Chronic lymphocytic leukemia (CLL)

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HOT SPOT

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the western world. The overall incidence is 4.6/100,000 with a median age at diagnosis of 72.

The disease incidence increases dramatically with age (33/100,000 > age 75) with 75% diagnosed above the age of 65.

CLL is classified as an indolent B cell lymphoma and is identical to small lymphocytic lymphoma (SLL) immunophenotypically, cytogenetically and histologically. Their treatments are interchangeable.

CLL is diagnosed by one or more of peripheral blood, bone marrow and lymph node testing. CLL cells have a characteristic immunophenotype (CD19+, CD20+, CD23+, CD38+, sIgw) and are one of only two B cell lymphomas that express the T cell marker CD5.

CLL is considered an incurable disease like most indolent lymphomas (without an allogeneic stem cell transplant). Therefore, the goals of therapy in most patients are disease control and extension of life. The classical clinical prognostic markers are:

- The Rai or Binet staging systems summarized in Tables One and Two. Fifty-five per cent of patients present with Binet stage A disease.
- The lymphocyte doubling time and BM histologic pattern.

Newer biological prognostic factors that refine the clinical stages further include:

- The mutational status of the immunoglobulin genes (IgVH).
- The karyotype.
- Over-expression of CD38.
- Increased β2 microglobulin.
- Increased expression of ZAP70.

Some of these factors are also prognostic for response to specific therapies. For example, patients with 17p deletions or p53 mutations respond less well to purine analogues and better to alemtuzumab.

Indications for treatment

In 2008, NCI guidelines were established to define criteria for initiating treatment:

- Evidence for progressive bone marrow failure.
- Massive, progressive or symptomatic splenomegaly.
- Massive nodes or progressive or symptomatic lymphadenopathy.
- Progressive lymphocytosis with an increase > 50% over two months or a lymphocyte doubling time of < 6 months.
- Autoimmune anemia and or thrombocytopenia poorly responsive to corticosteroids/standard therapy.

Any one of the following symptoms should also be present: unintentional weight loss within six months, significant fatigue, inability to work or perform usual activities, night sweats for > 1 month or unexplained fevers for ≥ 2 weeks without evidence for infection.

What guides therapy choice

Therapy is guided by symptoms, age, performance status, co-morbidities and the ability to travel for intravenous agents. In many instances, a watch and wait approach is adopted initially in asymptomatic low-disease-burden patients and this has been supported by randomized controlled trials.

When treatment is indicated, options include single agent alkylator (e.g., chlorambucil), single agent purine analogue (e.g., fludarabine), hybrid alkylator/purine analogue (bendamustine), fludarabine with cyclophosphamide, alemtuzumab (anti-CD52 antibody), and the addition of Rituximab to any one of the above.

Chlorambucil: while chlorambucil is often prescribed for frailer, more elderly patients, its use is associated with low CR rates (< 10%) and short remission durations (1 to 1.5 years). In a Cochrane meta-analysis of four randomized trials, purine analogues were associated with improved RR and PFS compared with chorambucil (HR 0.7, p<0.00001), but not OS (HR 0.89, p=.07).

FC has been shown to be superior to F alone in several large European cooperative group studies achieving remissions in up to 95% of previously untreated patients, higher complete remission rates (25% to 40%) and longer progression-free survival (32 to 48 months). Until recently, FC was considered in many countries to be the standard recommended first line therapy for untreated symptomatic CLL.

Adding Rituximab

Rituximab as monotherapy at traditional dosing is largely ineffective in CLL due to low CD20 expression and soluble CD20 consuming antibody. It may, however, sensitize CLL cells to chemotherapy and augment the chemotherapy response rates, depth and durations as seen with follicular lymphoma.

More recently, two large phase III trials in both first line and second line CLL have studied the effects of adding rituximab to a fludarabine-cyclophosphamide backbone and were presented at the American Society of Hematology Annual Meeting in 2008.

In the first trial **(CLL8)**, patients with untreated active CLL were randomized between either FC (n=396) or FCR (n=404) for six cycles. The schedule of chemotherapy is in Figure One. The primary endpoint was progression-free survival and the secondary endpoints were OS, response and safety.

With a median follow-up of 25.5 months, FCR was associated with improved median PFS (42.8 months versus 32 months p=.000007), higher CR rates (44.5% versus 23%, p< .01) and less primary progressive disease (3%

Table One. Rai Classification System

Stage	Description	Median survival (months)	Risk status (Modified Rai)
0	Lymphocytosis, lymphocytes in blood > 15 × 10^9/L and > 40% lymphocytes in the bone marrow	140	Low
1	Stage 0 with enlarged nodes	100	Intermediate
2	Stage 0–1 with splenomegaly, hepatomegaly or both	70	Intermediate
3	Stage 0–2 with hemoglobin < 11 g/dL or Hct < 33%	20	High
4	Stage 0–3 with plts < 100 × 10^9/L	20	High

Table Two. Binet Classification System

Stage	Description	Median Survival (months)
A	Hemoglobin > 10 g/dL and platelets > 100 × 10^9/L and < 3 involved nodal areas	Comparable to age-matched controls
B	Hemoglobin > 10 g/dl and platelets > 100 × 10^9/L and > 3 involved nodal areas	84
C	Hemoglobin < 10 g/dL and/or platelets < 100 × 10^9/L and any number of involved nodal areas	24

versus 8%, p <.01). Overall survival was not statistically different. FCR was associated with greater grade 3/4 neutropenia (34% versus 21%, p < .0001), but no increased incidence of infections or treatment-related death.

Minimal residual disease (MRD) as assessed by flow cytometry was significantly associated with progression-free survival regardless of treatment received with best PFS achieved with < 10^{-4} cells (49.6% of patients, PFS not reached) compared with ≥10^{-4} and < 10^{-2} (36.8% of patients, 34 months) ≥10^{-2} (13.6% of patients, 15 months).

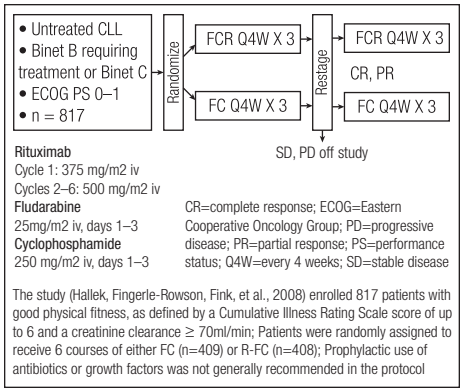

Figure One: Study design of CLL8 randomized controlled trial

A higher percentage of FCR-treated patients achieved maximal MRD in the peripheral blood (66% versus 34%, p=.005) (Figure Two).

Rituximab use in relapsed disease

The German CLL Study Group examined FCR versus FC (in the same dose and schedule as CLL8) in previously treated patients with CLL **(REACH study).** REACH was an open-label, multicentre, randomized phase III trial to evaluate the efficacy and safety of FCR versus FC in relapsed or refractory patients with CD20 positive CLL. The primary endpoint was PFS.

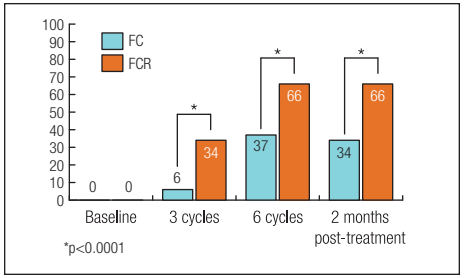

Figure Two. Per cent of patients achieving MRD in CLL8

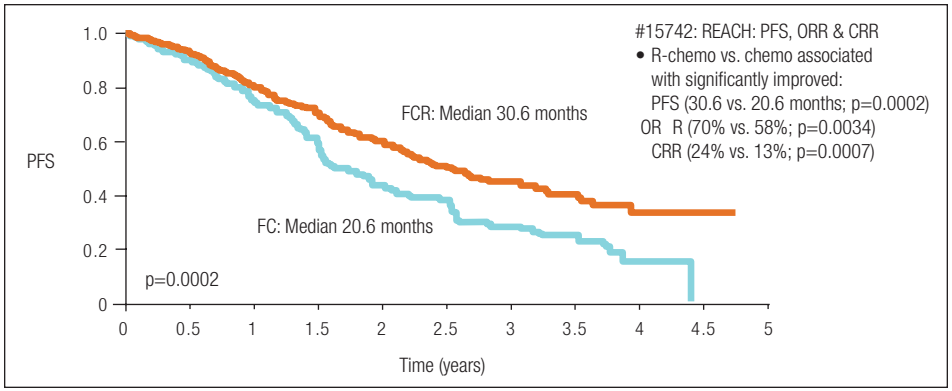

Figure Three. PFS in the German CLL REACH trial

Five hundred and fifty-two patients were randomized 1:1. The majority of patients had received one prior therapy with alkylator (66%) or COP/CHOP (18%) and 16% had previously been treated with Fludarabine as monotherapy.

With a median follow up of 25 months, PFS was prolonged by 10 months in the FCR arm (30.6 months) versus 20.6 months (p=0.0002, HR 0.65 95% CI: 0.51–0.82) (Figure Three).

The overall and response rates were also higher with FCR compared with FC (ORR 70 versus 58%; CR 24.3 versus 13%).

FCR was well tolerated with higher rates of grade 3/4 hematologic toxicity (chiefly neutropenia) compared with FC alone (55.7% versus 39.4 %). Notably, there were no differences in infections between the two arms.

Future randomized trials in CLL to look out for

- Rituximab-fludarabine (RF) versus Rituximab-chlorambucil in first line.
- Rituximab-bendamustine versus FCR in first line.
- RF versus observation in asymptomatic patients with higher risk CLL (unmutated VDJ rearrangements) first line.
- RF versus RF + lenalidomide consolidation versus FCR in relapsed disease.

Conclusions

The addition to Rituximab to the FC backbone in either untreated or relapsed/refractory CLL:

- Improves PFS by 13 and 10 months respectively.
- With relatively short follow-up, does not improve OS.
- Increases neutropenia, but not infections or treatment-related mortality.
- Achieves higher rates of complete remission and minimal residual disease (MRD).
- Higher degrees of MRD achievement correlate with improved PFS regardless of treatment received.

Key references

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