Treatment of chronic lymphocytic leukemia (CLL) in the untreated patient

HOT SPOT

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Chronic lymphocytic leukemia is an indolent B cell lymphoma with an incidence of two to six cases per 100,000 patients per year. In the Western world, it is the most common adult leukemia, making up 30% of all leukemias with a female to male ratio of 1.7:1. According to SEER data, the median age at diagnosis is 72. However, the majority of patients are diagnosed between the ages of 75–84 (Horner, Ries, Krapcho, et al., 2006).

The 2008 World Health Organization guidelines for the diagnosis of chronic lymphocytic leukemia (CLL) include (Swerdlow, Campo, Harris, et al., 2008):

1. Peripheral blood monoclonal B cell lymphocytosis of > 5.0 x 10 ^{9} /L with a CLL phenotype present for a minimum of three months.
2. Cytopenias with a typical bone marrow infiltrate of CLL, and typical CLL immunophenotype.

The characteristic immunophenotype of CLL consists of clonal B lymphocytes being positive for CD5, CD19, and CD23 with light chain restriction. Often, there is a weak expression of surface immunoglobulin, CD20, and CD79b. Notably, CLL does not include the molecular translocation t(11;14), which is associated with mantle cell lymphoma.

Prognostic factors

CLL is an incurable disease outside of allogeneic stem cell transplant. Specific prognostic markers have been developed allowing for the early identification of patients at risk of clinical progression. These markers include:

- Clinical stage (see Table 1). Please note the Binet Staging system is not presented
- Interphase Fluorescence In Situ Hybridization (FISH) analysis (see Table 2) Lymphocyte doubling time (LDT)
- > 30% CD38 expression
- Unmutated immunoglobulin variable heavy chain (IgVH). Patients with > 2% mutated IgVH are considered low risk
- Zeta associated protein-70 (ZAP70) expression (currently not available in Ontario)
- Increased Beta-2 microglobulin
- Micro-RNA expression profiles (currently not available in Ontario).

Table 1: RAI Clinical Staging

Stage	Characteristics	Modified RAI	Prognosis (months)
0	Absolute lymphocytosis in blood of > 15 x 10^9/L, without lymphadenopathy, hepatosplenopmegaly, anemia, or thrombocytopenia	Low	140
1	Absolute lymphocytosis (Stage 0) with lymphadenopathy, without hepatosplenomegaly, anemia or thrombocytopenia	Intermediate	100
2	Stage 0 with hepatomegaly or splenomegaly with or without lymphadenopathy	Intermediate	70
3	Stage 0 with anemia (Hb < 11 g/L); not due to AIHA	High	20
4	Stage 0 with platelets < 100 x 10^9/L; not due to ITP	High	20

Indications for treatment

CLL is typically an indolent lymphoma, with treatment recommended in the following settings, as per the CLLWG Guidelines (Hallek, Cheson, Catovsky, et al., 2008):

- Progressive bone marrow failure with cytopenias
- Massive splenomegaly (> 6 cm below costal margin), or progressive or symptomatic splenomegaly
- B symptoms or fall in ECOG performance status. This includes an unintentional loss of > 10% weight in the past six months, ECOG > 2, unexplained fevers for > 2 weeks, or night sweats of > 1 month without evidence of infection
- Massive (> 10 cm), progressive, or symptomatic lymphadenopathy
- Progressive lymphocytosis (> 50% increase over two months or a LDT < 6 months). Notably, in patients with a lymphocyte count of < 20 x 10 9/L, LDT should not be used as a single parameter for treatment initiation
- AIHA unresponsive to steroids or ITP refractory to standard care.

Treatment of the CLL naïve patient

The standard of care in the newly diagnosed CLL patient is a watch-and-wait approach, as previous randomized controlled trials show no benefit to early chemotherapeutic intervention. Once treatment is required (see Indications for treatment), several options exist with numerous clinical trials ongoing in identifying an optimal treatment strategy. Treatments are often dictated by stage, ECOG status, co-morbid status, age and, more recently, by FISH cytogenetics. For example, older treatments such as Chlorambucil are often given to the increasingly frail patient because of better tolerability, but at the expense of durable treatment response. On the contrary, asymptomatic patients with high-risk cytogenetics (i.e. del(17p)) should be referred early for clinical trial, as this group of patients is often refractory to standard treatment, and may be candidates for allogeneic stem cell transplant. Over the past decade, several agents have emerged for the initial treatment of the CLL patient, either as a single agent or in combination in clinical trials. These include, but are not all encompassing: Fludarabine, Cyclophosphamide, Pentostatin, Alemtuzumab, Bendamustine, and Lenalidomide.

Table 2: FISH cytogenetics and Median Overall Survival with CLL

FISH Cytogenetics	Median Overall Survival
Deletion 17p (p12.1)	32 months
Deletion 11q(q22.3)	79 months
Normal	111 months
Trisomy 12	114 months
Deletion 13q (q14)	133 months

Most studies now support the use of Fludarabine, a purine analogue, alone or in combination as first-line treatment in patients with CLL. Three randomized trials have shown the improved response rates with Fludarabine and Cyclophosphamide (FC) chemotherapy compared to Fludarabine (F) alone. The CLL4 trial (Catovsky, Richards, Matutes, et al., 2007) was the largest of such trials, comparing F to FC to chlorambucil (C) in newly diagnosed patients. Notably, FC resulted in a superior progression-free survival (PFS) of 43 months compared to 23 months with F alone, and a complete response (CR) rate of 38% (FC) versus 15% (F) versus 7% (C). For most centres, FC-based treatment is the standard of care for newly treated patients, up until the recently

anticipated results of the CLL8 Trial (Hallek, Fingerle-Rowson, Fink, et al., 2009) were presented at the American Society of Hematology meeting in December 2009. This is the first randomized controlled trial to profile whether adding Rituximab to FC can improve patient outcome. Rituximab is a chimeric monoclonal antibody, targeting CD20 and traditionally has been used in lymphomas with higher CD20 expression.

The CLL8 trial

In the CLL8 trial, patients were randomized to six 28 day cycles of Fludarabine 25 mg/m^2 iv days 1-3 and cyclophosphamide 250 mg/m^2 iv days 1–3 with or without Rituximab 375 mg/m^2 on day 0 cycle 1 followed by 500 mg/m^2 on day one of cycles 2–6. Groups were similar in terms of stage, age and FISH cytogenetics. However, there was a statistically higher proportion of patients with B symptoms in the FC-alone group (48% versus 41%). In total, 817 patients were subsequently followed with the primary endpoint of progression-free survival (PFS) and secondary endpoints of overall survival (OS), response (ORR), and safety.

In terms of primary endpoint, after a median follow-up of 37.7 months, PFS was in favour of the FCR group at 51.8 months versus 32.8 months (FC) in 790 patients ($p<0.001$). Secondary endpoint results showed a statistically significant achievement of complete response (CR) with FCR versus FC arm at 44.1% versus 21.8% respectively ($p<0.01$). Overall response rate, as well, was significant in favour of FCR at 95.1% versus 88.4%. In subgroup analysis, patients with 13q-, 11q- or trisomy 12 had a statistically significant higher proportion of CR when given the FCR regimen. Notably, patients with 17p deletion had the worst OS in the FCR versus FC arms at 38.1% and 36.5% respectively (see Figure 1). In addition to del(17p), B2M levels > 3.5 mg/dl were also associated with an overall poor PFS (HR 1.45, P=0.005) and OS (HR 2.287, P< 0.001). Overall survival three years post-randomization was 87.2% in the FCR versus 82.5% in the FC arm (p=0.012), and maturing data will be ongoing to ensure this statistical significance with OS persists.

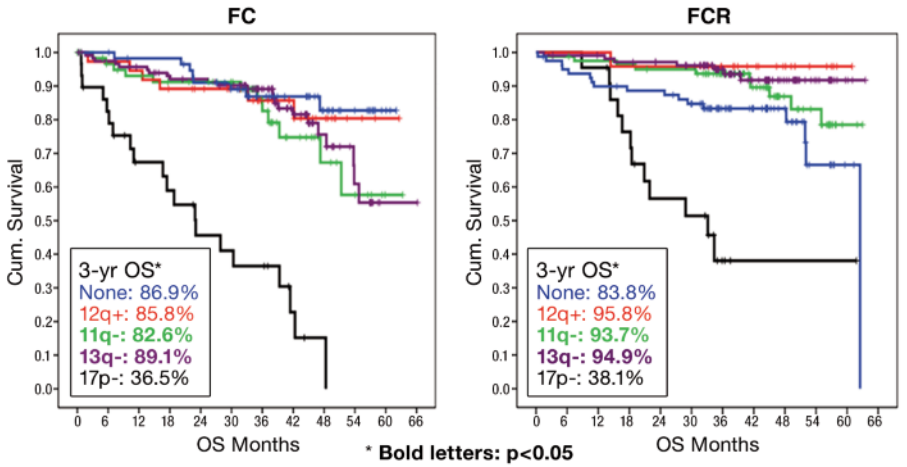

Figure 1: Overall survival and cytogenic abnormalities according to the hierarchical model

Despite the advantage of adding Rituximab to FC-based therapy, it does result in a higher degree of statistically significant adverse events. Specifically, ≥ grade 3 or 4 neutropenia was reported at 33.7% versus 21.0% ($p< 0.0001$) and leukocytopenia reported at 24.0% versus 12.1% ($p<0.0001$) in the FCR versus FC groups. There was no difference in anemia, infection, or tumour lysis syndrome between both groups. Treatment-related mortality was 2% for both arms.

The CLL8 trial is the first randomized controlled trial to prove the improved PFS and ORR with immunotherapy-based treatment in conjunction with FC. Several other trials are ongoing using immunotherapy-based regimens including Ofatumumab (anti-CD20) and Alentuzumab (anti-CD52), thereby highlighting the potential of superior treatments in the future for the untreated CLL patient.

Summary

1. The CLL8 trial supports the efficacy of adding Rituximab to Fludarabine and Cyclophosphamide in first-line treatment CLL naïve patients, particularly in patients with del (11q), del(13q), and trisomy 12.
2. FCR results in an improved PFS, OS, and response rates compared to FC chemotherapy.
3. Patients with del (17p) should be referred for clinical trial, as patients show a limited response to FC or FCR.
4. Future trials are ongoing to evaluate the efficacy of immune-based strategies in treating CLL.

References

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