for developing a number of disease-related complications, including infection,<sup>8</sup> autoimmune disease,<sup>9,10</sup> and Richter transformation.<sup>11</sup> The effects of CLL on the immune system, the risk of infectious complications, and details on infection management are out-



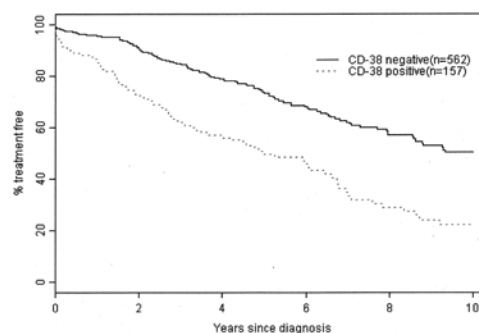
A. IgV<sub>H</sub> gene mutation status ( $P < .0001$ )



B. Zap-70  $P < .0001$ )



C. FISH ( $P < .0001$ ; only includes assays performed  $\leq 36$  months of diagnosis)



D. CD38 ( $P < .0001$ )

**Figure 1. Treatment-free survival for Rai 0 patients by IgV<sub>H</sub> gene mutation, ZAP-70 status, FISH, and CD38.**

Curves show the treatment free survival for Rai 0 patients in the Mayo Clinic CLL Database based on the results of IgV<sub>H</sub> gene mutation status (research assay results), ZAP-70 (routine clinical assay results), FISH (routine clinical assay results; only includes assays performed  $\leq 36$  months of diagnosis) and CD38 (routine clinical assay results),

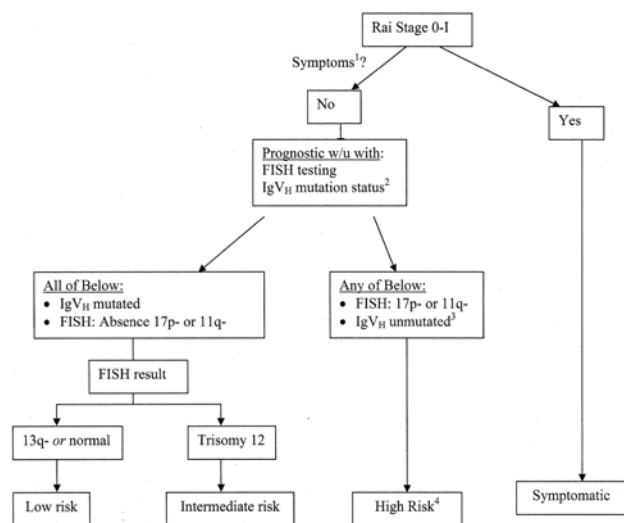
**Table 1. Recommended follow-up, supportive care, treatment, and anticipated survival by risk category for patients with early-stage (Rai 0-I) chronic lymphocytic leukemia (CLL).**

| Variable                                   | Low risk* | Intermediate risk*       | High risk*              | Symptomatic* |
|--|-----------|--------------------------|-------------------------|--------------|
| Median expected CLL-specific survival, y   | >15       | 10                       | 3–8                     | 2–6          |
| Median expected treatment-free interval, y | >5        | 3–4                      | 1–4                     | None         |
| Recommended follow-up, mo                  | 6–12      | Monthly during treatment |                         |              |
|  | 6–12      |                          |                         |              |
|  | 3–6       |                          |                         |              |
| Screening for second malignant disease     | Yes       | Yes                      | Yes                     | No           |
| Immediate treatment indicated              | Not†      | Not†                     | Consider clinical trial | Yes          |

\*See Figure 2.

†Unless as part of a clinical trial of agent with favorable toxicity profile.

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**Figure 2. Proposed use of prognostic tests to risk stratify patients with early-stage CLL.**

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<sup>1</sup> Fever, weight loss, night sweats, fatigue NOT due to other cause (see text).

<sup>2</sup> If available at your center.

<sup>3</sup> Less than 2% mutated compared with germline sequence.

<sup>4</sup> Although high ZAP-70 expression may be used to categorize early stage patients as high risk in the future, this assay cannot be recommended for routine clinical use until it can be standardized and shown to have reliable intralaboratory reproducibility.

lined in the accompanying chapter by Dr V. Morrison and will not be discussed here. Patients with frequent, recurrent infection should be evaluated for hypogammaglobulinemia by measuring quantitative serum immunoglobulins. Gamma-globulin replacement with intravenous Ig (IVIG) can reduce the risk of infection for patients with low IgG levels and recurrent infection.<sup>12</sup> The monitoring of serum Ig should be sequential, as the prevalence of this complication increases with disease duration. We also recommend

annual influenza vaccination and pneumonia vaccination every 5 years for all newly diagnosed patients with CLL. Although patients treated with purine nucleoside analogs (PNA) are at increased risk for herpes zoster, hematologic malignancies such as CLL are a contraindication for the Zostavax vaccine, which is a live attenuated dose of varicella that is 14-fold higher than the amount of live attenuated virus in the traditional varicella vaccination (Varivax).

Approximately 10% to 15% of patients with CLL will develop auto-immune cytopenias (so called autoimmune disease or AID).<sup>9,10</sup> Thus, all patients with CLL with anemia or thrombocytopenia out of proportion to absolute lymphocyte count and lymphadenopathy should undergo a thorough evaluation before attributing the cytopenia to CLL-induced marrow failure. Such distinctions are important since PNA can lead to life-threatening exacerbation of autoimmune cytopenias.<sup>13-15</sup> An elevated reticulocyte count, increased indirect bilirubin, and positive Coomb test readily identify autoimmune hemolytic anemia (AIHA), but a marrow biopsy is required in order to distinguish anemia due to pure red blood cell aplasia (PRBCA) or thrombocytopenia due to idiopathic thrombocytopenic purpura (ITP) from CLL-induced bone marrow failure. Immunosuppressive therapies and/or rituximab often effectively control autoimmune cytopenias. Patients with severe AIHA or ITP who fail to respond to the initial therapies can be considered for nonpurine nucleoside-based chemotherapeutic treatments or in selected cases, splenectomy.

The current estimated rate of Richter transformation of CLL to diffuse large B-cell lymphoma (DLBCL) is approximately 1% per year.<sup>11</sup> Studies suggest the DLBCL is clonally related to CLL in approximately 60% of patients with Richter's transformation.<sup>16</sup> CLL patients are also at increased risk of developing Hodgkin lymphoma and other histologic subtypes of non-Hodgkin lymphoma.<sup>17,18</sup> Purine nucleoside analog-based treatment appears to increase the risk of developing second lymphoid malignancy, possibly through the impairment of both T/natural killer (NK) cell immunosurveillance.<sup>19,20</sup> Richter transformation carries an ominous prognosis with significant resistance to most tra-

ditional treatment approaches. Appropriate patients who develop this complication should be referred for participation in clinical trials testing the efficacy of aggressive chemotherapy regimens or stem cell transplantation.<sup>21</sup>

### **Patient Counseling and Supportive Care Guidelines**

At the time of diagnosis, patients with CLL should be educated about the nature of their illness, current management strategies, and the typical experience of living with CLL. This should include an explanation that CLL is presently an incurable but treatable illness and that the best available evidence suggests that early treatment of patients with low- or intermediate-stage disease does not prolong survival.<sup>22,23</sup> Patients should receive explicit counseling as to what parameters indicate a need for treatment and how often they will be seen by their physician. In 2007, the currently accepted indications for treatment include bone marrow failure (anemia [Hb < 11.0 g/dL], thrombocytopenia [platelet count < 100,000 × 10<sup>9</sup>]), massive or progressive lymphadenopathy, a lymphocyte doubling time of less than 6 months, or constitutional symptoms (fever, weight loss, night sweats, profound fatigue).<sup>24</sup> There is no absolute lymphocyte count that mandates treatment in the absence of constitutional symptoms, bone marrow failure, or the presence of significant progressive organomegaly and lymphadenopathy. Explanation of the results of the patient's personal risk stratification profile can allow reassurance to patients with low-risk disease and help those with more aggressive biologic features to have more informed expectations.<sup>2</sup>

In addition to disease progression and the well-recognized infectious and autoimmune complications, CLL is also associated with an increased risk of second malignancy.<sup>25,26</sup> All early-stage patients should receive age-appropriate screening for breast, prostate, and colon cancer and, where appropriate, counseling regarding smoking cessation. Due to the risk for rapid progression of non-melanomatous skin cancer,<sup>27</sup> we recommend a complete skin (i.e., full skin) survey on an annual basis for all patients with CLL.

As with all forms of cancer, newly diagnosed patients often wonder how their CLL diagnosis influences the cancer risk of their children and relatives. As extensively discussed in the accompanying chapter by Drs Goldin and Slager, approximately 10% of patients with CLL have a strong family history of B-cell malignancy. The first-degree relatives of patients with such a history may be a greater risk of developing CLL and other lymphoproliferative disorders, and such individuals should be referred for participation in ongoing studies on familial CLL (Mayo Clinic Familial Chronic Lymphocytic Leukemia phone line: 1-800-610-7043; National Cancer Institute [NCI] Familial Chronic Lymphocytic Leukemia phone line: 1-800-518-8474; Chronic Lymphocytic Leukemia Research Consortium: <http://ccll.ucsd.edu>). These various groups are working with such families to uncover the gene or sets of genes responsible for CLL. For the remaining 90% of patients

with sporadic CLL, their diagnosis does not clearly imply an increased cancer risk for their children or siblings. It is not currently recommended that these individuals undergo any specific testing other than the standard screening for breast, prostate, and colon cancers.

### **Impact of CLL on Quality of Life**

A new diagnosis of CLL has a profound effect on QOL, even among patients without clinical symptoms. In addition to the uncertainty as to how rapidly their disease will progress, these individuals must deal with the diagnosis of a medical condition that (1) will likely shorten their life; (2) places them at risk for a number of disease-related complications; (3) is managed with toxic therapies for those needing treatment; and (4) can have significant social/financial implications for their family. While it is based on the best available evidence, the “watchful waiting” strategy often leaves patients feeling that they have a serious health problem but that “nothing is being done” to treat it.

Despite these substantial potential effects of CLL on QOL, few studies have evaluated the specific effects of CLL on patient QOL.<sup>28,29</sup> Nearly all historic studies of QOL in CLL have evaluated the effects of different treatment strategies on QOL<sup>30-33</sup> rather than evaluating the direct implications of the disease itself on the patient's physical, emotional, social, and functional well-being.<sup>28,29,34</sup>

Holzner et al evaluated QOL in 76 Swiss patients with CLL at a single academic medical center compared with 152 age- and sex-matched controls.<sup>35</sup> As a group, CLL patients in that study had a statistically significant lower QOL than controls in the “physical functioning” and “role functioning” domains, although assessment of QOL by disease stage was not presented, and the study excluded patients on active therapy.<sup>35</sup> In a recent study of 107 patients seen at Long Island National Jewish Medical Center, Levin and colleagues found no difference in depression, anxiety, or QOL in untreated patients (n = 58) compared with previously treated patients (n = 47).<sup>34</sup> Notably, no difference in emotional QOL based on time since diagnosis was observed, suggesting patients do not “acclimatize” to their diagnosis with time.<sup>34</sup>

In collaboration with patient advocacy groups, the Mayo Clinic recently conducted an international, web-based survey of QOL using validated QOL assessment tools in approximately 1500 patients with CLL.<sup>36</sup> While physical, functional, and overall QOL were strongly related to disease stage and chemotherapeutic treatment, a substantial negative effect on emotional QOL was observed among patients at all stages of the disease. Notably, patients with CLL had dramatically lower emotional QOL than both normative population samples and even published norms of patients with other types of cancer. Because early-stage patients with CLL typically have few or no disease-related symptoms and are perceived by their caregivers to have a better prognosis than patients with many other types of cancer, this psychological effect of the disease may be both

unanticipated and under appreciated by many physicians.

These facts illustrate the importance of physicians or care providers working with physicians explicitly asking all patients (including early-stage) about the effects of CLL on their mental, social, and functional well-being in addition to asking patients how they are emotionally coping with their illness. This line of questioning may uncover opportunities to address significant QOL challenges experienced by CLL patients that would otherwise be unrealized.

Validated tools to assess quality of life are available,<sup>37-39</sup> and additional studies of QOL in patients with CLL are needed, particularly prospective, longitudinal studies of early-stage patients from the time of diagnosis.

### **Selection of Therapies for Patients with Progressive CLL**

Conventional therapy for CLL is noncurative, and the standard of care is to treat patients only when their disease is symptomatic or progressive as defined by NCI-WG 1996 criteria.<sup>24</sup> Clinical trials, such as the North American Intergroup Group trial for asymptomatic, early-stage patients with unmutated IgVH genes, are appropriate for asymptomatic early-stage patients with high-risk molecular features. The efficacy of treatment for CLL has markedly improved with the development of both novel drugs and drug combinations that increase overall and complete response rates as well as duration of response. Treatment options available to the clinician range from use of single agents like chlorambucil to complex multi-agent combinations. The optimal therapy for an individual patient must take in to account multiple features, including the therapy itself, molecular characteristics of the patient's disease (cytogenetic abnormalities, IgV<sub>H</sub> status), clinical features of the patient's disease (disease bulk, presence of autoimmune cytopenias, etc.), and characteristics of the patient (age, organ function, comorbid conditions).

### **Characteristics of the Patient**

Patient characteristics (age, comorbid conditions, organ function, performance status, and preferences) are the first factor influencing therapy selection. These characteristics are the primary factor that determines whether the primary goal of treatment is palliation or an attempt to achieve maximal response and prolonged progression-free survival (PFS). For younger patients with normal organ function and no comorbid conditions, achieving maximal PFS/overall survival is typically the goal of care. Extensive alkylating agent exposure is undesirable in such patients due to the associated risk of myelodysplasia and acute myeloid leukemia. For older patients with decreased organ function and extensive comorbidities, palliation and minimizing treatment toxicity often become the focus. Most patients with CLL fall somewhere between these two extremes and make decisions about therapy more difficult. Physician judgment and patient preferences play major roles in such cases.

Renal insufficiency and auto-immune cytopenias are

co-morbidities that deserved special mention. PNA are subject to renal clearance and dose adjustments are required for patients with reduced creatinine clearance.<sup>40</sup> PNA can also cause or be associated with life-threatening exacerbation of hemolytic anemia and should not be administered to patients with active hemolysis.<sup>13-15</sup>

### **Characteristics of the Therapy**

An understanding of the results of randomized phase III trials of first-line treatment for CLL is essential to select appropriate therapy. The first generation of randomized trials suggested that single-agent PNA offer better response rates, PFS, and QOL than alkylating agent-based regimens.<sup>41-44</sup> Based on these trials, single-agent PNA became the de facto standard of care for treatment of CLL. The recently completed second generation of trials generally suggest that PNA in combination with cyclophosphamide offer better response rates and PFS than single-agent PNA but are associated with greater toxicity.<sup>40,45-47</sup> One recently completed randomized trial also suggests that single-agent alemtuzumab offers better response rates and PFS than single-agent chlorambucil,<sup>48</sup> however, the efficacy of this approach relative to single-agent PNA is unknown. Alemtuzumab causes significant and prolonged T-cell immunosuppression, an important complication not seen with chlorambucil.

None of these randomized trials have demonstrated a difference in overall survival favoring any one first-line treatment strategy to date. Many have mistakenly interpreted this finding to imply that "treatment for CLL does not improve survival." This statement is unequivocally false: none of these trials compared treatment with no treatment. Additionally, all of these trials have allowed cross-over (or salvage treatments) for patients progressing on one arm of therapy. Accordingly, the more appropriate interpretation is that "the sequence of the treatments administered does not appear to influence survival provided progressing patients receive appropriate salvage therapy." If the goal of treatment is to achieve a complete remission and prolong PFS, most CLL experts favor administering a highly active regimen up front to spare patients exposure to the toxic effects of multiple regimens and provide them a long treatment-free interval. This type of approach also delays the use of secondary treatments, which to date have diminished levels of response and significant toxicities.

Although standard dose, single-agent rituximab rarely leads to durable responses, pilot trials have attempted to use this monoclonal antibody to improve the effectiveness of PNA or PNA/cyclophosphamide combinations in previously untreated patients with CLL. Such combination approaches are commonly referred to as chemoimmunotherapy (CIT). Fludarabine and rituximab (FR);<sup>49</sup> fludarabine, cyclophosphamide, and rituximab (FCR);<sup>50</sup> and pentostatin, cyclophosphamide, and rituximab (PCR)<sup>51</sup> have been the most extensively used CIT regimens. These published strategies achieve a response in approximately 90% of patients,

with complete response (CR) rates of 40% to 70%. Comparison to historic controls suggests that CIT may improve patient survival.<sup>52</sup> Since rituximab is generally well tolerated, this observation has led to the widespread use of CIT in the United States. The randomized trial of the German CLL Study Group comparing FC to FCR will determine the validity of this approach.

### Characteristics of the Disease

While the results of these randomized trials provide global estimates of the efficacy of a given treatment regimen for a population of patients, characteristics of the patient's disease influence the efficacy for individual patients. Advanced-stage disease and greater tumor bulk have been repeatedly shown to decrease the likelihood of achieving a complete response.<sup>40-42,45</sup> Although there is randomized trial evidence that first-line treatment with single-agent alemtuzumab is superior to chlorambucil, this agent is unlikely to achieve a CR in individuals with bulky adenopathy.<sup>48,53</sup>

The molecular characteristics of the disease also influence the efficacy of treatment. The PFS of patients treated with fludarabine-containing regimens (fludarabine monotherapy, fludarabine + cyclophosphamide, and fludarabine + rituximab) appears to be substantially shorter for patients with del(17p13.1) or del(11q22.3) relative to those without these cytogenetic defects.<sup>54,55</sup> Notably, in the randomized North American Intergroup Trial, treatment with the FC combination failed to overcome the shorter PFS associated with these cytogenetic abnormalities.<sup>55</sup> Some data suggest the PCR regimen may overcome the shorter PFS associated with del(11q22.3) but not del(17p13.1).<sup>51</sup> Preliminary data suggest that alemtuzumab-based treatments may be equally efficacious in del(17p13.1),<sup>56</sup> and trials of first-line alemtuzumab for patients with del(17p13.1) are ongoing.<sup>57,58</sup>

### How We Select Treatment for Individual Patients

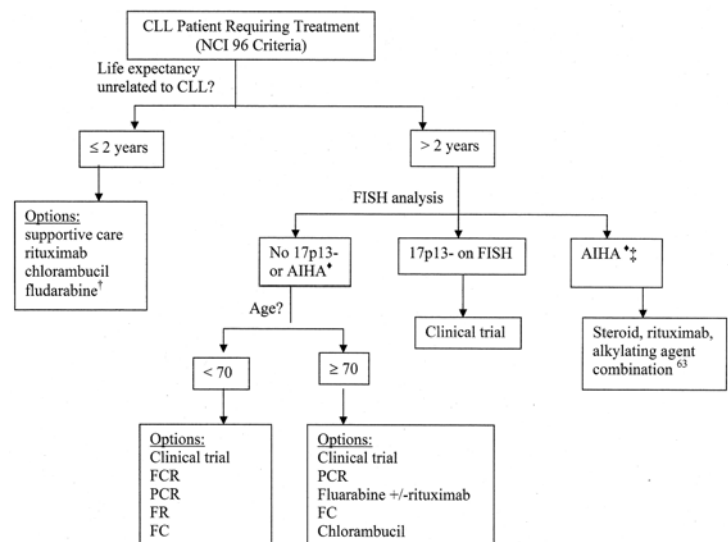
We begin the treatment selection process by assessing patient preferences and assessing how comorbid conditions influence the goals of therapy. CLL or disease-related complications will be the cause of death for most patients with progressive disease. After thoughtful discussion, achieving a complete or partial remission and durable PFS often becomes the goal of care, even among elderly patients. For the approximately 10% of individuals with a del(17p13.1) on FISH, we recommend referral for participation in a clinical trial. For the remaining individuals, we favor treatment with a CIT regimen. Among patients over the age of 65 to 70 years, we prefer PCR-based treatment based on indirect evidence it may be better tolerated than FCR in elderly patients.<sup>59</sup>

For the rare patients for whom temporary

relief of symptoms is the only goal of treatment, a number of treatment options are available, including chlorambucil, rituximab, short courses of single-agent fludarabine (with liberal dose reduction), and transfusion support. Here, selecting the therapy with the least side effects becomes a guiding principle (Figure 3).

### Minimal Residual Disease

With the introduction of more efficacious treatments that often result in CR using the NCI-96 criteria, an important and emerging question is whether eradication of minimal residual disease (MRD) should be a goal of therapy. Since it is simply a metric of a better response to treatment, not surprisingly, the absence of detectable disease by flow cytometry and/or polymerase chain reaction was associated with greater PFS in a number of trials.<sup>50,51,53,60</sup> This has, however, raised the question of whether additional treatment should be given to patients who have detectable disease at the completion of first-line therapy. Several alemtuzumab-based pilot trials have tested this strategy.<sup>61-63</sup> While these trials show that alemtuzumab can eradicate residual disease in a substantial fraction of patients, this therapy is associated with significant potentially life-threatening infectious complications.<sup>61,62</sup> At the present time, administering "consolidation" treatment for eradication of MRD cannot be recommended as a goal of therapy outside of clinical trials. In addition to molecular assays of residual disease, the role of CT scans to identify residual disease is also being explored and may assist in defining response in the future.



**Figure 3. Strategy for selection of first-line therapy for progressive CLL.**

† If used to treat disease-related symptoms; liberal dose reductions.

‡ Indicates our recommended approach for patients with AIHA who also meet NCI 96 criteria for treatment. In patients with AIHA for whom hemolysis is the only indication for treatment, hemolytic anemia can often be successfully managed with immunosuppressive therapies.

Abbreviations: AIHA, autoimmune hemolytic anemia.

**Table 2. Reported treatment options for patients with relapsed/refractory CLL.**

| Treatment regimen  | Response rate in pilot trials* |       |
|--|--------------------------------|-------|
|  | ORR, %                         | CR, % |
| Alemtuzumab  | 33-42                          | 2-4   |
| Alemtuzumab and rituximab                                    | 52                             | 8     |
| Fludarabine, cyclophosphamide, rituximab (FCR)               | 73                             | 25    |
| Cyclophosphamide, fludarabine, alemtuzumab, rituximab (CFAR) | 65                             | 24    |
| Lenalidomide   | 32-47                          | 5-9   |
| High-dose solumedrol ± rituximab                             | 55-100                         | 40    |

\* It should be noted that the pilot trials testing these regimens were phase II studies where the response rates reported are based on treatment of limited numbers of highly selected patients and can be profoundly influenced by the type(s) of prior treatment patients had received.

### Salvage Therapy and Stem Cell Transplantation

Two separate issues that often arise in treatment decisions include what to do with relapsed or refractory CLL and when does allogeneic stem cell transplantation (SCT) become an option? **Table 2** outlines some of the reported treatment options for the relapsed/refractory patient. The principles of considering characteristics of the patient, the disease, and the therapy when selecting treatment remain applicable in the selection of salvage therapy where the type of first-line therapy received and duration of response become important additional characteristics.

The role of SCT continues to be defined in ongoing trials. At the present time, allogeneic SCT is considered for younger patients who fail to respond to first-line therapy with PNAs, relapse shortly (<12 months) after PNA-based treatment, or who have 17p- on FISH testing.

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