Chronic Lymphocytic Leukemia

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Updates:

❖ Rituximab data

Introduction

Chronic Lymphocytic Leukemia (CLL) is the most common form of adult leukemia in the Western world, and accounts for 25% of all leukemias [1]. It is predominantly a disease of the elderly, with a median age at diagnosis of 65 years [2]. CLL is characterized by the clonal proliferation and accumulation of neoplastic B-lymphocytes in the blood, bone marrow, lymph nodes and spleen [2]. An excellent practice guideline on the management of CLL has been published by the British Committee for Standards in Haematology (BCSH) **www.bcshguidelines.com** [3]. The Odette Cancer Centre Hematology Site Group endorses this document.

Diagnosis

The diagnosis of CLL is made by demonstration of a persistent absolute peripheral blood lymphocytosis (> 5 x 10^9/L), with or without associated lymphadenopathy or splenomegaly. The lymphocytes appear small and mature, and have a characteristic immunophenotype: they typically co-express the B cell markers CD19, CD20 & CD23 with the T cell marker CD5, and are light chain restricted, but have low-density surface immunoglobulin [2, 4]. The entity should be distinguished from the other disorders of malignant B lymphocytes, including mantle cell lymphoma, prolymphocytic leukemia, follicular lymphoma, marginal zone B-cell lymphoma, splenic lymphoma with villous lymphocytes, hairy cell leukemia and lymphoplasmacytoid lymphoma.

MLUS: Recently it has been recognized that monoclonal B-cells with an immunophenotype compatible with CLL can be found in low numbers in as many as 3% of normal individuals over age 40 [5]. This has led to the concept of Lymphocytosis of Uncertain etiology (LGUS) akin to MGUS. While some patients may progress to symptomatic CLL, others may remain stable for long periods of time. Guarini, et al. have published criteria for how to recognize such patients [6]. It is essential that we counsel such patients appropriately and that they be reassured that outcome appears particularly favorable.

Baseline Investigations

The following investigations are indicated for most patients with CLL at diagnosis:

❖ CBC, differential, blood film
❖ Immunophenotyping of peripheral blood lymphocytes
❖ Serum electrolytes and creatinine
❖ Liver function tests
❖ Serum LDH
❖ Serum uric acid
❖ Serum protein electrophoresis
❖ Serum immunoglobulin levels
❖ Direct antiglobulin test
❖ Chest x-ray
❖ Abdominal ultrasound
❖ FISH for 17p13 or 11q22-23 deletions

Neither a lymph node biopsy nor a bone marrow biopsy is required in order to make the diagnosis of CLL [4]. However, if morphological and immunophenotypic investigations are inconclusive, these tests may be helpful in establishing the diagnosis. In cases with an atypical immunophenotypic profile for CLL, a FISH analysis to exclude a t(11;14) translocation may be warranted [3].

Cardiac Assessment

A cardiac assessment should be performed in any patient who is being considered for anthracycline-based chemotherapy. MUGA scan or echocardiogram should be performed in such patients with a history of:

- ❖ Age > 60
- ❖ Hypertension
- ❖ Congestive heart failure
- ❖ Peripheral vascular disease
- ❖ Cerebrovascular disease
- ❖ Angina
- ❖ Cardiac arrhythmia
- ❖ Myocardial infarction

Gallium scans are **not** routinely used in patients with CLL.

Staging & Prognosis

Patients with CLL should be staged according to the Rai Staging System. The Binet staging system is more widely used in Europe.

Rai Staging System: [7] (modified Rai)

Risk	Stage	Clinical Features	Median Survival
Low	0	Lymphocytosis alone	> 10 yrs
Intermediate	I	Lymphocytosis with lymphadenopathy	7 yrs
	II	Lymphocytosis with either hepatomegaly or splenomegaly with or without lymphadenopathy	
High	III	Lymphocytosis and anemia (Hb < 110 g/L)	1.5 yrs
	IV	Lymphocytosis and thrombocytopenia (plt < 100 000/mm^3)	

Binet Staging System: [8]

Stage	Clinical Features	Median Survival
A	Lymphocytosis with no anemia or thrombocytopenia and fewer than 3 lymphoid areas* involved	> 10 yrs
B	Lymphocytosis with no anemia or thrombocytopenia and greater than 3 lymphoid areas* involved	5 yrs
C	Lymphocytosis with anemia (Hb < 100 g/L), thrombocytopenia (plt < 100 000/mm^3), or both	2 yrs

*Lymphoid areas = cervical, axillary, inguinofemoral, spleen, liver

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Other factors felt to be associated with adverse prognosis include:

- ❖ IgVH gene status unmutated (<2% mutated compared to germline sequence)
- ❖ Diffuse pattern of bone marrow infiltration
- ❖ Lymphocyte doubling time of <12 months
- ❖ High levels of soluble CD23
- ❖ High Beta-2-microglobulin
- ❖ Adverse karyotype (17p13 or 11q22-23deletions)
- ❖ CD38 expression
- ❖ Zap 70 expression

These factors will not be routinely measured or used to guide therapy for most patients. In selected cases, biologic prognostic factors, particularly cytogenetics, may be used to assist in identifying patients who might be offered high-dose therapy and stem cell transplantation. Cytogenetics should be done at baseline and in patients with evidence of progressive disease, to identify the poor-risk subgroup of patients with the 17p (p53) deletion who are unlikely to respond fludarabine or alkylator-based therapies and who should be prioritized for clinical trials [9].

Management of CLL

CLL is presently an incurable disease. Treatment of indolent, early stage disease with alkylator-based therapy does not appear to prolong survival [10-12], so a "watch and wait" approach with close clinical observation is generally followed.

Treatment is generally deferred until patients develop one of the following indications for treatment:

1. Constitutional symptoms referable to CLL - fever, sweats, weight loss, fatigue
2. Symptomatic lymphadenopathy
3. Symptomatic splenomegaly
4. Progressive marrow failure: anemia (Hb < 100 g/L) or thrombocytopenia (PLT < 100 000 x 10^9/L)
5. Rapidly progressive lymphocytosis, with an estimated doubling time of less than 6 months

The absolute lymphocyte count should not be used as the sole indicator for treatment [4]. Early stage CLL with autoimmune hemolytic anemia or immune thrombocytopenic purpura may require therapy for the autoimmune cytopenias but may not require cytoreductive therapy for CLL.

These are merely guidelines; the decision of when to initiate therapy should be made on an individual patient basis.

Management of Advanced Stage or Symptomatic CLL

There are a variety of treatment options for patients with CLL. Treatment objectives are to achieve symptomatic control of the disease as well as to prevent potential complications, and not necessarily to achieve a complete remission. Options for therapy include:

Alkylating Agents: Alkylating agents such alone or in combination with other drugs have been the mainstay of CLL therapy in Canada for decades. Oral chlorambucil with or without prednisone is effective in palliating symptoms in CLL with overall response rates ranging from 45-86% (3). This agent has been administered in a number of dosing regimens with or without prednisone. Daily versus intermittent treatment with chlorambucil seems to yield similar results [13]. Addition of prednisone to chlorambucil does not improve overall survival [14]. Comparative trials of CVP to chlorambucil have shown more rapid responses with combination therapy but no impact on overall survival [15, 16].

Purine Analogs: The purine analogue fludarabine has been shown to have significant activity in CLL, either as a single-agent [17-19] or in combination with other drugs [20, 21], especially cyclophosphamide [22, 23]. Fludarabine is given at a dose of 25 mg/m²/d IV x 5 days q 4 weeks or 40 mg/m² orally for 5 days q 4 weeks, until maximal response or to a total of 6 cycles. Both formulations appear to be comparably effective with a slightly higher rate of GI intolerance with the oral formulation. Response rates are in the 70-80% ranges (with CR documented in approximately 30%) [3]. Addition of prednisone to fludarabine does not increase response rates, but it does increase the risk of opportunistic infections [24]. Only irradiated blood products should be used, due to the risk of transfusion-associated graft versus host disease, which can develop in immunosuppressed patients. Fludarabine treated patients are at increased risk of infections, and use of Septra DS 1 tab po bid times per week for PCP prophylaxis is recommended [25, 26]. While randomized studies comparing fludarabine to single agent chlorambucil [27, 28], CAP [29] and CAP and CHOP [30] showed higher response rates and improvement in progression free survival, there was no benefit on overall survival [31] (see CCO-EBR 6.1 at www.cancercare.on.ca).

Anthracycline-based Regimens: Anthracycline-based regimens such as CHOP are active in CLL. CHOP has been compared to chlorambucil/prednisone in randomized trials [32, 33]. No improvement in overall survival was observed.

Rituximab (Rituxan): The monoclonal anti-CD20 antibody rituximab has been studied in the treatment of patients with CLL. The data for this agent is summarized in **CCO-PEBC EBS 6.8 at www.cancercare.on.ca**. As a single agent, rituximab in the conventional dosing regimen has relatively low levels of activity with response rates of 10-30%. Greater activity has been observed when rituximab is given in higher doses or in combination with chemotherapy, however no randomized trials comparing chemotherapy to chemotherapy with rituximab have been reported.

Splenectomy (or splenic irradiation): Is indicated for patients with symptomatic splenomegaly and refractory cytopenias can often give less toxic relief of symptoms than a course of mutagenic chemotherapy, although there have been no randomized studies comparing splenectomy with other CLL treatments. Consideration of patients for splenectomy should be made relatively early in the disease (since cytopenias in many stage IV patients are related partially to splenomegaly). However, it is imperative that such patients be referred to a surgeon with expertise in this procedure in patients with hematological malignancies to avoid problems with infectious complications in this immunocompromised patient population.

Odette Cancer Centre Policy (Initial Therapy)

- ❖ Asymptomatic or minimally symptomatic patients will be observed without therapy.

- ❖ Chlorambucil 0.07 mg/kg (rounded off to nearest 2 mg) without prednisone will be given to symptomatic patients until clinical improvement in the indication, which led to initiation of therapy.

- ❖ Patients will have CBC monitored within 2 weeks of initiation of therapy and every 4-6 weeks while on therapy and will be seen every 4-6 weeks until therapy is discontinued.

Assessment of Response

Responses to treatment in CLL can be defined by the criteria established by Cheson et al [4]. Complete remission is defined as disappearance of clinically evident disease, normalization of CBC and resolution of radiologic evidence of disease [4]. Response will be felt to be incomplete if one of the following occurs: progression on therapy or within one month of completing therapy, biopsy proven persistent CLL, strong clinical suspicion. As the goal of treatment is symptomatic improvement, attainment of a CR is not an objective of therapy outside of clinical trials, in practice a response will be considered to have occurred if symptomatic improvement occurs.

Management of Incomplete Response

Unless symptomatic, patients with incomplete response should be observed. Treatment may be offered at the time of disease progression.

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Follow-Up

Following treatment, recurrence is inevitable. Stable patients should be followed every 3-4 months for the first 2 years and every 6-12 months thereafter. Patients with active disease may need more frequent follow-up. Assessment should consist of:

- ❖ History and physical exam
- ❖ CBC and differential
- ❖ Serum LDH

Imaging of involved areas should not be performed as routine follow-up, but should be restricted to investigation of symptoms as clinically indicated.

Management of Relapsed Disease

Relapse of CLL is inevitable. If patients relapse one or more years after treatment, they will often respond again to the same or a similar chemotherapy regimen, though the quality of the response is usually inferior and the response duration shorter. Treatment of CLL is generally palliative in intent; therefore patients who have relapsed disease may be followed without treatment until they experience disease related symptoms or progressive disease as described above [4]. A lymph node and/or bone marrow biopsy should be performed if the clinical pattern of relapse suggests that the disease is behaving in a more aggressive manner, suggesting histologic transformation.

Patients who experience a relapse can often have their disease controlled with systemic therapy. If remission duration was >1 year, we recommend retreatment with chlorambucil. If remission duration was < 1 year, one should proceed to second line therapy with fludarabine. Consideration of experimental therapies may be appropriate for this group of patients and the sequence of therapies used must be individualized to the patient.

Progressive disease > 1 year of previous fludarabine therapy may be treated again with fludarabine alone. Patients who develop progressive disease within 1 year of previous fludarabine therapy may be treated with a combination of fludarabine and cyclophosphamide [22]. Rituximab in combination with a fludarabine-based regimen has activity and may be an option for selected patients, however, is not funded by CCO [34, 35]. For patients under 60 years of age, it is strongly recommended that an allogeneic transplant procedure be considered and such patients should be discussed with a transplant center at this time. Favorable long-term outcomes have been reported following allogeneic transplantation, but only a highly selected population of patients would be potentially eligible for this therapy [36-40]. Only scant observational data are available for autotransplantation in CLL.

High-dose methylprednisolone (HDMP 1 g/m²) daily IV for 5 days monthly (with or without rituximab) is another option for patients who have failed fludarabine or who have the 17p- cytogenetic abnormality[41] and [42]. At these doses, HDMP appears to act by cell membrane disruption rather than through transcriptional changes. Appropriate prophylaxis against herpes viruses and PCP should be given.

Alemtuzumab is a monoclonal antibody directed at CD-52. The data for this agent in CLL is summarized in **CCO-PEBC EBS 6-16 (www.cancercare.on.ca)**. This agent is approved by the US FDA for treatment of patients with B-CLL who have been treated with alkylating agents and have failed fludarabine. No randomized trials comparing Alemtuzumab to other agents have been published. In phase II trials, response rates of ~30% in fludarabine-refractory patients have been reported. Alemtuzumab appears to be more effective in the peripheral blood than in other sites, with particularly poor activity with nodal disease larger than 5 cm [43]. This agent has significant toxicities with frequent infusion related toxicities, particularly when it is administered intravenously and profound immunosuppression with a risk of life-threatening sepsis. However, it may have a role in select patients who have failed alkylator, anthracycline, and purine anal0g therapies, have preserved functional status, no serious intercurrent infections, and no bulky adenopathy.

Other agents are currently under investigation. These include compound novel monoclonal antibodies, oblimersen, flavopiridol, UCN-O1, bryostatin, and Revlimid [1].

A sequence appropriate for many patients is as follows:

| Chlorambucil | → | Fludarabine | → | CHOP | → | Alemtuzumab (Campath) |

Histological Transformation

Transformation to Prolymphocytic Leukemia (PLL)

Prolymphocytic transformation is often marked by rapidly progressive splenomegaly and very high WBC count, with an increase in the number of prolymphocytes in the peripheral blood (> 15-30 %).

It occurs in ~10% of patients, and is associated with a poor prognosis. Response to treatment with alkylating agent or combination chemotherapy is generally poor, and mean survival from time of transformation is 9 months [44]. There are several reports of use of purine analogues such as fludarabine [45] and Pentostatin [46] in de novo PLL. Campath shows promise in this setting. [47].

Richter's Transformation

Transformation to an aggressive lymphoma (diffuse large cell lymphoma) occurs in 3-5% of cases of CLL [48]. Preliminary evidence suggests a higher rate of transformation (up to 12%) in patients exposed to previous fludarabine therapy [49]. The presence of EBV latent antigens in a subset of transformed cases raises the possibility that fludarabine-associated immunosuppression may allow EBV to transform an existing CLL clone or allow a new clone to develop [49, 50]. Patients present with progressive clinical deterioration, lymphadenopathy and systemic symptoms. Diagnosis requires biopsy. Median survival from time of transformation is < 6 months. Conventional lymphoma regimens are generally ineffective [51, 52]. Nonetheless, patients are usually treated with an anthracycline-based regimen, such as CHOP. The addition of rituximab for documented CD20+ large-cell transformation is reasonable and recommended. Combinations of fludarabine and ARA-C with cyclophosphamide (CFA) or cisplatin (PFA) have been tried in a small subset of patients [53]. Pulse Solu-Medrol may be of use in this situation and may be a better option than alkylator based therapy.

Special Considerations

Autoimmune complications:

❖ Autoimmune hemolytic anemia (AIHA)
❖ Idiopathic thrombocytopenic purpura (ITP)
❖ Pure red cell aplasia (PRCA)

Autoimmune Hemolytic Anemia (AIHA)

AIHA occurs in 5-37% of CLL patients, usually in advanced stage disease. It manifests with an acute hemolytic picture and positive direct antiglobulin test (DAT). Autoantibodies are polyclonal IgG antibodies, which do not originate from the malignant clone. Standard treatment is with prednisone 1 mg/kg/d; if no response is seen within 7-10 days, consider adding IVIgG. Cyclosporin A is a reasonable third choice. Splenectomy plays a minor role in management of AIHA in CLL. If patients respond to steroids, maintenance treatment is often required [54]. Exacerbation and precipitation of AIHA have been linked to the use of fludarabine [55, 56]. Fludarabine should therefore be avoided in patients with AIHA, and used with caution in patients with a positive DAT.

Idiopathic Thrombocytopenic Purpura (ITP)

ITP occurs in 2-3% of patients with CLL, usually early in the course of the disease. It may occur in association with an AIHA, as an Evans syndrome. Therapy should begin with prednisone 1 mg/kg/d. CLL-associated ITP patients do not seem to benefit from splenectomy as much as patients with primary ITP [54].

Pure Red Cell Aplasia (PRCA)

PRCA actually occurs in 6% of cases of CLL, but tends to be under-recognized. It usually develops in the early stages of the disease, presenting as severe anemia with reticulocytopenia. It occurs as a result of a T-cell mediated process. Standard treatment is with prednisone 1 mg/kg/d, if steroids fail, cyclosporin A should be added. It is also recommended to treat the CLL concurrently, as control of the CLL seems to be necessary for long-term control of the PRCA [54].

Infectious Complications

Infections are a major cause of morbidity and mortality in patients with CLL, accounting for up to 60% of deaths in these patients [57]. The pathogenesis is multifactorial, but includes disease related systemic hypogammaglobulinemia and therapy related side effects. The most common infections occur at mucosal sites, especially the respiratory tract. The main organisms responsible for infection include Staph. Aureus, Strep. Pneumoniae, H. Influenza, E. Coli, Klebsiella Pneumonia and Pseudomonas aeruginosa [57].

No studies have shown benefit for using prophylactic antimicrobial therapy in CLL. Several studies have examined the use of prophylactic IVIgG in CLL. A randomized controlled study comparing 400 mg/kg IV q 3 weeks versus placebo showed that patients receiving IVIgG did have significantly fewer bacterial infections, but there was no benefit on survival [58]. A subsequent study suggested that the routine use of IVIgG was not cost effective [59]. Several studies demonstrated that IVIgG used in lower doses was equally effective in reducing the incidence of infections [60, 61].

The optimal dose and schedule, as well as which subset of patients are likely to benefit from IVIgG remains unclear. In patients who are hypogammaglobulinemic and suffering from recurrent severe or life-threatening infections, it is reasonable to attempt monthly prophylaxis with IVIgG 400 mg/kg IV.

Supportive Care

Immunizations

Immunizations may produce a suboptimal response, because of impairments in the immune system, however it is recommended that patients with CLL should be vaccinated annually with the influenza vaccine and should also receive a pneumonia vaccination (Pneumovax) every 5 years [57].

Cytopenias

Patients should receive red blood cell or platelet transfusions if clinically indicated. Growth factors such as Erythropoietin [62] and G-CSF/GM-CSF have been demonstrated to be of benefit in CLL patients with refractory cytopenias [63, 64]. Use of these agents should be guided by the recent ASH/ASCO clinical practice guideline on use of erythroid stimulating agents **(please see related chapter)**.

T-CLL

T-CLL does appear to be a real, albeit rare entity, representing < 1% of all cases of CLL. Patients present with lymphocytosis, mild to moderate lymphadenopathy and splenomegaly, and bone marrow infiltration with clonal T-cells. The cells are morphologically similar to B-CLL cells, but phenotypically mark as mature T cells (CD3+, CD5+, CD7+), which are predominantly CD4+. T-CLL typically follows an aggressive clinical course, and displays poor response to chemotherapy [65, 66]. There is evidence that CAMPATH should be first-line treatment here – requires special access.

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