A Canadian Perspective on the Management of Chronic Lymphocytic Leukemia

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Background

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world, accounting for approximately 7% of non-Hodgkin’s lymphomas. In Canada, the median age at diagnosis is approximately 72 years, with less than 10% of cases diagnosed in patients under 50 years. Age-adjusted incidence rates are 7.5/100,000 person-years (p-yrs), with males representing approximately 57% of cases (male:female ratio = 1.3:1). The five-year relative survival is about 80% (95% CI: 73–86) in men and tends to be higher in women (85%; 95% CI: 78–92).

Purpose of this document

There is no uniform standard of care for the treatment of CLL and at present, no national guidelines for managing CLL have been developed in Canada. In determining the optimal treatment for CLL, individual patient characteristics including performance status and disease stage must be considered. Based on these criteria, a number of patient subgroups therefore exist and should be included in treatment decisions.

Diagnosing CLL

The World Health Organization (WHO) defines CLL and small lymphocytic lymphoma (SLL) as “a neoplasm composed of monomorphous small, round to slightly irregular B lymphocytes in the peripheral blood, bone marrow, spleen, and lymph nodes, admixed with prolymphocytes and paraimmunoblasts forming proliferation centers in tissue infiltrates.”

According to the International Workshop on CLL (IWCLL) 2008 guidelines, the diagnosis of CLL requires ≥5 x 10⁹ B lymphocytes/L in the peripheral blood for the duration of at least three months. In Canada, bone marrow biopsies and computed tomography (CT) scans are not routinely used in the diagnosis or management of CLL. Although CLL and SLL are considered together 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 <5 x 10⁹/L.

As many as 12% of healthy individuals >40 years of age may have low levels (<5 x 10⁹/L) of circulating monoclonal B cells. These cells are phenotypically identical to CLL cells, but there is no evidence of tissue infiltration. This recently identified condition is referred to as monoclonal B-cell lymphocytosis (MBL). MBL progresses to CLL at a rate of 1%–2% 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 (AIHA), 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.

Table 1. Immunophenotype in the differential diagnosis of CLL*

<table>
<thead>
<tr>
<th>Disease</th>
<th>slg</th>
<th>CD5</th>
<th>CD23</th>
<th>CD10</th>
<th>CD11c</th>
<th>CD43</th>
<th>CD103</th>
<th>FMC7</th>
<th>CD25</th>
<th>Cyclin D1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>–/+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–/+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PLL</td>
<td>++</td>
<td>–/+</td>
<td>–/+</td>
<td>–</td>
<td>+/−</td>
<td>−/+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>HCL/v</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+/−</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>−</td>
</tr>
<tr>
<td>MCL</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>−/−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+/−</td>
<td>−/−</td>
<td>+</td>
</tr>
<tr>
<td>FL-L</td>
<td>+</td>
<td>–</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>LPL</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−/+</td>
<td>+</td>
<td>−/+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>

*Adapted from Kalil, et al. 1999; Rothel, et al. 1996

†All express pan B-cell-associated antigens (e.g., CD19, CD20) and HLA-DR class II antigens; –/+, +, −, ++, +/− symbols refer to the frequency a marker is expressed.

CLL = chronic lymphocytic leukemia; FL-L = follicular lymphoma-leukemic phase; HCL/v = hairy cell leukemia/hairy cell leukemia variant; LPL = lymphoplasmacytoid lymphoma; MCL = mantle cell lymphoma; PLL = prolymphocytic leukemia; slg = surface immunoglobulin
Clinical staging
Two widely accepted staging methods are used at diagnosis in both patient care and clinical trials: the modified Rai and the Binet systems, with the modified Rai system being the most commonly used in Canada. (Tables 2 and 3) These staging systems are relatively simple, relying solely on physical examination and standard laboratory tests.3,5,10

Prognostic tests
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. However, these tests may not be routinely available and, with the current state of knowledge, should not determine when to initiate first-line treatment outside the setting of a clinical trial.5

Cytogenetic testing
Interphase fluorescence in situ hybridization (FISH) can be used to identify cytogenetic abnormalities in more than 80% of patients.5 The most common are del(13q) in 14%–40%, deletions and/or trisomy in chromosome 12 in 11%–18%, del(11q) in 10%–32%, del(6q) in 2%–9%, and del(17p) in 3%–27% of patients (the higher value for del(17p) occurring with disease progression and treatment).11 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.11 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).11,12 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.5,11 FISH analysis may therefore be useful in the selection of patients with high-risk disease who might benefit from allogeneic stem cell transplantation (allo-SCT). 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.13 Though the prognostic value of FISH cytogenetics is best validated when performed at diagnosis, repeat analysis may be justified to identify additional genetic defects acquired with disease progression.5

<table>
<thead>
<tr>
<th>Table 2. Rai and modified Rai classification system*</th>
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<tbody>
<tr>
<td><strong>Stage (Rai)</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>

*Adapted from the 2008 IWCLL guidelines; 2008 NCI guidelines; BC Cancer Agency 2008 guidelines3,5
†These median survival estimates are based on earlier study data and do not take into account the revision of CLL diagnostic techniques and the improved efficacy of treatment. A recent retrospective study by Shanafelt, et al. examined median estimated survival times by Rai stage category in CLL patients from the Mayo Clinic patient database. Results showed that median survival times were not reached for low-risk, were approximately 10 years for intermediate-risk, and around 7 years for high-risk patients.10

<table>
<thead>
<tr>
<th>Table 3. Binet classification system*†</th>
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</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
</tbody>
</table>

*Adapted from the 2008 NCI guidelines5
†Areas of involvement considered for staging are as follows: (1) Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of nodes is enlarged), (2) Axillae (involvement of both axillae counts as one area), (3) Groins, including superficial femorals (involvement of both groins counts as one area), (4) Palpable spleen, (5) Palpable liver (clinically enlarged).
IgVH mutational status and VH3.21 gene usage

Approximately half of all CLL patients have leukemic cells with somatic hypermutations in the immunoglobulin heavy chain variable region (IgVH) genes. Patients with IgVH mutations (mutated CLL) have improved survival as compared to those with unmutated IgVH (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% of CLL patients. ZAP-70 analysis is hampered by variation in technique, leading to inconsistent results across centres.

CD38 is an ectoenzyme involved in transmembrane signalling 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.

Serum markers

Serum markers such as CD23, thymidine kinase (TK), and β2-microglobulin (β2M) may predict survival or progression-free survival (PFS). 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 centres and correlate with both clinical stage and overall survival (OS).

Assessing patient fitness

Patient fitness and co-morbidities should be considered in treatment decisions to determine whether aggressive treatments can be tolerated. Several systems 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). In determining whether a patient can be categorized as fit, one of these scoring systems should be used.

In 1982, ECOG developed a set of performance status criteria that categorizes patients into one of five categories from high to low levels of physical function. These categories were designed to assess how the patient’s disease affects daily living. The ECOG Performance Status categories are also commonly used within the context of CLL to assess treatment intensity and whether elderly patients could be included in specific clinical trials.

| Table 4. ECOG Performance Status categories* |
|---|---|
| Grade | Description |
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | 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 |
| 2 | Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self care. Totally confined to bed or chair |
| 5 | Dead |

*Adapted from Oken, et al.1982
ECOG = Eastern Cooperative Oncology Group
A second system for assessing patient fitness is the Cumulative Illness Rating Scale (CIRS). 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, where a low score indicates optimal health. This scoring system in combination with creatinine clearance (CrCl) has been used by the German CLL Study Group to assess patient fitness for eligibility in a phase III study evaluating the efficacy of FCR (rituximab, fludarabine, cyclophosphamide) versus FC (fludarabine, cyclophosphamide). See Appendix A for a detailed description of how to calculate the CIRS score.

Categorizing patients into fitness types
Once a fitness score has been determined based on one of the systems discussed, it is possible to group patients into a fit or frail group. (Table 5)

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Description</th>
</tr>
</thead>
</table>
| Fit group     | One of the following:  
                       a) ECOG Performance Status 0–2  
                       b) CIRS ≤6 and CrCl ≥70 mL/min |
| Frail group   | One of the following:  
                       a) ECOG Performance Status 3–4  
                       b) CIRS >6 or CrCl <70 mL/min |

CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group

Decision to treat and determining response in the management of CLL

The 2008 National Cancer Institute (NCI) guidelines support the initiation of treatment based on a combination of clinical staging, the presence of symptoms, and disease activity. These criteria are also supported by the 2008 National Comprehensive Cancer Network (NCCN) Guidelines on Non-Hodgkin’s Lymphomas. To date, no studies have demonstrated a clear benefit of early treatment for asymptomatic CLL. However, a number of ongoing studies in otherwise healthy patients with poor prognosis are being performed, examining whether early intervention improves outcomes in this group. These studies by the German CLL Study Group and several U.S. cooperative groups will address whether early intervention with chemoimmunotherapy can improve long-term survival in high-risk patient groups. Whether or not treatment is indicated at the time of assessment, patients should continue to be evaluated for possible infections and disease-related complications, as outlined in the Managing complications and supportive care in CLL section on page 12.

Determining 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 3–6 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). (Table 7) 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 after ≥6 months of treatment, who have previously achieved a CR or PR, are identified as having relapsed disease.

### Table 5. Patient fitness types

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Description</th>
</tr>
</thead>
</table>
| Fit group     | One of the following:  
                       a) ECOG Performance Status 0–2  
                       b) CIRS ≤6 and CrCl ≥70 mL/min |
| Frail group   | One of the following:  
                       a) ECOG Performance Status 3–4  
                       b) CIRS >6 or CrCl <70 mL/min |

### Table 6. NCI minimum criteria for initiating treatment

- Evidence of progressive marrow failure as manifested by the development or worsening of anemia and/or thrombocytopenia
- Massive (i.e., at least 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
- Massive nodes (i.e., at least 10 cm in the longest diameter), or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis, with an increase >50% over two months, or lymphocyte doubling time of <6 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

*Adapted from the 2008 NCI guidelines*
†Any one of the following symptoms should also be present: unintentional weight loss ≥10% within the previous six months, significant fatigue, inability to work or perform usual activities, fevers of >38.0°C for ≥2 weeks without other evidence of infection, or night sweats for >1 month without evidence of infection.
‡Despite the availability of guidelines for the initiation of treatment, these should be viewed as minimum criteria. Good clinical judgement is always required to determine whether an individual patient will benefit from cytotoxic therapy.

NCI = National Cancer Institute
Common endpoints used in clinical trials

Overall survival

Overall survival (OS) is defined as the interval between diagnosis and death from any cause. Until recently, no phase III studies in CLL had shown a significant improvement in OS for one therapy over another. Lack of improvements in OS may be due to ineffective therapy, but may also be due to the natural history of the disease, as well as to the success of salvage therapies and the length of follow-up needed to show a significant effect. For example, in the case of follicular lymphoma, early study results of rituximab added to chemotherapy initially showed an improvement in progression-free survival (PFS) with no OS benefit. However, with longer follow-up, an improvement in OS was observed after 48 months.  

Progression-free survival

PFS is defined as the interval between the first treatment day to the first sign of disease progression, or death from any cause. The International Workshop in CLL (IWCLL) and a publication by Chakravarty and colleagues support the use of PFS as a primary endpoint of phase III clinical trials. Chakravarty, et al. suggest that in the absence of an effect on OS, clinical practice should be guided by trials demonstrating clinically significant improvements in PFS. For example, based on studies showing an improvement in PFS with no established survival benefit, fludarabine-based therapy became a preferred first-line treatment option over chlorambucil in many Canadian provinces.

Table 7. 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 10^7/L without need for exogenous growth factors</td>
<td>&gt;1.5 x 10^7/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 Hypocellular marrow with no clonal infiltrates defines CRi</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>

*Adapted from 2008 NCI guidelines
†Assessed at least 3 months after treatment
‡At least one parameter must be documented for a minimum of 2 months to establish PR
§Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical exam or ultrasound in general practice)
BM = bone marrow; CR = complete response; CRi = complete response with incomplete marrow recovery; NCI = National Cancer Institute; PD = progressive disease; PR = partial response; SD = stable disease

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Minimal residual disease

Minimal residual disease (MRD) assessment in patients who have achieved a CR by standard criteria is typically performed using four-colour flow cytometry or allele-specific oligonucleotide polymerase chain reaction (PCR). With these techniques, one can identify residual CLL cells to a sensitivity of <1 CLL cell per 10^4 leukocytes. Recent studies have suggested that complete elimination of the CLL clone with achievement of an MRD-negative CR may be associated with an improved outcome and a longer PFS. However, whether treatments designed to eradicate MRD will improve clinical outcomes requires further clinical study. In clinical trials, the number of MRD-positive CRs is often used as an endpoint and is presumed to be a more sensitive prognostic indicator than CR alone.

First-line treatment options for CLL

Goals of therapy

The ultimate treatment goal in CLL is to achieve a long OS, while minimizing toxicity and improving quality of life (QoL). In the absence of an OS benefit, achieving a long PFS is a reasonable goal of therapy. However, for some frail patients, less aggressive treatments may be required; for others, supportive/palliative treatment may be the best course. Considering the patient’s preference is always important in the determination of any treatment decision.

Chlorambucil

Chlorambucil is an oral antineoplastic nitrogen mustard that acts as an alkylating agent. For over 40 years since its discovery, chlorambucil has been used as a mainstay treatment for CLL. Many different dosing schedules have been used in CLL, including intermittent dosing from 40 mg/m^2 every 28 days to 10 mg/m^2 x 7 every 28 days, or continuous daily dosing of 0.1 mg/kg/day. In clinical trials, chlorambucil leads to overall response (OR) rates of 40%–70% and complete response (CR) rates ranging from 2%–7%. (Table 8) Median time-to-progression is approximately 1–1.5 years with this treatment. 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-cyclophosphamide (FC)

Studies of the combination of fludarabine and cyclophosphamide (FC) for second-line treatment in CLL have demonstrated good clinical response, with acceptable toxicity. These promising results in refractory settings led to the examination of FC in treatment-naïve patients.

Three randomized trials comparing fludarabine (F) or FC for frontline therapy in CLL have been published. A study by Eichhorst, et al. from the German CLL Study Group randomized 375 previously untreated patients to FC or F. The OR rate (95% vs. 83%), CR rate (24% vs. 7%), median PFS (48 vs. 20 months), and treatment-free survival (37 vs. 25 months) were higher with FC versus F, with no difference in OS. A study by Flinn, et al. from the U.S. ECOG randomized 278 patients to F or FC. FC achieved higher OR (74% vs. 60%), CR (24% vs. 7%), median PFS (48 vs. 20 months), and treatment-free survival (37 vs. 25 months) were higher with FC versus F, with no difference in OS. Despite improved efficacy, rates of neutropenia are higher with fludarabine (41%) than with chlorambucil (28%) (p <0.0001), reflecting greater hematologic toxicity. Fludarabine is now used in preference to chlorambucil for first-line treatment in many provinces. However, chlorambucil remains a valuable option in frail patients, given the lower rates of neutropenia.

Fludarabine

Fludarabine is a purine analogue that is typically administered intravenously, but is also available in an equally efficacious oral formulation in Canada and Europe. In patients refractory to traditional alkylating-agent therapy, fludarabine was shown to achieve OR rates of approximately 60%. Following the success of second-line treatment, fludarabine monotherapy was subsequently studied in treatment-naïve patients. The superior activity of fludarabine has been confirmed in randomized comparisons to alkylating agents. Studies showed prolonged PFS (median approximately 2 years), as compared to chlorambucil. Fludarabine also demonstrated superior clinical response, with response rates of 60%–80% and CR rates of 15%–40%. (Table 8) A Cochrane meta analysis of four randomized trials (Steurer, et al. 2006) supported the findings of superior PFS with fludarabine (Hazard ratio [HR] 0.70; 95% CI: 0.61–0.82). Recently, a long-term survival analysis of patients from a previous study by Rai, et al. (2000) has shown evidence of an OS advantage of F (63 months; 55–75 months) over chlorambucil (59 months; 51–70 months) (p = 0.04). Despite improved efficacy, rates of neutropenia are higher with fludarabine (41%) than with chlorambucil (28%) (p <0.0001), reflecting greater hematologic toxicity. Fludarabine is now used in preference to chlorambucil for first-line treatment in many provinces. However, chlorambucil remains a valuable option in frail patients, given the lower rates of neutropenia.

Fludarabine-cyclophosphamide (FC)

Studies of the combination of fludarabine and cyclophosphamide (FC) for second-line treatment in CLL have demonstrated good clinical response, with acceptable toxicity. These promising results in refractory settings led to the examination of FC in treatment-naïve patients.

Three randomized trials comparing fludarabine (F) or FC for frontline therapy in CLL have been published. A study by Eichhorst, et al. from the German CLL Study Group randomized 375 previously untreated patients to FC or F. The OR rate (95% vs. 83%), CR rate (24% vs. 7%), median PFS (48 vs. 20 months), and treatment-free survival (37 vs. 25 months) were higher with FC versus F, with no difference in OS. A study by Flinn, et al. from the U.S. ECOG randomized 278 patients to F or FC. FC achieved higher OR (74% vs. 60%), CR (24% vs. 7%), median PFS (48 vs. 20 months), and treatment-free survival (37 vs. 25 months) were higher with FC versus F, with no difference in OS. Despite improved efficacy, rates of neutropenia are higher with fludarabine (41%) than with chlorambucil (28%) (p <0.0001), reflecting greater hematologic toxicity. Fludarabine is now used in preference to chlorambucil for first-line treatment in many provinces. However, chlorambucil remains a valuable option in frail patients, given the lower rates of neutropenia.
FC was superior in all age groups, including patients over 70 years old. However, patients with del(17p) and del(11q) had inferior CR and OR rates, irrespective of treatment group.\textsuperscript{34}

The above trials demonstrated that FC administered intravenously is more efficacious than fludarabine or chlorambucil as monotherapy, achieving higher CR rates (25\%-40\%) and longer median PFS (32–48 months). (Table 8)

Despite the improved efficacy of FC versus F, the UK CLL-4 and U.S. ECOG studies found higher neutropenia rates in the FC group; however, less hemolytic anemia was observed with FC (5\%) than with fludarabine (11\%) or chlorambucil (12\%).\textsuperscript{34} A second study by Eichhorst, et al. (2007)\textsuperscript{44} showed no difference in quality of life (QoL) between treatment groups, while the FC group had a significantly longer PFS.

FC is now considered by many CLL study groups worldwide to be a standard first-line treatment. The FC combination is not approved in most provinces in Canada; however, its use as first-line treatment has been adopted by physicians as a common treatment option. The improvement in response seen 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.

**Table 8. Phase II and III studies in first-line CLL\textsuperscript{*17,26,34-42**

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>Remission duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil</td>
<td>40–70</td>
<td>&lt;10</td>
<td>–1 year</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>60–80</td>
<td>15–40</td>
<td>1.5–2 years</td>
</tr>
<tr>
<td>Fludarabine-cyclophosphamide</td>
<td>75–95</td>
<td>25–40</td>
<td>3–4 years</td>
</tr>
<tr>
<td>Fludarabine-cyclophosphamide-rituximab (FCR)</td>
<td>95.1</td>
<td>44.1</td>
<td>–6–7 years</td>
</tr>
</tbody>
</table>

*These regimens have not been compared in head-to-head clinical trials. CR = complete response; OR = overall response

**Addition of rituximab to chemotherapy backbones**

Rituximab is a chimeric monoclonal antibody that selectively targets CD20-positive B cells. Rituximab is currently indicated for use in non-Hodgkin’s lymphoma (NHL), where it is recommended as first-line treatment for CD20-positive, diffuse large B-cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and for untreated Stage III/IV follicular, CD20-positive, B-cell NHL in combination with CVP (cyclophosphamide, vincristine, prednisolone). Rituximab is also indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20-positive, B-cell NHL and as maintenance therapy for patients with follicular NHL who have responded to induction therapy with either CHOP or R-CHOP.\textsuperscript{15,45}

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.\textsuperscript{46} In a study by Byrd, et al. examining the efficacy of rituximab (375 mg/m\textsuperscript{2}) monotherapy in CLL, the OR, CR, and PR rates were 45\% (95\% CI: 28–64\%), 3\%, and 42\%, respectively.\textsuperscript{46} Rituximab has been studied in a number of clinical trials evaluating its additional impact in combination therapy. The NCCN guidelines on CLL currently recommend the use of rituximab in combination with F, FC, or PC (pentostatin, cyclophosphamide) for fit patients. In frail patients, rituximab monotherapy may be a reasonable first-line option; however, results are moderate as mentioned above.\textsuperscript{19,43}

**Fludarabine-rituximab (FR)**

Initial studies of rituximab combinations explored the addition of rituximab to fludarabine. Byrd, et al. (2003)\textsuperscript{47} 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. 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 CR rate of 28\% in the sequential group.

In a subsequent retrospective analysis, Byrd, et al. (2005)\textsuperscript{48} compared the treatment outcome for patients given FR in the CALGB 9712 trial to patients given fludarabine monotherapy in the CALGB 9011 trial. Results showed statistically significant higher PFS and OS in patients who received fludarabine and rituximab, as compared with patients who received fludarabine alone.

Despite the lack of phase III studies, the Byrd, et al. phase II results suggest that adding rituximab to fludarabine improves PFS and OS, compared to F monotherapy.\textsuperscript{3} 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)

The successful addition of rituximab to fludarabine led to the development of other rituximab chemotherapy regimens. Phase II studies examining the addition of rituximab to FC (FCR) demonstrated a high CR and OR rate of ≈70% and ≈95%, respectively.\textsuperscript{37,49}

The impressive results of 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.\textsuperscript{17} Study participants included 817 patients selected for minimal co-morbidity (CIRS <6). Patients were randomly assigned to receive 6 courses of either FC (F: 25 mg/m\textsuperscript{2} iv on days 1–3 plus C: 250 mg/m\textsuperscript{2} iv on days 1–3) or FC with the addition of rituximab (375 mg/m\textsuperscript{2} iv on day 0 of the first cycle and 500 mg/m\textsuperscript{2} on day 1 of all subsequent cycles). Prophylactic use of antibiotics or growth factors were used at the discretion of the treating physician, but were not specifically recommended in the protocol.

The median observation time was 37.7 months, at which point 761 patients were evaluable for response. The median patient age was 61 years, with a range of 30 to 81 years. Median PFS was reported as 32.8 months in the FC arm and 51.8 months in the FCR arm (HR 0.56; \textit{p} < 0.0001). The PFS shown in the FC arm was similar to that shown in previous studies using FC, which have reported a range of 32 to 48 months.\textsuperscript{42,43} Statistically significant differences were observed in OS between the two treatment arms. The OS rate at 37.7 months was 87.2% in the FCR arm versus 82.5% in the FC arm (\textit{p} = 0.012). In both arms, the median OS has not been reached. Only patients in Binet stages A and B showed a superior OS after FCR treatment (Binet A: HR 0.19, \textit{p} = 0.09; Binet B: HR 0.45, \textit{p} < 0.001; Binet C: HR 1.4, \textit{p} = 0.168). Response rates were higher in the FCR group versus the FC group and are the highest rates of any chemotherapy regimen used to date. (Tables 8 and 9) Grade 3/4 hematological toxicity, neutropenia, and leukocytopenia rates were higher in the FCR versus FC arm (55.7% versus 39.6%, 33.7% versus 21.0%, and 24.0% versus 12.1%, respectively; \textit{p} < 0.0001).

Based on a high level of evidence from this phase III randomized trial, FCR is currently the best option for the first-line treatment of fit patients with CLL.\textsuperscript{17} Given that the dose of rituximab used in the FCR regimen for the phase III study was cycle 1–375 mg/m\textsuperscript{2} and cycles 2 to 6–500 mg/m\textsuperscript{2}, in combination with 25 mg/m\textsuperscript{2} of fludarabine and 250 mg/m\textsuperscript{2} of cyclophosphamide on days 1–3 of each cycle, it is reasonable to recommend this dose of FCR in clinical practice. However, there is a lack of evidence to show that 500 mg/m\textsuperscript{2} per cycle is superior to 375 mg/m\textsuperscript{2} per cycle; a study comparing the efficacy of these two doses is needed to determine the optimal dose of FCR in CLL. 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 are reasonable options.

Other rituximab combinations

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, and rituximab (CFAR); reduced-dose FCR (FCR-Lite); pentostatin, cyclophosphamide, and rituximab (PCR); rituximab with alemtuzumab (R-A); and rituximab with fludarabine, cyclophosphamide, and mitoxantrone (R-FCM).\textsuperscript{50–54} A study investigating R-chlorambucil in the first-line treatment of CLL is also being conducted, as well as a study comparing R-chlorambucil to R-bendamustine. The results of these and ongoing studies suggest that the benefits of adding rituximab may extend beyond FCR to other R-chemo regimens. As phase III data become available, these regimens may become valuable options for the first-line treatment of CLL.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Efficacy parameter} & \textbf{FC (n = 371)} & \textbf{FCR (n = 390)} & \textbf{\textit{p}-value} \\
\hline
\textbf{Response rates (%)} & & & \\
\textit{Overall response (OR)} & 88.4 & 95.1 & <0.01 \\
\textit{Complete response (CR)} & 21.8 & 44.1 & <0.01 \\
\textit{Partial response (PR)} & 66.6 & 51.0 & <0.01 \\
\textit{Progression-free survival (PFS) (months)} & 32.8 & 51.8 & <0.001 \\
\textit{Overall survival (OS) (%)} & 82.5 & 87.2 & 0.012 \\
\hline
\end{tabular}
\caption{Efficacy of FCR versus FC as first-line treatment of CLL (median observation time 37.7 months)*}
\end{table}

*Adapted from Hallek, et al. ASH 2009\textsuperscript{17}
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. Treatments with chlorambucil, fludarabine, and rituximab have shown poor response rates in patients with this cytogenetic abnormality. Alemtuzumab, a humanized anti-CD52 monoclonal antibody that acts via a p53 independent mechanism, may have beneficial results in patients with del(17p).

Evidence of the beneficial role of alemtuzumab was first shown in the refractory setting. A study by Moreton, et al. found an overall response rate of 54% in fludarabine-refractory patients. A subsequent trial performed by Lozanski, et al. found a partial response in 40% of patients with del(17p) or p53 mutations. In the first-line setting, results of a randomized controlled trial (RCT) comparing alemtuzumab to chlorambucil were reported by Hillmen, et al. Of the 282 patients who underwent FISH cytogenetic analysis, 21 (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.

Current options for the first-line treatment of CLL

To date, only the phase III studies by Hallek, et al. comparing FCR with FC and by Rai, et al. comparing F to chlorambucil have shown evidence of improved OS with one regimen over another. The recommended regimens, as presented in Table 10, are therefore based on the results of studies also showing improvements in remission, with the understanding that the optimal sequence of treatments has not been adequately evaluated in clinical trials.

### Table 10. Recommendations for first-line treatment in CLL

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recommended regimen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit group</td>
<td>First choice: FCR*</td>
</tr>
<tr>
<td></td>
<td>Alternative choice: FR†</td>
</tr>
<tr>
<td>Frail group</td>
<td>First choice: F, Chlorambucil</td>
</tr>
</tbody>
</table>

*In areas where rituximab is not funded for CLL or there exists a contraindication to the use of rituximab, FC may be considered as an alternative to FCR in fit patients.
†To date, there have been no data available from randomized studies examining the efficacy of FR, and no studies have compared FCR to FR. An ongoing NCI randomized study (NCIC CL.3) that includes a number of Canadian centres is currently comparing FCR, FR, and FR with lenalidomide in symptomatic patients. Therefore, in balancing toxicity with efficacy, FR remains a reasonable first-line option in CLL until results from randomized studies are available.

Individualizing patient treatment

In some cases, fit patients may require less aggressive therapy to minimize toxicities. In addition, certain frail patients with borderline performance status and normal organ function may be able to tolerate more aggressive therapies than F or chlorambucil. In these instances, FR may be a reasonable treatment option. For patients with del(17p), alemtuzumab may be preferable to standard options due to the poor response to standard therapies. In patients who decline intravenous therapy, oral chlorambucil or fludarabine are acceptable options, although these are associated with lower response durations.

Treatment for relapsed or refractory CLL

Second-line treatment options for relapsed and refractory patients with CLL

As defined earlier, patients experiencing treatment failure within six months of treatment are identified as having refractory disease. Those demonstrating PD after ≥6 months of treatment, who have previously achieved a CR or PR, are identified as having relapsed disease. Initiation of second-line treatment should be based on NCI criteria, as discussed in the Decision to treat and determining response in the management of CLL section on page 4.

When initial remission is long, re-treatment with the initial regimen may be a reasonable option. When initial remission is short, however, a better response may be achieved by giving a different regimen as second-line treatment. A long remission may be arbitrarily defined as one that is over 1 year, and a short remission as one that is ≤1 year. These second-line treatment options are discussed in the following section.

Second-line options for frail patients

Fludarabine and chlorambucil

Where patients have not previously been given fludarabine or chlorambucil, these regimens may be reasonable options for second-line treatment. As discussed earlier, in patients refractory to traditional alkylating-agent therapy, fludarabine has achieved response rates of approximately 60% and may be a good second-line option. Data on the use of chlorambucil or other alkylators as second-line treatment after fludarabine is limited, but may also be reasonable.
Fludarabine-rituximab (FR)
Where not given previously, or after a long first remission, FR may be considered as a second-line option in otherwise healthy patients with borderline performance status or in fit patients requiring less aggressive treatment, as discussed in the First-line treatment options for CLL section on page 6.

Second-line options for fit patients
Fludarabine-cyclophosphamide-rituximab (FCR)
In a phase II study by Wierda, et al. FCR was evaluated in 177 previously treated patients. Treatment consisted of fludarabine (25 mg/m² on days 2–4 of course 1 and days 1–3 of courses 2–6); cyclophosphamide (250 mg/m² on days 2–4 of course 1 and days 1–3 of courses 2–6); and rituximab (375 mg/m² on day 1 of course 1 and 500 mg/m² on day 1 of courses 2–6). Courses were repeated every 4 weeks. The overall CR rate in this study was the highest reported in previously treated patients with CLL; however, low response rates were seen in fludarabine-refractory patients. (Table 11)

In a recent phase III study conducted by the German CLL Study Group (REACH study), FCR was compared to FC in previously treated patients. A median of one prior treatment had been administered, consisting of single-agent alkylator therapy (66%), purine-analogs (16%), or combination treatments (18%). Combination treatments administered were CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), CVP (cyclophosphamide, vincristine, and prednisolone) or F-containing therapy. Patients with prior FC combination treatment or prior rituximab were not eligible. Treatment consisted of fludarabine (25 mg/m² iv/day over 3 days for 6 cycles), cyclophosphamide (250 mg/m² iv/day over 3 days for 6 cycles), and rituximab (375 mg/m² iv for cycle 1 and 500 mg/m² iv for cycles 2–6) for a total of 6 treatment cycles at intervals of 28 days. Patients with a CIRS >6, decreased kidney function, or who had previously received FC were excluded. PFS, the primary endpoint, was prolonged by a median of 10 months (a 50% improvement) in the FCR arm (30.6 months) compared with the FC arm (20.6 months) (p = 0.0002; HR 0.65 [95% CI: 0.51–0.82]). Response rates were also superior in the FCR versus the FC group. (Table 12) Median OS was not reached for FCR and was 53 months for FC (p = 0.29; HR 0.83).

<table>
<thead>
<tr>
<th>Table 11. Response to FCR by prior treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Prior treatment</td>
</tr>
<tr>
<td>Alkylating agent</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td>FC</td>
</tr>
<tr>
<td>Fludarabine sensitive</td>
</tr>
<tr>
<td>Fludarabine refractory</td>
</tr>
</tbody>
</table>

*Adapted from Wierda, et al. 2005

CR = complete response; nPR = nodular partial response; OR = overall response; PR = partial response

<table>
<thead>
<tr>
<th>Table 12. Efficacy of FCR versus FC as second-line treatment of CLL (median observation time 25 months)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rates (%)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
</tr>
<tr>
<td>Partial response (PR)/ nodular partial response (nPR)</td>
</tr>
<tr>
<td>Overall response (OR)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
</tr>
<tr>
<td>Not evaluable†</td>
</tr>
</tbody>
</table>

*Adapted from Robak, et al. 2008
†Mainly patients with response that was not confirmed through a second assessment
The studies by Wierda, et al.\textsuperscript{55,57} and Robak, et al.\textsuperscript{58} show that FCR may be a reasonable second-line option in fit patients not previously given rituximab or FC. Re-treatment with FCR may also be reasonable in those experiencing a long remission after initial treatment. As previously discussed in the First-line treatment options for CLL section on page 6, frail patients should be given less aggressive treatments due to the potential toxicity of the FCR regimen.

Allogeneic stem cell transplantation (allo-SCT)

In the past 20 years, remarkable advances have been made in allogeneic stem cell transplantation (allo-SCT) for CLL. Traditionally, allo-SCT have been myeloablative, involving the depletion of bone marrow cells through administration of high doses of chemotherapy or radiation prior to transplantation. More recently, non-myeloablative techniques have been developed that require less intensive conditioning in an effort to reduce transplant-related mortality (TRM) rates.\textsuperscript{61}

Myeloablative allo-SCT achieved promising results in chemosensitive patients, with OS and PFS rates of approximately 80% after 5 years.\textsuperscript{56,61} Unfortunately, the beneficial response of myeloablative procedures is tempered by high TRM rates of approximately 38%–50%\textsuperscript{61,64}. Registry data indicate that while one-third of patients will be cured after myeloablative allo-SCT, approximately two-thirds will not survive as a result of TRM or recurrent disease. Experimental studies using non-myeloablative allo-SCT have achieved OS and PFS rates of 60%–72% and 52%–67%, respectively, with low non-relapse mortality rates of 15%–22% after 2 years.\textsuperscript{65,66} However, the risk of relapse may be higher with non-myeloablative versus myeloablative techniques.\textsuperscript{67}

After the failure of first-line therapy, allo-SCT may be considered for patients <65 years with no response to therapy or early relapse (within 12 months), relapse within one year of fludarabine treatment or within two years of fludarabine-based combination therapy, or del(17p) abnormalities requiring treatment.\textsuperscript{11}

**Subsequent treatment options for relapsed and refractory patients with CLL**

**Alemtuzumab (Campath-1H)**

Alemtuzumab is a humanized monoclonal antibody against CD52, which is expressed on all CLL cells. An initial phase II study in relapsed patients achieved an OR rate of 54% and CR rate of 36%. In addition, approximately 20% of relapsed patients were categorized as minimum residual disease (MRD) negative. A subsequent study showed a favourable response of approximately 40% in patients with del(17p) abnormalities.\textsuperscript{53,57} A phase III study in previously untreated patients (CAM307) has shown a reduction in the risk of progression of 42% with alemtuzumab versus chlorambucil (HR 0.58; \( p = 0.0001 \)). OR rates (83% versus 55%) and CR rates (24% versus 2%) were higher in the alemtuzumab versus chlorambucil group.\textsuperscript{39}

As a result of promising monotherapy results, alemtuzumab has been examined as part of a number of combination regimens. A UK phase II study (UKCLL02) examined alemtuzumab monotherapy in fludarabine-refractory patients, where patients not responding to alemtuzumab could be given concurrent fludarabine. Interim results presented at ASH 2005 in 36 evaluable patients showed OR rates of 44% in all patients combined.\textsuperscript{68} Another phase II study added alemtuzumab to FCR (R-FCA) to determine if efficacy could be improved in previously treated high-risk patients. Preliminary results presented at ASH 2008 showed OR and CR rates of 94% and 69%, respectively.\textsuperscript{69} Currently, an ongoing NCI phase III study is comparing FCA with FCR as first-line treatment for CLL, with the primary outcome being PFS at 36 months. A second phase III study is examining the efficacy of FA versus F in previously treated patients, with PFS also the primary outcome. Alemtuzumab may be a reasonable third-line option in fit patients who are fludarabine-resistant or as a method to debulk the disease in preparation for allo-SCT.

**Fludarabine-cyclophosphamide-mitoxantrone (FCM)**

In a phase II study by Hendry, et al., fludarabine, cyclophosphamide and mitoxantrone (FCM) was evaluated in 24 patients with relapsed or refractory CLL. Patients were treated with mitoxantrone (5 mg/m\(^2\) iv on day 1), fludarabine (25 mg/m\(^2\) iv for 3 days or 24 mg/m\(^2\) orally for 5 days), and cyclophosphamide (250 mg/m\(^2\) iv for 3 days or 150 mg/m\(^2\) orally for 5 days). Eighteen patients had previously received fludarabine, and most were heavily pre-treated, with 40% having >2 prior treatments. Results showed an OR rate of 78.5%, CR rate of 32%, and PR rate of 46.5%. Median duration of response was 19 months and median survival was 42 months.\textsuperscript{10} A second phase II study by Bosch, et al. examined FCM in 37 patients with recurrent or resistant CLL. Treatment consisted of up to six cycles of fludarabine (25 mg/m\(^2\) iv for 3 days), cyclophosphamide (200 mg/m\(^2\) iv for 3 days), and mitoxantrone (6 mg/m\(^2\) iv for 1 day). The CR rate was 50%, with 10 cases of negative MRD. The PR rate was 28% and the median duration of response was 19 months.\textsuperscript{70} FCM was later examined as front-line therapy in a phase II study by Bosch, et al. Sixty-nine patients <65 years received six cycles of fludarabine (25 mg/m\(^2\) iv for 3 days), cyclophosphamide (200 mg/m\(^2\) iv for 3 days), and mitoxantrone (6 mg/m\(^2\) iv for 1 day). The OR, MRD-negative CR, MRD-positive CR, nPR, and PR rates were 90%, 26%, 38%, 14%, and 12%, respectively. Patients with del(17p) failed to attain CR.\textsuperscript{71}

**Rituximab–high-dose methylprednisolone (R-HDMP)**

Rituximab combined with high-dose methylprednisolone (R-HDMP) was evaluated in a phase II study by Castro, et al. in fludarabine-refractory CLL patients. Fourteen patients were treated with three cycles of rituximab (375 mg/m\(^2\) weekly for 4 weeks) in combination with HDMP (1 gm/m\(^2\) daily for 5 days). The OR and CR rates were 93% and 36%, respectively;
median time-to-progression was 15 months.\textsuperscript{72} Recently, R-HDMP was examined in a second study by Castro, et al. as first-line treatment of CLL. Twenty-eight patients received HDMP (1 g/m\textsuperscript{2} each day for 3 days) together with rituximab and prophylactic antimicrobial therapy. The OR and CR rates were 96\% and 32\%, respectively.\textsuperscript{73}

**Other rituximab combinations**

A number of other rituximab-containing regimens have been studied as second-line treatment for CLL. Results of these studies are presented in Appendix B. Future data from phase III studies should help determine whether these regimens are potential second-line options for fit patients. Studies examining less aggressive treatments, such as R-bendamustine and R-chlorambucil, are also underway and may provide additional options in frail patients, pending phase III study results.

**Evolving therapeutic approaches for CLL**

A number of new treatments for CLL are currently being evaluated in clinical trials. Therapies such as lenalidomide and flavopiridol, as well as new monoclonal antibodies such as ofatumumab, GA101, and lumiliximab have shown promising preliminary results. Completed and ongoing clinical trials evaluating these new therapies are presented in Appendix C. As discussed earlier, numerous rituximab combination regimens have been examined in clinical trials (see the First-line treatment options in CLL section on page 6 and Appendix B). A number of ongoing studies are also exploring newer rituximab combinations for first- and second-line treatment and for maintenance treatment in CLL. These ongoing rituximab combination studies are also presented in Appendix C. Participating in ongoing and future clinical trials can help identify optimal treatment regimens for CLL, bringing us closer to reaching our treatment goals.

**Recommendations for relapsed or refractory CLL**

Recommendations for second-line treatment of CLL should consider individual factors such as co-morbidities and the length of the disease-free interval. 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.\textsuperscript{36,38} 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 after initial treatment.\textsuperscript{60} After the failure of first-line therapy, allo-SCT may be considered for patients <65 years with no response to therapy, with PD within one year of fludarabine treatment or within two years of fludarabine-based combination therapy, or with del(17p) abnormalities requiring treatment.\textsuperscript{13}

**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. (Table 13) The use of live vaccines in patients with CLL is not inadvisable.\textsuperscript{3} However, the use of inactivated vaccines such as annual influenza and pneumococcal polysaccharide (PPV) every 5 years for patients in remission for more than three months is recommended.\textsuperscript{3,74,75}

<table>
<thead>
<tr>
<th>Table 13. Antibiotic prophylaxis in patients with CLL\textsuperscript{3,5,19,76–78}</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Possible infection</td>
<td>Antibiotic prophylaxis</td>
<td>Vaccine</td>
<td>Other</td>
</tr>
<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 allo-SCT</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 for six 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>PJP</td>
<td>Bactrim or equivalent may be considered</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{CMV = cytomegalovirus; n/a = not applicable; PJP = pneumocystis juroveci pneumonia; PCR = polymerase chain reaction; SCT = stem cell transplant}
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), or 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 <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 5–7 g/L.

Autoimmune cytopenias

Patients with CLL are at increased risk of developing autoimmune cytopenias, such as autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenia purpura (ITP), and pure red cell aplasia (PRCA). AIHA will develop in approximately 11% 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, or increased bone marrow erythropoiesis in the absence of bleeding) with direct or indirect evidence of an autoimmune mechanism (positive direct antiglobulin 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 2%–3% of CLL patients at diagnosis or during early stage disease. ITP can be identified where platelet counts are ≤100 × 10^9/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 6% of CLL patients who are tested. PRCA can be diagnosed when hemoglobin concentration is ≤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 blood polymerase chain reaction (PCR) assay.

ITP and AIHA, as a single abnormality caused by CLL, should be treated initially using glucocorticoids. Second-line options for AIHA include splenectomy, intravenous immunoglobulins, and/or immunosuppressive therapy with cyclosporine A, azathioprine, or low-dose cyclophosphamide. Good responses have also been obtained using rituximab or alemtuzumab.

Most patients with PRCA will respond initially using glucocorticoids. Second-line options that require intravenous antibiotics or hospitalization, antimicrobials should be given as needed. In patients with recurrent infections and where serum IgG is <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 5–7 g/L.

Richter’s syndrome

The majority of Richter syndrome (RS) cases involve the transformation of CLL to an aggressive lymphoma, 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 RS 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, RS may be treated with cytoreductive chemotherapy appropriate for DLBCL, such as 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.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) occurs when the release of large amounts of intracellular components of lysed malignant cells leads to a number of metabolic imbalances. Resulting hyperuricemia, hyperkalemia, hypocalcemia, and hyperphosphatemia may then lead to renal failure and cardiac arrhythmias. TLS usually occurs within 2–3 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, hospitalization should be considered for patients with white blood cell counts (WBC) >50,000/μm3 to ensure adequate hydration and monitoring. In patients with previous episodes of TLS, 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 >200 × 10^9/L). Allopurinol should also be given to patients with significant renal dysfunction or chronic hyperuricemia.

The advent of TLS, it may be necessary to interrupt treatment until symptoms are resolved. In hospitalized patients, cardiac activity should be monitored continuously and frequent monitoring of electrolyte levels is recommended.

Blood product support

Transfusion-related graft-versus-host disease has been described in patients actively receiving fludarabine or alemtuzumab. The Canadian Blood Service recommends that patients on fludarabine or alemtuzumab should receive irradiated and CMV negative blood products.
Conclusions

Over the last decade, the management of CLL has evolved considerably, with the introduction of treatments that extend progression-free survival (PFS) and dramatically improve response rates. The recent phase III study comparing FCR to FC is one of the first to show an improvement in overall survival (OS) of one regimen (FCR) over another (FC). These findings, as well as results showing the highest response rates to date in a phase III study, make FCR the best first-line option for fit patients. Another reasonable option for the initial treatment of CLL is fludarabine-rituximab (FR), which may result in a more favourable safety profile. A randomized study comparing FR to FCR and FR with lenalidomide is underway and will provide further insight into the balance between efficacy and toxicity of the FR regimen. In frail patients, less aggressive treatments such as fludarabine and chlorambucil remain valuable options for the initial treatment of CLL.

When initial remission is long (over one year), re-treatment with the initial regimen is a reasonable option; in shorter remissions, a different second-line regimen may yield a superior response. 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, results of a phase III study demonstrating a 50% improvement in PFS over FC show that FCR is an effective treatment choice in patients naïve to rituximab or FC; FCR may also be reasonable in those experiencing a long initial remission. After the failure of first-line therapy, allo-SCT may be considered for patients under 65 years with no response to therapy or early relapse (within 12 months), with progressive disease within a year of fludarabine treatment or within two years of fludarabine-based combination therapy, or with del(17p) abnormalities requiring treatment.

Subsequent treatment with alemtuzumab, FCM, R-HDMP, and other rituximab combinations may be reasonable options based on results of preliminary phase II studies. Future studies on these and evolving new treatments such as lenalidomide, flavopiridol, ofatumumab, GA101, and lumiliximab may provide additional options for the treatment of patients with CLL.

Variability in patient characteristics such as performance status, disease progression, and individual preference should be considered in the development of treatment goals. In addition, the development of prognostic factors aiding in the stratification of patients into high- and low-risk groups may aid in decisions concerning optimal treatment strategies. Positive developments in the treatment of CLL and recent findings from a number of phase III studies move us closer to the creation of a Canadian guideline for its management.
APPENDIX A: Calculating the fourteen-system modified Cumulative Index Rating Scale (CIRS)*

<table>
<thead>
<tr>
<th>Systems</th>
<th>Description</th>
<th>Scores</th>
</tr>
</thead>
</table>
| Cardiac                                   | - Any cardiac problem (angina, myocardial infarction, arrhythmia, valve problems)?  
  - If affirmative, any medication taken for these problems?  
  - Any heart surgery in the past?                                                                                                                    | 0      |
| Vascular                                  | - Any circulatory problem (includes peripheral atherosclerotic disease, aneurysm of the abdominal aorta…), hypertension, or cholesterol problem?  
  - If affirmative, any medication taken for these problems?  
  - Any vascular surgery in the past (bypass graft surgery of lower limbs, carotid endarterectomy…)?  
  Note: Vertigo and dizziness are included in this section, unless they are of neurological origin.                                                    | 1      |
| Hematological                             | - Any blood problem (anemia, leukemia, hypercoagulability or any other problem affecting the blood, the blood cells, the spleen or the lymphatic system)?  
  - If affirmative, any medication taken for these problems (such as iron)?  
  Note: Patients taking anticoagulants belong to this system if the main problem is hypercoagulability (thrombosis or recurrent embolism). If anticoagulants were taken for arrhythmias, rate the problem in Cardiac. | 2      |
| Respiratory                               | - Any respiratory problem (asthma, emphysema, bronchitis, pulmonary embolism)?  
  - If affirmative, any medication taken for these problems (such as pressurized aerosols)?  
  - Any lung surgery?  
  - Cigarette smoking? How many packs per day? For how long?  
  Pack years = number of packs per day x the number of years smoked  
  (example: 1 pack per day for 20 years = 20 pack years)  
  Smoker up to 20 pack years: Rated 1  
  Smoker from 21 to 40 pack years: Rated 2  
  Smoker over 40 pack years: Rated 3 | 3      |
| Ophthalmological and otorhinolaryngology  | - Any problem with eyes (glaucoma, cataract, important lost of vision), ears (includes important hearing impairment), nose, throat, voice?  
  - Any medication taken for these problems (such as eye drops)?  
  Note: Vertigo and dizziness are included in this section, unless they are of neurological origin.                                                | 4      |
<table>
<thead>
<tr>
<th>Systems</th>
<th>Description</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper gastrointestinal</td>
<td>- Any problem with stomach or digestion (includes the esophagus, the stomach, and the duodenum)?&lt;br&gt;  - If affirmative, any medication taken for these problems?&lt;br&gt;  - Any surgery for the stomach or the esophagus?</td>
<td></td>
</tr>
<tr>
<td>Lower gastrointestinal</td>
<td>- Any intestinal problem (includes intestinal hernias, constipation, anal problems, incontinence...)?&lt;br&gt;  - If affirmative, any medication taken for these problems?&lt;br&gt;  - Any surgery for the abdomen?</td>
<td></td>
</tr>
<tr>
<td>Hepatic and pancreatic</td>
<td>- Any problem in the liver or the pancreas?&lt;br&gt;  - Any medication taken for these problems?&lt;br&gt;  - Any surgery for the liver or the pancreas?  &lt;br&gt;Note: Cholecystectomy is rated in this section.</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>- Any problem in the kidneys (impairment in function, infection...)?&lt;br&gt;  - If affirmative, any medication taken for these problems?&lt;br&gt;  - Any surgery for the kidneys?</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>- Any urinary problem (lithiasis, incontinence...)?&lt;br&gt;  - If affirmative, any medication taken for these problems?&lt;br&gt;  - Any surgery for the urinary bladder, for renal lithiasis?</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and tegumental</td>
<td>- Any problem in the skin, the joints, the bones, the muscles (includes arthrosis, osteoporosis, carpal tunnel, and any other skin or musculoskeletal problem)?&lt;br&gt;  - Any medication, anti-inflammatory drugs? Infiltrations? Creams prescribed by a doctor?&lt;br&gt;Note: Fibromyalgia is rated in this section, but it may also be rated in Psychiatric if necessary.</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>- Any neurological problem (cerebrovascular accident, peripheral neuropathy, headaches...)?&lt;br&gt;  - If affirmative, any medication taken for these problems?&lt;br&gt;  - Any surgery for these problems?</td>
<td></td>
</tr>
<tr>
<td>Endocrine, metabolic, breast</td>
<td>- Any problem of the thyroid gland, obesity, diabetes, or any other hormonal problem?&lt;br&gt;  - For obesity:&lt;br&gt;  BMI ≥30: Rated 1&lt;br&gt;  BMI ≥30 + medication or moderate disability: Rated 2&lt;br&gt;  BMI ≥45: Rated 3&lt;br&gt;  - Any medication? Surgery for any of these problems?&lt;br&gt;  - Any problem with breasts (dysplasia, cancer...)?&lt;br&gt;  - Surgery for these problems?&lt;br&gt;  - Menopause (or andropause in men)? Any hormone (the same for men in andropause)?&lt;br&gt;  Menopause or andropause:&lt;br&gt;  Without hormonotherapy or symptoms: Rated 0&lt;br&gt;  Symptomatic or with hormonotherapy: Rated 1</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>- Any problem of depression, anxiety, alcohol, drug abuse, or other problems?&lt;br&gt;  - Any medication taken for these problems?&lt;br&gt;Note: Personality problems are rated in this section, but the patient’s chart should be checked.</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from the Abbreviated guidelines for scoring the Cumulative Illness Rating Scale (CIRS) in family practice. J Clin Epidemiol 2007.*
APPENDIX B: Studies evaluating rituximab-based regimens for second-line treatment in CLL

<table>
<thead>
<tr>
<th>Authors</th>
<th>Phase</th>
<th>Treatment arms</th>
<th>Primary/Secondary endpoints</th>
<th>Dose</th>
<th>Patient characteristics</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>German CLL Study Group (GCLLSG) REACH ASH 2008 Abstract: lba-1</td>
<td>III</td>
<td>Rituximab-fludarabine-cyclophosphamide (FCR) vs. fludarabine-cyclophosphamide (FC) (n = 552, none with previous rituximab or FC treatment)</td>
<td>-OR -CR -PR -PS</td>
<td>R: 375 mg/m² iv on day 0 of cycle 1; 500 mg/m² iv on day 1 of cycles 2-6 F: 25 mg/m² iv on days 1–3 C: 250 mg/m² iv on days 1–3</td>
<td>-CIRS score &lt;6 -Creatinine clearance ≥70 mL/min</td>
<td>Efficacy: -OR: FCR = 70%, FC = 58% (p = 0.0034) -CR: FCR = 24%, FC = 13% (p = 0.0007) -PR/nPR: FCR = 46%, FC = 45% (p = 0.86) -PS: FCR = 30.6 months, FC = 20.6 months (10 months difference, HR = 0.65) Safety: -AEs (grade 3/4): FCR = 80%, FC = 74% -SAEs: FCR = 50%, FC = 48% -Neutropenia (grade 3/4): FCR = 42%, FC = 40% -Thrombocytopenia (grade 3/4): FCR = 11%, FC = 9% -Infections (grade 3/4): FCR = 18%, FC = 19% -Anemia (grade 3/4): FCR = 2%, FC = 5% Fatal AEs: FCR = 13%, FC = 10%</td>
</tr>
<tr>
<td>Wierda, et al. 2005 J Clin Oncol 2005;23(18): 4070–4078</td>
<td>II</td>
<td>Rituximab-fludarabine-cyclophosphamide (FCR) (n = 177)</td>
<td>-OR -CR -PR -nPR</td>
<td>R: 375 mg/m² iv on day 1 of course 1 and 500 mg/m² iv on day 1 of courses 2-6 F: 25 mg/m²/day iv on days 2–4 of course 1 and days 1–3 of courses 2-6 C: 250 mg/m²/day iv on days 2–4 of course 1 and days 1–3 of courses 2-6</td>
<td>-Performance status ≤3 -Adequate kidney and liver function</td>
<td>Efficacy: -OR: 73% -CR: 25% -PR: 32% -nPR: 16% Safety: -First infusion: 63% adverse events, but all grade 1/2 Neutropenia:15% (grade 3), 66% (grade 4) Thrombocytopenia:16% (grade 3), 18% (grade 4) Anemia (grade 3/4): 24% Major infections: 16% Minor infections: 18%</td>
</tr>
<tr>
<td>Wierda, et al. ASH 2008 Abstract: 2095 Blood (ASH Annual Meeting Abstracts) 2008;112(11):2095</td>
<td>II</td>
<td>Rituximab-fludarabine-cyclophosphamide-alemtuzumab (CFAR) (n = 60 high-risk patients; 48 evaluable)</td>
<td>-OR -CR -PR -nPR</td>
<td>C: 200 mg/m² on days 3–5 F: 20 mg/m² on days 3–5 A: 30 mg iv on days 1, 3, 5 R: 375–500 mg/m² iv on day 2</td>
<td>Not available</td>
<td>Efficacy: -OR: 94% -CR: 69% Safety: -Myelosupression an issue vs. historical FCR control -No difference in infection vs. historical FCR control</td>
</tr>
<tr>
<td>Hillmen, et al. ASH 2007 Abstract: 752 Blood (ASH Annual Meeting Abstracts) 2007;110(11):752</td>
<td>II</td>
<td>Rituximab-fludarabine-cyclophosphamide-mitoxantrone (R-FCM) vs. fludarabine-cyclophosphamide-mitoxantrone (FCM) (n = 52)</td>
<td>-OR -CR -CRI -MRD</td>
<td>F: 24 mg/m² oral for 5 days C: 150 mg/m² for 5 days M: 6 mg/m² iv on day 1 of each cycle R: 375 mg/m² iv cycle 1; 500 mg/m² iv cycles 2-6</td>
<td>Median number of prior therapies = 2 (1–6)</td>
<td>Efficacy: -OR: R-FCM = 70%, FCM = 57% -CR + CRI: R-FCM = 43%, FCM = 13% -MRD negativity: R-FCM = 22%, FCM = 9% Safety: -No difference in the number of patients with SAEs between the arms</td>
</tr>
<tr>
<td>Castro, et al. 2008 Leukemia 2008;22(11): 2048–2053</td>
<td>II</td>
<td>Rituximab-methylprednisolone (R-M) (n = 14)</td>
<td>-OR -CR</td>
<td>R: 375 mg/m² iv weekly for 4 weeks High-dose methylprednisolone: 1 gm/m² daily for 5 days</td>
<td>F-refractory</td>
<td>Efficacy: -OR: 93% -CR: 36% -Median time-to-progression: 15 months -Median time-to-next-treatment: 22 months</td>
</tr>
<tr>
<td>Authors</td>
<td>Phase</td>
<td>Treatment arms</td>
<td>Primary/Secondary endpoints</td>
<td>Dose</td>
<td>Patient characteristics</td>
<td>Main results</td>
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</tr>
<tr>
<td>Tsimberidou, et al. 2008 J Clin Oncol 2008;26(2): 196–203</td>
<td>I–II</td>
<td>Rituximab-oxaliplatin-cytarabine (OFAR) (n = 50) (CLL: n = 30; RT: n = 20)</td>
<td>-OR</td>
<td>R: 375 mg/m² iv on day 3 of cycle 1 and day 1 of subsequent cycles Oxaliplatin: 17.5, 20, or 25 mg/m²/day on days 1–4 F: 30 mg/m² on days 2,3 Cytarabine: 1 g/m² on days 2,3 Pegfilgrastim: 6 mg on day 6, every 4 weeks for a maximum of 6 courses</td>
<td>-Confirmed Richter’s transformation or F-refractory CLL -Adequate kidney and liver function</td>
<td>Efficacy (CLL patients): -OR: 33% -Responses achieved: 33% of patients with 17p deletion, 20% of patients with 11q deletion, 0% of patients with trisomy 12, and 33% of patients with 13q deletion -Median response duration: 10 months Safety: -Mainly hematologic: OFAR caused grade 3/4 neutropenia and/or thrombocytopenia in the majority of patients -Prolonged myelosuppression was not observed</td>
</tr>
<tr>
<td>Eichhorst, et al. ASH 2005 Abstract: 2126 Blood (ASH Annual Meeting Abstracts) 2005;106(11):2126</td>
<td>II</td>
<td>Rituximab-cyclophosphamide-doxorubicin-vincristine-prednisolone (R-CHOP) (n = 34; 25 data available)</td>
<td>-OR</td>
<td>C: 750 mg/m² iv Doxorubicin: 50 mg/m² iv Vincristine: 1.4 mg/m² iv on day 1 Prednisolone: 100 mg/m² po for 5 days R: 375 mg/m² iv on day 0 from the second treatment course</td>
<td>Included F-refractory patients, patients with AIHA, and patients with RT</td>
<td>Efficacy: -OR: 70% in all patients; 69% in F-refractory patients -No CR documented Safety (% of courses): -Myelosuppression: 59% -Anemia: 32% -Thrombocytopenia: 29% -Leukocytopenia/neutropenia (grade 3/4): 10.8% -Thrombocytopenia (grade 3/4): 11.9% -CTC grade 3/4 infections: 4 episodes</td>
</tr>
<tr>
<td>Faderl, et al. 2003 Blood 2003;101(9): 3413–3415</td>
<td>II</td>
<td>Rituximab-alemtuzumab (R-A) (n = 48)</td>
<td>-OR</td>
<td>A: 3 mg, 10 mg, and 30 mg on 3 consecutive days followed by 30 mg on days 3 and 5 of weeks 2–4 R: 375 mg/m² iv weekly for 4 weeks</td>
<td>-Performance status &lt;3 -Adequate kidney and liver function</td>
<td>Efficacy: -OR: 52% -CR: 8% -PR: 40% -nPR: 4% -Median time-to-progression: 6 months Safety: -Infections in 52% of patients</td>
</tr>
</tbody>
</table>

AE = adverse event; AIHA = autoimmune hemolytic anemia; CIRS = Cumulative Illness Rating Scale; CR = complete response; CRi = complete response with incomplete marrow recovery; EFS = event-free survival; HR = hazard ratio; MRD = minimal residual disease; nPR = nodular partial response; OR = overall response; OS = overall survival; PFS = progression-free survival; PR = partial response; RT = Richter’s transformation; SAE = serious adverse event
## APPENDIX C. Completed and ongoing studies evaluating new treatment regimens in CLL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Authors/Patient setting</th>
<th>Dose</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lenalidomide</strong> (Revlimid)</td>
<td>Chanan-Khan, et al. 2006/Relapsed setting (n = 45)</td>
<td>25 mg on days 1–21 of a 28 day cycle</td>
<td>OR: 47% CR: 9%</td>
</tr>
<tr>
<td></td>
<td>Ferrajoli, et al. 2008/Relapsed setting (n = 45)</td>
<td>10 mg daily with dose escalation up to 25 mg daily</td>
<td>OR: 32% and 25% in F-refractory patients CR: 7%</td>
</tr>
<tr>
<td></td>
<td>Chen, et al. ASH 2008/Previously untreated CLL (n = 25)</td>
<td>10 mg daily with dose escalation up to 25 mg daily</td>
<td>PR: 65% SD: 35%</td>
</tr>
<tr>
<td></td>
<td>RV-CLL-PI-0099: University Health Network (UHN) Ongoing/Previously untreated CLL (n = 27)</td>
<td>2.5 mg/day for 3 weeks escalating to 10 mg/day for 3 weeks, followed by 1 week off therapy on a 28 day cycle</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>RV-CLL-PI-0188: German CLL Study Group (GCLLSG) Ongoing/Previously untreated CLL (n = 60)</td>
<td>5 mg daily for 28 days</td>
<td>Not available</td>
</tr>
</tbody>
</table>
|                            | CC 5013-CLL-008: Celgene Ongoing/Previously untreated CLL (n = 428) | Arm 1: Lenalidomide – 5 mg daily on days 1–28 of cycle 1; 10 mg daily on days 1–28 of cycle 2; 15 mg daily for remainder  
Arm 2: Chlorambucil – 0.8 mg/kg on days 1 and 15 of each 28-day cycle | Not available                                                                |
| **Flavopiridol** (Alvocidib) | Lin, et al. 2009/Relapsed high-risk setting (n = 64)        | 30 mg/m² iv bolus + 30 mg/m² iv continuous for dose 1, with escalation to 30 mg/m² iv bolus + 50 mg/m² iv continuous at dose 2 and all subsequent treatments | OR: 53% PR: 47% CR: 1.6%  
Median PFS: 10–12 months                                                      |
|                            | CLLRC-OSU-0491: National Cancer Institute (NCI) Ongoing/Relapsed setting (n = 70) | Infusion (iv) over 30 minutes followed by a 4-hour infusion on days 1, 8, 15, and 22 | Not available                                                                |
|                            | EFC6663: Sanofi-Aventis Ongoing/Relapsed setting (n = 165)  | Flavopiridol given weekly                                            | Not available                                                                |
| **Ofatumumab** (HuMax-CD20)  | Coiffier, et al. 2008/Relapsed setting (n = 33)             | Three cohorts: A) 100 mg and three 500 mg doses;  
B) 300 mg and three 1000 mg doses;  
C) 500 mg and three 2000 mg doses | Response in largest dose combination (cohort C):  
OR: 50% PR: 46%                                                             |
|                            | Osterborg, et al. ASH 2008/Relapsed setting (failed fludarabine; failed/ineligible for alemtuzumab) (n = 138) | 8 weekly infusions followed by 4 monthly infusions (dose 1: 300 mg; doses 2–12: 2000 mg) | Response in double-refractory cohort:  
OR: 51%  
Time-to-next-therapy:  
9.0 months  
OS: 13.7 months                                                              |
|                            | OMB110911: GlaxoSmithKline Ongoing/Previously untreated CLL (n = 444) | Arm 1: Ofatumumab – 300 mg on day 1 and 1000 mg on day 8 of cycle 1; subsequent cycles, 1000 mg on day 1 every 28 days; Chlorambucil – 10 mg/m² on days 1–7 every 28 days  
Arm 2: Chlorambucil – 10 mg/m² on days 1–7 every 28 days | Not available                                                                |
|                            | OMB110913: GlaxoSmithKline Ongoing/Relapsed setting (n = 352) | Arm 1: Fludarabine – 25 mg/m² on days 1–3 for 6 cycles;  
Cyclophosphamide – 250 mg/m² on days 1–3 for 6 cycles  
Arm 2: Ofatumumab – 300 mg on day 1 and 1000 mg on day 8 of cycle 1; 1000 mg on day 1 of cycles 2–6; FC as above | Not available                                                                |
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Authors/Patient setting</th>
<th>Dose</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA101</td>
<td>Salles, et al. ASH 2008/ Relapsed setting (n = 24)</td>
<td>Escalating doses from 50 mg to 2000 mg iv as a flat dose on days 1, 8, and 22, and subsequently every 3 weeks for a total of 9 infusions</td>
<td>Data for first 12 patients: OR: 58% CR: 25% PR: 33%</td>
</tr>
<tr>
<td>BO21004 (CLL11): Hoffman-La Roche Ongoing/ Previously untreated CLL (n = 786)</td>
<td>Arm 1: Chlorambucil – 0.5 mg/kg on days 1 and 15 of cycles 1–6 Arm 2: Rituximab – 375 mg/m² on day 1 of cycle 1; 500 mg/m² for cycles 2–6; Chlorambucil as above Arm 3: GA101–1000 mg on days 1, 8, and 15 of cycle 1, and on day 1 of cycles 2–6; Chlorambucil as above</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>Lumiliximab</td>
<td>Byrd, et al. ASCO 2008/ Relapsed setting (n = 31)</td>
<td>Either 375 mg/m² or 500 mg/m² of lumiliximab + FCR for up to six 28-day cycles</td>
<td>OR: 65% CR: 52% PR: 13% Median PFS: 19.3 months</td>
</tr>
<tr>
<td>Veltuzumab</td>
<td>Immunomedics Ongoing/ Patients with previously treated or untreated NHL and CLL (n = 72)</td>
<td>Subcutaneous administration at different doses</td>
<td>Not available</td>
</tr>
<tr>
<td>Rituximab-bendamustine</td>
<td>German CLL Study Group (GCLLSG) Ongoing/ Previously untreated CLL (n = 550)</td>
<td>Arm 1: FC – iv on days 1–3; Rituximab – iv on day 0 of course 1 and on day 1 of courses 2–6 Arm 2: Bendamustine – iv on days 1 and 2; Rituximab – as in arm 1</td>
<td>Not available</td>
</tr>
<tr>
<td>Rituximab-pentostatin-cyclophosphamide</td>
<td>U.S. Oncology Research Ongoing/ Previously untreated or treated CLL (n = 280)</td>
<td>Arm 1: Fludarabine-cyclophosphamide-rituximab; doses not given Arm 2: Rituximab-pentostatin-cyclophosphamide; doses not given</td>
<td>Not available</td>
</tr>
<tr>
<td>Fludarabine-cyclophosphamide-rituximab-lumiliximab 152CL201: Biogen Idec Ongoing/ (n = 627)</td>
<td>Arm 1: Fludarabine – 25 mg/m² daily, every 4 weeks for 21 weeks; Cyclophosphamide – 250 mg/m² daily, every 4 weeks for 21 weeks; Rituximab – 50 mg/m² on day 1 and 325 mg/m² on day 3 for the first week, then single doses of 500 mg/m² every four weeks for 21 weeks Arm 2: Lumiliximab – 50 mg/m² on day 2 and 450 mg/m² on day 4 for the first week, then single doses of 500 mg/m² every four weeks, for 21 weeks; FCR as above</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>Fludarabine-rituximab-lenalidomide CL.3 CALGB 10404: Cancer and Leukemia Group B; National Cancer Institute of Canada (NCIC) Ongoing/ (n = 405)</td>
<td>Arm 1 (remission-induction [RI] therapy with FR): Rituximab iv on days 1, 3, and 5 of course 1 and on day 1 of all subsequent courses; Fludarabine phosphate iv or orally on days 1–5; treatment repeats every 28 days for up to 6 courses Arm 2 (RI therapy with FR followed by remission-consolidation [RC] therapy with lenalidomide): RI therapy as in Arm 1; patients with a CR, PR, or SD proceed to RC therapy beginning approximately 4 months after completion of RI, comprising oral lenalidomide once daily on days 1–21, treatment repeats every 28 days for 3–6 courses Arm 3 (RI therapy with FCR): Rituximab iv on days 1 and 3 of course 1 and on day 1 of all subsequent courses; Fludarabine phosphate iv or orally on days 1–3; Cyclophosphamide iv on days 1–3; treatment repeats every 28 days for up to 6 courses Arm 4 [del(11q22.3)-positive] (RI therapy with FCR followed by RC therapy with lenalidomide): First course of RI therapy as in Arm 1 or 2; Rituximab iv on day 1 of all subsequent courses; Fludarabine iv and Cyclophosphamide iv on day 1 on days 1–3; treatment repeats every 28 days for up to 6 courses; beginning approximately 4 months after completion of RI therapy, patients receive RC therapy comprising oral lenalidomide as in Arm 2.</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
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<td>Main results</td>
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<tr>
<td>Rituximab-chlorambucil</td>
<td>Hoffman-La Roche Global Ongoing/ (n = 100)</td>
<td>Rituximab: 375 mg/m² iv in cycle 1 and 500 mg/m² iv subsequently Chlorambucil: 10 mg/m² oral on days 1–7 of each cycle</td>
<td>Not available</td>
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<tr>
<td></td>
<td>Hoffman-La Roche Global Ongoing/ (n = 300)</td>
<td>Arm 1: Rituximab-chlorambucil; doses not given Arm 2: Rituximab-bendamustine; doses not given</td>
<td>Not available</td>
</tr>
<tr>
<td>Rituximab-lenalidomide</td>
<td>CLL Research Consortium Ongoing/ Previously untreated CLL (n = 80)</td>
<td>Rituximab: 375 mg/m² iv weekly for cycle 2, then every 4 weeks for subsequent cycles Lenalidomide at increasing doses orally</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>German CLL Study Group (GCLLSG) Ongoing/ Relapsed setting (n = 36)</td>
<td>Rituximab: 375 mg/m² iv on days 1, 8, 15, 22, then continued every 4 weeks during cycles 3–12 (not given in cycle 2) Lenalidomide: 10 mg orally starting day 9 of cycle 1</td>
<td>Not available</td>
</tr>
<tr>
<td>Rituximab-lenalidomide-pentostatin-cyclophosphamide</td>
<td>National Cancer Institute (NCI) Ongoing/ Previously untreated CLL (n = 45)</td>
<td>Rituximab: iv on days 1 and 2 for course 1, and on day 1 subsequently PC: iv on day 1 Lenalidomide: 2 months after completion of induction therapy, once daily orally on days 1–28</td>
<td>Not available</td>
</tr>
<tr>
<td>Rituximab maintenance</td>
<td>Del Poeta, et al. 2007 (n = 28)</td>
<td>Arm 1: Consolidation with rituximab – 375 mg/m² for 4 monthly doses, followed by 150 mg/m² for 12 monthly doses, in patients with a clinical response to FR Arm 2: Observation</td>
<td>Patients receiving rituximab consolidation had a significantly longer response duration than those without consolidation therapy (87% versus 32%, $p = 0.001$)</td>
</tr>
<tr>
<td></td>
<td>ML19514: Hoffman-La Roche Global/ Previously untreated CLL (n = 85)</td>
<td>Maintenance with rituximab: 375 mg/m² every 3 months for 2 years after a clinical response to R-FCM</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>National Cancer Institute (NCI) Ongoing/ (n = not given)</td>
<td>Arm 1: Maintenance with rituximab every 2 months in patients with a clinical response to FCR Arm 2: Observation</td>
<td>Not available</td>
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<tr>
<td></td>
<td>ML21283 Hoffman-La Roche Global Ongoing/ (n = 218)</td>
<td>Arm 1: Maintenance with rituximab at 375 mg/m² in patients with a clinical response to rituximab-cladribine-cyclophosphamide Arm 2: Observation</td>
<td>Not available</td>
</tr>
</tbody>
</table>

CR = complete response; FC = fludarabine-cyclophosphamide; FCR = fludarabine-cyclophosphamide-rituximab; FR = fludarabine-rituximab; OR = overall response; OS = overall survival; PC = pentostatin-cyclophosphamide; PFS = progression-free survival; PR = partial response; R-FCM = rituximab-fludarabine-cyclophosphamide-mitoxantrone; RC = remission-consolidation; RI = remission-induction; SD = stable disease
References:


17. Hallek M, Fingerle-Rowson G, Fink A-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;114(22):535.


