The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Chronic lymphocytic leukemia (CLL) is characterized by the progressive accumulation of functionally incompetent monoclonal lymphocytes. CLL is the most common adult leukemia in the Western world, accounting for approximately seven percent of non-Hodgkin lymphomas. In Canada, the median age at diagnosis is approximately 72 years, with ten percent of cases diagnosed in patients younger than 50 years of age. Age-adjusted incidence rates are 7.5 per 100,000 person-years, with males representing approximately 56 percent of the cases. The five-year survival is approximately 80 percent in men and 85 percent in women. In determining the optimal treatment for CLL, individual patient characteristics including performance status and disease stage must be considered.

GUIDELINE QUESTIONS

- What are the recommended diagnostic and staging criteria for adult patients in Alberta with CLL?
- What are the recommended treatment strategies for adult patients in Alberta with newly diagnosed, relapsed, or refractory CLL?
- What are the recommended follow-up and supportive care practices for adult patients in Alberta with CLL?

DEVELOPMENT PANEL

Portions of this guideline document were adapted, with permission, from recommendations developed by a steering committee consisting of hematologists from across Canada. This guideline document was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team. Members of the Alberta Provincial Hematology Tumour Team include hematologists, medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, pharmacists, and a knowledge management specialist from the Guideline Utilization Resource Unit.

SEARCH STRATEGY

An updated review of the literature was conducted by searching journal articles using the Medline (1950 to April Week 1, 2010), EMBASE (1980 to April Week 1, 2010), Cochrane Database of Systematic Reviews (1st Quarter, 2010), and PubMed electronic databases. The MeSH heading “Leukemia, Lymphocytic, Chronic, B-Cell” was combined with the search terms “drug therapy” and “therapy”. The results were limited to adults, practice guidelines, systematic reviews, meta-analyses, multicentre studies, randomized controlled trials, and clinical trials. Articles were excluded from the final review if they: had a non-English abstract, were not available through the library system, or were published before the year 2000. The references and bibliographies of articles identified through these searches were scanned for additional sources. A search for practice guidelines published since January 2000 was conducted by accessing the websites of the following organizations: Cancer Care Ontario, British Columbia Cancer Agency, the National Comprehensive Cancer Network, the European Society for Medical Oncology, and the Italian Society of Hematology/Italian Group for Bone Marrow Transplantation.

TARGET POPULATION

The following guidelines apply to adults over 18 years of age. Different principles apply to pediatric patients.
RECOMMENDATIONS

**Diagnosis and Prognosis:**

1. The initial diagnosis of CLL relies on the detection of a circulating B-lymphocyte count greater than or equal to $5 \times 10^9/L$ in the peripheral blood, for the duration of at least 3 months associated with a characteristic flow cytometry immunophenotype profile including CD19/CD5/CD23/CD43 positivity and cyclin D1 negativity. Small lymphocytic lymphoma is diagnosed when a lymph node or other tissue biopsy demonstrates a malignant lymphocytic infiltration with cells showing the same immunophenotype as CLL, but associated with a circulating B-lymphocyte count that does not exceed $5 \times 10^9/L$.

2. Flow cytometry for ZAP-70 and CD38 expression should be performed at diagnosis to help with prognosis, and guide the frequency of follow-up visits and predict time to initial therapy.

3. FISH cytogenetic analysis for del(17p) or del(11q) should be performed at the time when patients are started on first line treatment. FISH analysis for del(17p) should be repeated at the time of second or third line therapy if patients are potential candidates for allogeneic stem cell transplantation or alemtuzumab.

**First-Line Treatment Options:**

4. The majority of patients with early-stage CLL are managed initially with watchful waiting. The decision to initiate treatment should be based upon symptoms, advanced disease (bulky adenopathy/ splenomegaly or cytopenias), or evidence for rapid disease progression (eg. lymphocyte count doubling within 6 months).

5. Patient fitness and co-morbidities should be considered to determine whether aggressive treatments can be tolerated. In physically fit CLL patients who are able to tolerate more aggressive treatment, the combination of fludarabine + cyclophosphamide + rituximab (FCR) is recommended. The potential for toxicity of this regimen suggests that patients who have some co-morbidities may benefit from less aggressive treatments such as rituximab + fludarabine (FR).

6. In frail patients with significant co-morbidities and competing causes of death, less toxic treatment options are warranted. In such cases, or if a patient declines intravenous treatment, oral chlorambucil is recommended as first choice, followed by oral fludarabine monotherapy as an alternative treatment.

7. Patients whose CLL possesses del(17p) usually do not respond to standard chemotherapy options for CLL. In such cases, alemtuzumab or early use of allogeneic stem cell transplantation could be considered as reasonable options.

**Second-Line Treatment Options:**

8. In fit patients, FCR is an effective regimen for patients naïve to rituximab or FC. Re-treatment with FCR may also be a reasonable treatment option for patients experiencing a long remission (more than two years) after initial FCR treatment.

9. In frail patients, fludarabine or chlorambucil are reasonable second-line treatment options. If the initial remission is greater than 1 year, re-treatment with the initial chemotherapy agent is recommended. If the initial remission is shorter than 1 year, treatment with a different second-line agent is indicated.

10. Allogeneic stem cell transplantation may also be considered for fit patients who are younger than 65 years of age and who have not responded to therapy, have progressive disease within 1 year of fludarabine treatment or within 2 years of fludarabine-based combination treatment, or those whose CLL possesses del(17p) and require treatment.

**Follow-up and Supportive Care:**

11. Patients with CLL often have compromised immune systems due to either the disease itself and/or the associated treatments. Antibiotic prophylaxis and regular vaccinations are recommended, depending on the type of treatments administered.

12. Special attention should also be paid to the appearance of autoimmune cytopenias, such as autoimmune hemolytic anemia, immune thrombocytopenia purpura, and pure red-cell aplasia, which occur in up to 11 percent of patients with CLL.
DISCUSSION

I. Diagnosis

CLL is described by the World Health Organization (WHO) as a neoplasm composed of monomorphic small, round-to-slightly irregular B-lymphocytes in the peripheral blood, bone marrow, spleen, and lymph nodes, admixed with prolymphocytes and paraimmunoblasts forming proliferation centres in tissue infiltrates. According to the 2008 International Workshop on CLL (IWCLL) guidelines, the diagnosis of CLL requires a circulating B-lymphocyte count \( \geq 5 \times 10^9/L \) in the peripheral blood, for the duration of at least 3 months. Although CLL and small lymphocytic lymphoma (SLL) are categorized by the WHO as similar entities, the term SLL is used to indicate neoplastic tissue infiltration in lymph nodes, spleen, or other organs associated with a circulating B-lymphocyte count that does not exceed \( 5 \times 10^9/L \).

Monoclonal B-cell lymphocytosis (MBL) is a condition that resembles CLL, but does not require treatment. As many as 12 percent of healthy individuals over the age of 40 may have low levels (less than \( 5 \times 10^9/L \)) of circulating monoclonal B-cells that are phenotypically identical to CLL cells, but with no evidence of tissue infiltration. MBL progresses to CLL at a rate of one to two percent of patients per year.

Clinical features of CLL vary in their presentation, course, and outcome. Patients are often asymptomatic at diagnosis, but fatigue, autoimmune hemolytic anemia, infections, splenomegaly, hepatomegaly, lymphadenopathy, or extra-nodal infiltrates may be present. Some patients may also exhibit a small serum monoclonal protein, an M-component. Although in rare cases patients may not have lymphocytosis at diagnosis, peripheral blood and bone marrow are usually involved as the disease progresses. Lymph nodes, liver, and spleen are commonly infiltrated, with other extra-nodal sites becoming involved in some patients.

Although some CLL cases may have an atypical immunophenotype, the characteristic profile includes CD19/CD5/CD23/CD43 positivity with weak CD20 and CD11c positivity and dim surface immunoglobulin expression with restricted light chain expression.

II. Staging

Two widely accepted staging methods, the modified Rai and the Binet systems, are used in both patient care and for clinical trials; the modified Rai system is the most commonly used in Canada. These staging systems are relatively simple, relying solely on physical examination and standard laboratory tests.

<table>
<thead>
<tr>
<th>Stage (Rai)</th>
<th>Description</th>
<th>Risk Status (Modified Rai)</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis, with lymphoid cells &gt;30% in the blood and/or bone marrow</td>
<td>Low</td>
<td>11.7</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 with enlarged node(s)</td>
<td>Intermediate</td>
<td>8.3</td>
</tr>
<tr>
<td>II</td>
<td>Stage 0–1 with splenomegaly, hepatomegaly, or both</td>
<td>Intermediate</td>
<td>5.8</td>
</tr>
<tr>
<td>III</td>
<td>Stage 0–II with hemoglobin &lt;110 g/L</td>
<td>High</td>
<td>2.0-4.0</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 0–III with platelets &lt;100 x 10^9/L</td>
<td>High</td>
<td>2.0-4.0</td>
</tr>
</tbody>
</table>
Table 2. Binet Classification System for CLL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hemoglobin ≥100 g/L and platelets ≥100 x 10^9/L and &lt;3 involved nodal areas</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>B</td>
<td>Hemoglobin ≥100 g/L and platelets ≥100 x 10^9/L and ≥3 involved nodal areas</td>
<td>5</td>
</tr>
<tr>
<td>C</td>
<td>Hemoglobin &lt;100 g/L and or platelets &lt;100 x 10^9/L and any number of involved nodal areas</td>
<td>2.0-4.0</td>
</tr>
</tbody>
</table>

III. Prognostic and Predictive Biomarkers

A number of predictive and prognostic markers have been identified that may predict for responsiveness to chemotherapy and survival and may contribute to decisions in the optimal management of CLL.

Cytogenetic testing. Interphase fluorescence in situ hybridization (FISH) can be used to identify cytogenetic abnormalities in more than 80 percent of patients. The most common abnormalities include:

- del(13q) in 14 to 40% of patients
- deletions and/or trisomy in chromosome 12 in 11 to 18% of patients
- del(11q) in 10 to 32% of patients
- del(6q) in 2 to 9% of patients
- del(17p) in 3 to 27% of patients

In general, patients with a normal karyotype or isolated del(13q) can be categorized as low risk with prolonged time to disease progression and better chances of long-term survival, whereas patients with del(17p), and del(11q) are more likely to have a poor prognosis. Patients with trisomy 12 have a treatment advantage over those with del(17p) or del(11q), as they tend to respond better to fludarabine-based therapy. In addition, patients with del(11q) appear to benefit from the addition of cyclophosphamide to fludarabine (FC), and do particularly well with FC plus rituximab (FCR). Del(17p) leads to loss of the p53 tumour suppressor gene, which mediates cell death induced by alkylating agents and purine analogues. Hence, patients with del(17p) are typically less responsive to these agents, but may respond to agents such as alemtuzumab, flavopiridol, and lenalidomide. FISH analysis may therefore be useful in the selection of patients with high risk disease who might benefit from allogeneic stem cell transplantation. Such patients are at high risk of treatment failure and are likely to become refractory to treatment or to relapse early after fludarabine-based therapy.

IgVH mutational status and VH3.21 gene usage. Approximately half of all CLL patients have leukemic cells with somatic hyper-mutations in the immunoglobulin heavy chain variable region (IgVH) genes. Patients with mutated CLL have improved survival as compared to those with unmutated CLL. Patients with unmutated CLL exhibit faster disease progression, atypical peripheral blood cell morphology, adverse cytogenetic features, and clonal evolution. The VH3.21 gene is an unfavourable prognostic marker, regardless of IgVH mutational status. Sequencing of the genome required to determine IgVH mutational status is expensive, time-consuming, and not readily available for clinical purposes at most sites.

ZAP-70 and CD38 expression. In the course of identifying surrogate markers for IgVH mutational status, a small number of genes were identified that allow the separation of mutated and unmutated CLL. The most specific of these genes is the one that encodes for a 70-kD zeta-associated protein (ZAP-70). The majority of mutated CLL cases are ZAP-70 negative (defined as ≤20% positive cells), whereas unmutated forms are more often ZAP-70 positive (defined as >20% positive cells). Discordance of ZAP-70 expression and IgVH mutational status is reported in about 25 percent of CLL patients. Positive ZAP-70
predicts more rapid disease progression and poorer survival. At present, ZAP-70 analysis is hampered by variation in technique, leading to inconsistent results across centres.

CD38 is an ectoenzyme involved in transmembrane signaling and cell adhesion, and can correlate with unmutated IgVH status, predicting a poor prognosis. Though easy to perform through flow cytometric techniques, CD38 is discordant with IgVH mutational status in a significant proportion of cases and variability in results over time are drawbacks for its use.³

**Serum markers.** Serum markers such as CD23, thymidine kinase (TK), and β2-microglobulin (β2M) may predict overall- or progression-free survival (PFS).³ Even in cases of early stage disease, serum TK levels correlate with tumour mass and proliferative activity of CLL cells. In addition, high levels of CD23 are associated with diffuse bone marrow infiltration and rapid lymphocyte doubling time. Serum TK and CD23 assays are not routinely used in Canada. Alternatively, serum levels of β2M are easily available at most Canadian centres and correlate with both clinical stage and overall survival.⁹

### IV. Patient Fitness and Response Assessments

**Assessing patient fitness.** Patient fitness and co-morbidities should be considered in treatment decisions to determine whether aggressive treatments can be tolerated. Several scales exist for determining patient fitness, two of the most common being the Eastern Cooperative Oncology Group (ECOG) Performance Status and the Cumulative Illness Rating Scale (CIRS), both of which can be found in Appendix A.¹³,¹⁴ The CIRS assesses co-morbidities in different organ systems by assigning points to various conditions such as heart disease. The physician tabulates the number of points in a variety of body systems, with a low score indicating optimal health.¹⁵ The CIRS has been used in combination with creatinine clearance (CrCl) by the German CLL Study Group to assess patient fitness for eligibility in a phase III study.¹⁵

Once a fitness score has been determined, it is possible to group patients into a *fit* or *frail* group:

- **Fit Group**
  - ECOG Performance Status 0-2, or
  - CIRS ≤6 and CrCl ≥70 mL/min

- **Frail Group**
  - ECOG Performance Status 3–4, or
  - CIRS >6 or CrCl <70 mL/min

**Initiating treatment.** The IWCLL guidelines describe the initiation of treatment based on a combination of clinical staging, the presence of symptoms, and disease activity.³ These criteria include:

- Evidence of progressive marrow failure as manifested by the development or worsening of anemia and/or thrombocytopenia
- Massive (at least 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
- Massive nodes (at least 10 cm in the longest diameter), or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis, with an increase of more than 50 percent over two months, or lymphocyte doubling time of less than six months (factors contributing to lymphocytosis or lymphadenopathy other than CLL such as infections should be excluded)
- Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids/standard therapy
In addition, any one of the following symptoms should also be present:
- Unintentional weight loss of ten percent or more within the previous six months
- Significant fatigue
- Inability to work or perform usual activities
- Fever higher than 38.0°C for two weeks or more without other evidence of infection
- Night sweats for more than one month without evidence of infection

**Assessing response to treatment.** In assessing the response to treatment, a thorough physical examination and blood analysis should be performed. Although useful in clinical trials, imaging studies, including CT scans, are not an essential part of general practice. Patients in remission should be re-evaluated every three to six months to monitor disease status. Based on the results of the assessment, patients may be categorized as having a complete response (CR), a partial response (PR), progressive disease (PD), or stable disease (SD), as outlined in Table 3. Patients with a clinically beneficial response include those achieving CR and PR; treatment failure includes those with SD, non-response, PD, or death from any cause. Patients experiencing treatment failure during or within six months of treatment are identified as having refractory disease. Those demonstrating PD more than six months after treatment has ended, who have previously achieved a CR or PR, are identified as having relapsed disease.

**Table 3. Criteria for Identifying Treatment Response**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Complete response (CR)</th>
<th>Partial response (PR)</th>
<th>Progressive disease (PD)</th>
<th>Stable disease (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>None &gt;1.5 cm</td>
<td>Decrease ≥50%</td>
<td>Increase ≥50% or appearance of any new lesion</td>
<td>Change of –49% to +49%</td>
</tr>
<tr>
<td>Liver and/or spleen size</td>
<td>Normal size</td>
<td>Decrease ≥50%</td>
<td>Increase ≥50% or new enlargement when previously normal</td>
<td>Change of –49% to +49%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes</td>
<td>&gt;1.5 x 10^9/L without need for exogenous growth factors</td>
<td>&gt;1.5 x 10^9/L or &gt;50% improvement over baseline without need for exogenous growth factors</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Circulating clonal B-lymphocytes</td>
<td>None</td>
<td>Decrease ≥50% over baseline</td>
<td>Increase ≥50% over baseline</td>
<td>Change of –49% to +49%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&gt;100 x 10^9/L without need for exogenous growth factors</td>
<td>&gt;100 x 10^9/L or increase ≥50% over baseline</td>
<td>Decrease ≥50% from baseline or to &lt;100 x 10^9/L secondary to CLL</td>
<td>Change of –49% to +49%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt;110 g/L (untransfused and without need for exogenous erythropoietin)</td>
<td>&gt;110 g/L or increase ≥50% over baseline</td>
<td>Decrease of &gt;20 g/L from baseline or to &lt;100 g/L secondary to CLL</td>
<td>Increase ≤110 g/L or &lt;50% over baseline, or decrease &lt;20 g/L</td>
</tr>
<tr>
<td>Marrow</td>
<td>Normocellular for age, &lt;30% lymphocytes, no B-lymphoid nodules</td>
<td>No BM requirements to document PR</td>
<td>No BM requirements to document PD</td>
<td>No BM requirements to document SD</td>
</tr>
</tbody>
</table>
V. Treatment

First Line Treatment Options for CLL

The ultimate treatment goal in CLL is to achieve a long overall survival, while minimizing toxicities and improving quality of life. In the absence of a survival benefit, achieving a long PFS is a reasonable goal of therapy. For some frail patients, less aggressive treatments may be required; for others, supportive or palliative treatment may be the best course. Consideration of the patient’s preference is always important in the determination of any treatment decision.

Chlorambucil

Chlorambucil has been used as a mainstay treatment for CLL for over 40 years. Many different dosing schedules have been used in CLL, including intermittent dosing from 40 mg/m² every 28 days to 10 mg/m² x 7 every 28 days, or continuous daily dosing of 0.1 mg/kg/day. A convenient oral dosing and well-established side effect profile make chlorambucil a valuable option for frail patients or for those who decline or are unsuitable for more intensive intravenous therapy.

Fludarabine

Fludarabine has been shown to produce response rates of between 50 and 60 percent in patients refractory to traditional alkylating-agent therapy. The superior activity of fludarabine has also been confirmed in treatment-naive patients. In randomized comparisons to alkylating agents, fludarabine has demonstrated a superior clinical response, with response rates of 60 to 80 percent and CR rates of 15 to 20 percent. A Cochrane meta analysis of four randomized trials confirmed the findings of superior PFS with fludarabine (HR=0.70; p <0.00001). In addition, in a recent long-term follow-up analysis of a previous study, Rai et al. reported a survival advantage of fludarabine (63 months versus 59 months, p = 0.04). Despite improved efficacy, however, rates of neutropenia are higher with fludarabine than with chlorambucil, reflecting greater hematologic toxicity; therefore, chlorambucil remains a valuable option in frail and/or elderly patients.

Fludarabine-Cyclophosphamide

Three randomized trials comparing fludarabine (F) or fludarabine-cyclophosphamide (FC) for frontline therapy in CLL have been published to date. In a German CLL Study Group trial, Eichhorst et al. randomized 375 previously untreated patients to FC or F. The overall response (OR) rate (94% versus 83%), CR rate (24% versus 7%), median PFS (48 versus 20 months), and treatment-free survival (37 versus 25 months) were higher with FC compared to F alone, with no difference in overall survival. In the US ECOG study, Flinn et al. randomized 278 patients to F or FC. Patients treated with FC achieved a higher OR rate (74% versus 59%), CR rate (23% versus 5%), and median PFS (32 versus 19 months), with no improvement in overall survival. However, the presence of del(17p) and del(11q) negatively affected PFS (HR=3.43 and 1.90, respectively). Finally, in the CLL-4 study in the United Kingdom, Catovsky et al. randomized patients to chlorambucil alone, fludarabine alone, or FC. Patients treated with FC had better CR and overall survival rates than patients treated with fludarabine alone or chlorambucil alone. A statistically significant advantage in PFS was seen for the FC arm compared with the other arms (36% for FC versus 10% for both the fludarabine and chlorambucil arms; p <0.00005). FC was superior in all age groups, including patients over 70 years old. However, patients with del(17p) had inferior CR and overall response rates, irrespective of treatment group.
Despite improved efficacy, the UK CLL-4 and US ECOG studies both reported higher neutropenia rates in the patients treated with FC. The improvement in response observed with FC as compared to fludarabine or chlorambucil monotherapy makes FC a reasonable option in fit patients who are able to tolerate more aggressive treatment. In frail patients, less aggressive treatment options may be warranted to ensure side effects can be tolerated. In cases where a patient declines intravenous treatment, oral fludarabine or chlorambucil are alternatives.

**Addition of Rituximab to Chemotherapy Backbones**

As a single agent in CLL, rituximab has only moderate activity, perhaps because of the dim CD20 expression on B-CLL cells. However, with higher doses than are typically used in lymphoma, the activity of single-agent rituximab in CLL is greatly enhanced.\(^{32,33}\) In a study examining the efficacy of rituximab (375 mg/m\(^2\)) monotherapy in CLL, Byrd et al. reported OR, CR, and PR rates of 45, 3, and 42 percent, respectively.\(^{33}\) Rituximab has been studied in a number of clinical trials evaluating its additional impact in combination therapy. The National Comprehensive Cancer Network (NCCN) currently recommends the use of rituximab in combination with F, FC, or PC (pentostatin-cyclophosphamide) for fit patients with CLL.\(^{34}\) In frail patients, rituximab monotherapy may be a reasonable first-line option; however, results are moderate as mentioned above.

**Fludarabine-rituximab (FR).** Initial studies of rituximab combinations explored the addition of rituximab to fludarabine. Byrd et al. conducted the randomized CALGB 9712 phase II study to determine the efficacy, safety, and optimal administration schedule for rituximab with fludarabine in previously untreated CLL patients.\(^{35}\) Patients were randomized to receive either six monthly courses of fludarabine concurrently with rituximab, followed two months later by four weekly doses of rituximab as consolidation therapy; or sequential fludarabine monotherapy, followed two months later by rituximab consolidation therapy. A total of 104 patients were randomized to the concurrent (n = 51) and sequential (n = 53) regimens. An OR rate of 90% and CR rate of 47% was observed in the concurrent group, as compared to an OR rate of 77% and a CR rate of 28% in the sequential group. In a subsequent retrospective analysis published in 2005, patients given FR in the CALGB 9712 trial were compared to patients given fludarabine monotherapy in the CALGB 9011 trial.\(^{36}\) Results revealed statistically significant higher PFS and overall survival in patients who received fludarabine and rituximab, as compared with patients who received fludarabine alone. Based on the results of phase II trials, some Canadian centres have adopted the use of FR as the standard first-line treatment in both fit and frail patients. Further studies evaluating the FR regimen are currently underway, which may help to clarify its role in CLL patient subsets.

**Fludarabine-cyclophosphamide-rituximab (FCR).** Recent phase II studies examining the addition of rituximab to FC (FCR) have demonstrated a high CR and OR rate of approximately 70% and 95%, respectively.\(^ {25,37}\) The impressive results of these phase II studies drove the design and execution of a phase III study by the German CLL Study Group (CLL-8 study) comparing the primary endpoint of PFS after treatment with FCR or FC.\(^ {15}\) Study participants included 817 patients selected for minimal co-morbidity (CIRS <6). Patients were randomly assigned to receive six courses of either FC (F: 25 mg/m\(^2\), days 1–3 + C: 250 mg/m\(^2\), days 1–3) or FC with the addition of rituximab (375 mg/m\(^2\), day 0 of the first cycle and 500 mg/m\(^2\), day 1 of all subsequent cycles) plus FC. Median PFS was reported as 32.8 months in the FC arm and 51.8 months in the FCR arm (HR 0.56; \(p < 0.0001\)). The PFS observed in the FC arm was similar to that observed in previous studies using FC, which have reported a range of 32 to 48 months.\(^ {30}\) Statistically significant differences were observed in overall survival rates between the two treatment arms (87.2% in the FCR arm versus 82.5% in the FC arm at 37.7 months, \(p = 0.012\)). Only patients in Binet stages A and B showed a superior overall survival after FCR treatment (Binet A: HR 0.19, Binet B: HR 0.77, Binet C: HR 0.73).
\( p = 0.09; \) Binet B: HR 0.45, \( p < 0.001; \) Binet C: HR 1.4, \( p = 0.168). \) Response rates were higher in the FCR group versus the FC group and are the highest reported rates of any chemotherapy regimen used to date. Grade 3 and 4 hematological toxicity, neutropenia, and leukocytopenia rates were higher in the FCR versus FC arm (55.7\% versus 39.6\%, 33.7\% versus 21\%, and 24.0\% versus 12.0\%, respectively; \( p < 0.0001).^{15}\) Based on the results from the CLL-8 trial, FCR is currently the best option for the first-line treatment of fit patients with CLL.\(^{15}\)

The doses of rituximab recommended in clinical practice are: 375 mg/m\(^2\) for cycle 1, 500 mg/m\(^2\) for cycles 2 through 6, in combination with 25 mg/m\(^2\) of fludarabine and 250 mg/m\(^2\) of cyclophosphamide on days 1–3 of each cycle. Despite the improved efficacy, the potential toxicity of FCR suggests that frail patients may benefit from less aggressive treatments. In balancing toxicity with efficacy, FR remains a reasonable first-line option in CLL until results from randomized studies are available. For those patients who decline intravenous treatments, oral fludarabine and chlorambucil remain reasonable options.

The addition of rituximab to other chemotherapy backbones in first-line treatment has been explored in a number of phase II studies. These studies have shown promising results using cyclophosphamide, fludarabine-alemtuzumab-rituximab (CFAR); reduced-dose FCR (FCRLite); pentostatin-cyclophosphamide-rituximab (PCR); rituximab with alemtuzumab; and rituximab with fludarabine-cyclophosphamide-mitoxantrone (R-FCM).\(^{38-42}\)

**Alemtuzumab for Patients with del(17p)**

In cases where FISH analysis has been performed and reveals the presence of del(17p), standard treatments which rely on the p53 pathway for activity may be less effective.\(^3\) Treatments with chlorambucil, fludarabine, and rituximab have shown poor response rates in patients with this cytogenetic abnormality.\(^{43}\) Alemtuzumab acts via a p53 independent mechanism, and therefore may have beneficial results in patients with del(17p).\(^{44}\) Evidence of the role of alemtuzumab in high-risk patients was first shown in the refractory setting in a study by Stilgenbauer et al., who reported a response rate of 54\% in fludarabine-refractory patients with del(17p) or p53 abnormalities.\(^{45}\) In a subsequent trial, Lozanski et al. reported a 31\% response in patients with this high-risk profile.\(^{43}\) In the first-line setting, results of a randomized controlled trial comparing alemtuzumab to chlorambucil were reported by Hillmen et al.\(^{21}\) Of the 282 patients who underwent FISH cytogenetic analysis, 20 (7\%) patients had del(17p). Patients with del(17p) who were treated with alemtuzumab had a PFS of 10.7 months compared to 2.2 months for patients who received chlorambucil. Although there was a trend of increased PFS in the del(17p) group treated with alemtuzumab, it did not reach statistical significance. Overall response rates for these two groups were 64 and 20\%, respectively. Given the limited effectiveness of standard therapy in patients with del(17p), alemtuzumab may be considered a valuable alternative in this poor-risk group.
Second-Line Treatment Options for Relapsed and Refractory Patients with CLL

Recommendations for second-line treatment of CLL should consider individual factors such as comorbidities and the length of the disease-free interval. Patients experiencing treatment failure within six months of treatment are identified as having refractory disease. Those demonstrating progressive disease after more than six months of treatment, who have previously achieved a CR or PR, are identified as having relapsed disease. When initial remission is greater than one year, re-treatment with the initial regimen is reasonable; in shorter remissions, treatment with a different second-line regimen is indicated. In frail patients, fludarabine and chlorambucil are reasonable second-line options where they have not been given previously, or in those experiencing a long remission from either regimen. In fit patients, FCR is an effective regimen in patients naïve to rituximab or FC; reuse of FCR may also be reasonable in patients experiencing a long remission (more than two years) after initial treatment.

Allogeneic stem cell transplantation. Allogeneic stem cell transplantation may be considered for fit patients younger than 65 years who:
- Have no response to initial CLL therapy
- Have progressive disease within one year of fludarabine treatment or within two years of fludarabine-based combination therapy, or
- Have CLL with del(17p) abnormalities and require treatment

VI. Managing Complications and Supportive Care in CLL

Prevention and management of infections. Patients with CLL often have compromised immune systems due to the disease itself and/or its associated treatments. Infections are therefore common, and prophylaxis is appropriate, depending on the type of treatment given. The use of live vaccines in patients with CLL is not recommended. However, the use of inactivated vaccines such as annual influenza and pneumococcal polysaccharide (PPV) every five years for patients in remission for more than three months is recommended. Table 4 summarizes antibiotic prophylaxis and recommended vaccinations for patients with CLL.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Possible infection</th>
<th>Antibiotic prophylaxis</th>
<th>Vaccine</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>Encapsulated bacteria</td>
<td>Penicillin</td>
<td>Pneumococcal, Hemophilus, and Meningococcal prior to splenectomy</td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab or allogeneic stem cell transplant</td>
<td>CMV</td>
<td>Valgancyclovir pre-emptive therapy for increased PCR</td>
<td>n/a</td>
<td>CMV monitoring by PCR every 1–2 weeks</td>
</tr>
<tr>
<td>Alemtuzumab, fludarabine, or rituximab</td>
<td>Hepatitis B</td>
<td>Lamivudine 100 mg/day orally for the entire duration of chemotherapy and 6 months afterwards</td>
<td>n/a</td>
<td>Avoid in patients with known prior hepatitis B</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Varicella Zoster</td>
<td>Acyclovir or equivalent</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Fludarabine-based treatment</td>
<td>Pneumocystisjiroveci pneumonia</td>
<td>Bactrim or equivalent may be considered</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>
When infections occur, they should be diagnosed, treated, and reported. The etiology of any infection should be identified as bacterial, viral, or fungal, and the severity should be quantified as:  
- Minor: requiring either oral antimicrobial therapy or symptomatic care alone  
- Major: requiring hospitalization and systemic antimicrobial therapy  
- Fatal: death as a result of the infection

Where patients experience recurrent infections that require intravenous antibiotics or hospitalization, antimicrobials should be given as needed. In patients with recurrent infections and where serum IgG is less than 5 g/L, monthly intravenous immunoglobulins should be given at 0.3–0.5 g/kg; dose and interval should be adjusted to maintain a nadir level of more than 5 to 7 g/L.

**Auto-immune cytopenias.** Patients with CLL are at increased risk of developing auto-immune cytopenias, such as autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenia purpura (ITP), and pure red cell aplasia (PRCA). AIHA will develop in approximately 11 percent of advanced-stage CLL patients. AIHA is diagnosed by the presence of at least one marker of hemolysis (increased indirect bilirubin not due to liver disease, increased lactate dehydrogenase without alternative etiology, increased absolute reticulocyte count, increased bone marrow erythropoiesis in the absence of bleeding, or decreased haptoglobin) with direct or indirect evidence of an autoimmune mechanism (positive direct antiglobulin test (DAT) for either IgG or C3d, cold agglutinins, or at least two markers of hemolysis in the absence of evidence of bleeding or hypersplenism).

ITP is less common, occurring in two to three percent of CLL patients at diagnosis or during early stage disease. ITP can be identified where platelet counts are less than or equal to 100 × 10⁹/L with no evidence of hypersplenism, no evidence of increased platelet consumption due to other causes, and normal or increased megakaryocytes on bone marrow examination. PRCA is present in six percent of CLL patients that are tested. PRCA can be diagnosed when hemoglobin concentration is less than or equal to 120 g/L, with reticulocytopenia and isolated absence of erythrocyte precursors in the bone marrow. Parvovirus infection must be ruled out, which can be done by using a blood polymerase chain reaction (PCR) assay.

ITP and AIHA, as a single abnormality caused by CLL, should be treated initially using glucocorticoids. Several case reports and small series have described an increased risk of AIHA following single-agent fludarabine therapy, particularly in patients with a positive DAT. Combination therapy or chlorambucil monotherapy may be preferable in the treatment of patients with CLL with a history of AIHA. Second-line options for AIHA include splenectomy and intravenous immunoglobulins. Good responses have also been obtained using rituximab or alemtuzumab. Refractory cases could be considered for immune suppressive therapy with cyclosporine A, azathioprine, or low-dose cyclophosphamide, although these agents are associated with high rates of infection and other complications. Most patients with PRCA will respond to therapy with cyclosporine A or corticosteroids, but prolonged high doses are usually needed; steroid-sparing agents such as cyclophosphamide may therefore be required. Rituximab may be an additional option for the treatment of PRCA, but success rates are lower than those seen for AIHA or ITP.

**Richter syndrome.** The majority of Richter syndrome cases involve the transformation of CLL to diffuse large B-cell lymphoma (DLBCL). The morphology of DLBCL consists of sheets of large neoplastic B-lymphocytes clearly distinguishable from small lymphocytes, with sparse cytoplasm and clumped chromatin typical of CLL. Diagnosis of Richter syndrome requires the pathologic identification of CLL transformation to aggressive lymphoma. Ideally, this should be determined by histology using a biopsy of the index lesion.
Based on existing data, Richter syndrome may be treated with cytoreductive chemotherapy appropriate for DLBCL (e.g. R-CHOP), with the goal of achieving a response. The role of consolidation therapies previously tested for CLL or DLBCL in patients responding to initial therapy as well as the impact of new first-line therapies, may aid in the development of an ideal treatment approach in these patients. Allogeneic stem cell transplantation should also be considered in younger fit patients with Richter syndrome who respond to initial therapy.

**Tumour lysis syndrome.** Tumour lysis syndrome occurs when the release of large amounts of intracellular components of lysed malignant cells leads to a number of metabolic imbalances. Resulting hyperuricemia, hyperkalemia, and hyperphosphatemia may then lead to renal failure and cardiac arrhythmias. Tumour lysis syndrome usually occurs within two or three days after the initiation of therapy, with rare cases occurring after second-line treatment. Major risk factors include high tumour burden, high rate of proliferation, and disease that is highly responsive to therapy.

Before the initiation of treatment, patients with a white blood cell (WBC) count higher than 50,000/mm$^3$ should be adequately hydrated and monitored frequently. In patients with previous episodes of tumour lysis syndrome, consultation with a nephrologist should be considered. Where overt uremic symptoms are present, dialysis may be necessary in order to prevent acute renal failure. In outpatients, frequent monitoring of serum electrolytes and uric acid is recommended as a preventative measure. Prophylactic allopurinol (300 mg/day orally) is necessary when a rapid lysis of large numbers of lymphocytes is anticipated (initial WBC count >200 x 10$^9$/L). Allopurinol should also be given to patients with significant renal dysfunction or chronic hyperuricemia. In the advent of tumour lysis syndrome it may be necessary to interrupt treatment until symptoms are resolved. Cardiac activity should be monitored continuously, and frequent monitoring of electrolyte levels is recommended. Rasburicase may also be considered for the prevention and treatment of tumour lysis syndrome in patients with a high WBC count, coexistent renal insufficiency, and an allopurinol intolerance or allergy.

Close monitoring for tumour lysis syndrome is recommended for patients with lymphocytosis greater than 30 x 10$^9$/L who are receiving a first cycle of rituximab. Consideration may be given to dividing the dose over two days for the first infusion.

**Blood product support.** Transfusion-related graft-versus-host disease has been described in patients actively receiving fludarabine or alemtuzumab. Canadian Blood Services recommends that patients on fludarabine or alemtuzumab should receive irradiated and cytomegalovirus-negative blood products.
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIHA</td>
<td>autoimmune hemolytic anemia</td>
</tr>
<tr>
<td>β2M</td>
<td>beta-2-microglobulin</td>
</tr>
<tr>
<td>CALG-B</td>
<td>Cancer and Leukemia Group B</td>
</tr>
<tr>
<td>CFAR</td>
<td>cyclophosphamide + fludarabine + alemtuzumab + rituximab</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CIRS</td>
<td>Cumulative Illness Rating Scale</td>
</tr>
<tr>
<td>CLL</td>
<td>chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CrCl</td>
<td>creatinine clearance</td>
</tr>
<tr>
<td>DAT</td>
<td>direct antiglobulin test</td>
</tr>
<tr>
<td>DLBCL</td>
<td>diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>FC</td>
<td>fludarabine + cyclophosphamide</td>
</tr>
<tr>
<td>FCR</td>
<td>fludarabine + cyclophosphamide + rituximab</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
</tr>
<tr>
<td>FR</td>
<td>fludarabine + rituximab</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
</tr>
<tr>
<td>IgVH</td>
<td>immunoglobulin heavy chain variable regions</td>
</tr>
<tr>
<td>ITP</td>
<td>idiopathic thrombocytopenia purpura</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>IWCLL</td>
<td>international workshop on chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>MBL</td>
<td>monoclonal B-cell lymphocytosis</td>
</tr>
<tr>
<td>OR</td>
<td>overall response</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>PC</td>
<td>pentostatin + cyclophosphamide</td>
</tr>
<tr>
<td>PCR</td>
<td>pentostatin + cyclophosphamide + rituximab</td>
</tr>
<tr>
<td>PCR assay</td>
<td>polymerase chain reaction assay</td>
</tr>
<tr>
<td>PD</td>
<td>progressive disease</td>
</tr>
<tr>
<td>PFS</td>
<td>progression-free survival</td>
</tr>
<tr>
<td>PO</td>
<td>by mouth, orally</td>
</tr>
<tr>
<td>PPV</td>
<td>pneumococcal polysaccharide vaccine</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
<tr>
<td>PRCA</td>
<td>pure red cell aplasia</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>rituximab + cyclophosphamide + Adriamycin + vincristine + prednisone</td>
</tr>
<tr>
<td>R-FCM</td>
<td>rituximab + fludarabine + cyclophosphamide + mitoxantrone</td>
</tr>
<tr>
<td>SD</td>
<td>stable disease</td>
</tr>
<tr>
<td>SLL</td>
<td>small lymphocytic lymphoma</td>
</tr>
<tr>
<td>TK</td>
<td>thymidine kinase</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>ZAP-70</td>
<td>70 kD zeta associated protein</td>
</tr>
</tbody>
</table>

IMPLEMENTATION STRATEGY

- Discuss the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
EVALUATION STRATEGY

A formal review will be conducted in 2011, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

REFERENCES

15. Hallek M, Fingerle-Rowson G, Fink A, Busch R, Mayer J, Hensel M, et al. First-line treatment with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) improves overall survival (OS) in previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL): Results of a randomized phase III trial on behalf of an international group of investigators and the German CLL Study Group. Blood (ASH Annual Meeting Abstracts) 2009 Nov;114(22): Abstract 535.


### Eastern Cooperative Oncology Group (ECOG) Performance Status Categories

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
### APPENDIX B: CUMULATIVE ILLNESS RATING SCALE (CIRS)\(^4\)

<table>
<thead>
<tr>
<th>Systems</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Ophthalmological and ORL</td>
<td></td>
</tr>
<tr>
<td>Upper Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Lower Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Hepatic and Pancreatic</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Tegumental</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Endocrine, Metabolic, Breast</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
</tr>
<tr>
<td><strong>Total Score</strong>(^*)</td>
<td></td>
</tr>
</tbody>
</table>

* Only one score is given to each system; total score is the sum of all the scores.

### CIRS Severity Rating

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no problem affecting that system</td>
</tr>
<tr>
<td>1</td>
<td>current mild problem or past significant problem</td>
</tr>
<tr>
<td>2</td>
<td>moderate disability or morbidity and/or requires first-line therapy</td>
</tr>
<tr>
<td>3</td>
<td>severe problem and/or constant and significant disability and/or hard to control chronic problems</td>
</tr>
<tr>
<td>4</td>
<td>extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment</td>
</tr>
</tbody>
</table>

### Medical Problems by System

#### Cardiac
- Any cardiac problem (angina, myocardial infarction, arrhythmia, valve problems)?
- If affirmative, any medications taken for these problems?
- Any heart surgery in the past?

#### Vascular
- Any circulatory problem (i.e., peripheral atherosclerotic disease, aneurysm of the abdominal aorta), hypertension, or cholesterol problem?
- If affirmative, any medications taken for these problems?
- Any vascular surgery in the past (i.e., bypass graft surgery of lower limbs, carotid endarterectomy)?

#### Hematological
- Any blood problem (i.e., anemia, leukemia, hypercoagulability or any other problem affecting the blood, blood cells, spleen, or lymphatic system)?
- If affirmative, any medications taken for these problems (i.e., iron)?
- **Note:** patients taking anticoagulants belong to this system if the main problem is of hypercoagulability (i.e., thrombosis or recurrent embolism). If anticoagulants were taken for arrhythmias, rate the problem in “Cardiac”.  

Respiratory
- Any respiratory problem (i.e., asthma, emphysema, bronchitis, pulmonary embolism)?
- If affirmative, any medications taken for these problems? Pressurized aerosols?
- Any lung surgery?
- Cigarette smoking: how many packs per day? For how long?
  - Pack years = number of packs/day x number of years smoked
    - Smoker up to 20 pack-years = rated 1
    - Smoker from 21 to 40 pack-years = rated 2
    - Smoker over 40 pack-years = rated 3

Ophthalmological and Otorhinolaryngology
- Any problem with eyes (i.e., glaucoma, cataract, vision loss), ears (i.e., important hearing impairment), nose, throat, voice?
- Any medications taken for these problems? Eye drops?
- Note: vertigo and dizziness are included in this section, unless they are of neurological origin.

Upper Gastrointestinal
- Any problems with stomach or digestion (includes esophagus, stomach, and duodenum)?
- If affirmative, any medication taken?
- Surgery for the stomach or esophagus?

Lower Gastrointestinal
- Any intestinal problems (i.e., intestinal hernias, constipation, anal problems, incontinence)?
- If affirmative, any medications taken?
- Surgery for the abdomen?

Hepatic and Pancreatic
- Any problem in the liver or the pancreas?
- Any medications taken for these problems?
- Surgery for the liver or the pancreas (i.e., cholecystectomy)?

Renal
- Any problems in the kidneys (i.e., impairment in function, infection)?
- If affirmative, any medications taken for these problems?
- Surgery for the kidneys?

Genitourinary
- Any urinary problems (i.e., lithiasis, incontinence)?
- If affirmative, any medications taken for these problems?
- Any surgery for the urinary bladder or for renal lithiasis?

Musculoskeletal and Tegumental
- Any problem in the skin, joints, bones, or muscles (i.e., arthrosis, osteoporosis, carpal tunnel, any other skin or musculoskeletal problem)?
- Note: Fibromyalgia is rated in this section; it may also be rated in “Psychiatric” if necessary.
- Any medication or anti-inflammatory drugs? Infiltrations? Creams prescribed by a doctor?

Neurological
- Any neurological problem (i.e., cerebrovascular accident, peripheral neuropathy, headaches)?
- If affirmative, any medications taken for these problems?
- Surgery for these problems?
Endocrine, Metabolic, Breast
- Any problem of the thyroid gland, obesity, diabetes, or any other hormonal problem?
- For obesity:
  - Body Mass Index (BMI) > 30 = rated 1
  - BMI > 30 + medication or moderate disability = rated 2
  - BMI > 45 = rated 3
- Any medication taken for these problems?
- Any surgery for these problems?
- Menopause or andropause in men? Any hormones?
  - Menopause/andropause without hormone therapy or symptoms = rated 0
  - Menopause/andropause with hormone therapy or symptoms = rated 1

Psychiatric
- Any problem of depression, anxiety, alcohol, drug abuse, or other problems?
- If affirmative, any medications taken for these problems?
- Note: personality problems are rated in this section, but the patient’s chart should be checked.
APPENDIX C: CHEMOTHERAPY REGIMENS FOR ADULT PATIENTS WITH CLL

Chlorambucil:
- 40 mg/m^2 every 28 days, or
- 10mg/m^2 days 1-7, every 28 days, or
- 0.1 - 0.2 mg/kg/day for 4-8 weeks, then usually reduce for maintenance.

Fludarabine:
- 25mg/m^2 IV days 1-5, every 28 days, or
- 40mg/m^2 PO days 1-5, every 28 days (round down to nearest multiple of 10mg)

Fludarabine + Cyclophosphamide (FC):
- Fludarabine 25 mg/m^2 IV, days 1–3
- Cyclophosphamide 250 mg/m^2, days 1–3
- Cycles: every 28 days

Fludarabine + Rituximab (FR):
- Fludarabine 40mg/m^2 PO days 1-5, every 28 days (round down to nearest multiple of 10mg)
- Rituximab 375 mg/m^2 day 0 of cycle 1, then 500 mg/m^2 day 1 for cycles 2-6
- Cycles: every 28 days

Fludarabine + Cyclophosphamide + Rituximab (FCR):
- Fludarabine 25 mg/m^2 IV days 1-3
- Cyclophosphamide 250 mg/m^2, days 1-3
- Rituximab 375 mg/m^2 day 0 of cycle 1, then 500 mg/m^2 day 1 for cycles 2-6
- Cycles: every 28 days

Fludarabine + Cyclophosphamide + Rituximab (FCR PO alternative):
- Fludarabine 32 mg/m^2 PO, days 1-5 (round down to nearest multiple of 10mg tablet)
- Cyclophosphamide 600 mg/m^2 IV, day 1
- Rituximab 375 mg/m^2 IV day 0 of cycle 1, then 500 mg/m^2 day 1 for cycles 2-6
- Cycles: every 28 days

Alemtuzumab (for patients with del17p):
- Dose-escalation phase: escalated daily (3, 10, 30 mg) until tolerated at an IV dose of 30 mg over 2 hours
- Subsequently, 30 mg IV three times/week for no more than 12 weeks, including the dose-escalation phase.

Allogeneic Stem Cell Transplantation:
- May also be considered for patients who are younger than 65 years of age, have not responded to therapy, have progressive disease within one year of fludarabine treatment or within two years of fludarabine-based combination treatment, or with del(17p) abnormalities requiring treatment.