

## Review Article

# Overview of recent developments in chronic lymphocytic leukemia

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## Abstract

Multiple advances have been made in our understanding of pathobiology of chronic lymphocytic leukemia (CLL). These developments in the laboratory include new prognostic markers, risk stratification of the disease and newer therapeutic agents in CLL. These advances in CLL have come a long way in the past three decades since the development of Rai and Binet clinical staging systems. Important strides in the pathobiology, from defining mutational status of IGHV, to B-cell receptor (BCR) signaling pathways and CLL microenvironment have made a major difference in our understanding of this disease. Mutational status of immunoglobulin heavy chain genes (IGHV), CD38 and Zap-70, chromosomal aberrations and newer mutations, are the most clinically relevant prognostic markers. Chemoimmunotherapy (CIT) has become the treatment of choice for young and fit CLL patients. Various inhibitors of BCR signaling pathways and immunomodulatory drugs have shown efficacy in clinical trials. The most recent advance is the use of chimeric antigen receptor therapy (CAR) based on autologous T-lymphocytes. Nevertheless, CLL remains an incurable disease today. Coordinated developments between laboratory and clinic will hopefully translate into a cure for CLL. This short review focuses on advances in prognostication and therapy in CLL.

**Key words:** Advances in chronic lymphocytic leukemia, chronic lymphocytic leukemia, chronic lymphocytic leukemia

## Introduction

Chronic lymphocytic leukemia (CLL) was traditionally considered as the disease of the western world only, but recently surge in scientific reports from Chinese investigators show that this is not the case. Clinicians in India are also identifying more patients with CLL in their practices than was the case several decades ago. One report from the UK shows that patients of South-Asian origin with CLL have more aggressive disease compared to those among white population.<sup>[1]</sup> This observation suggests that prospective studies relating to CLL and other

lymphoproliferative disorders need to be initiated in India. In the present article we present a summary of recent advances in prognosis and therapy in CLL.

The recent (2008) revision of 1996 Cheson *et al.* guidelines provide an update for criteria of diagnosis and response to therapy in CLL.<sup>[2]</sup>

Diagnostic Criteria – iwCLL Diagnostic Criteria (2008) #

- $\geq 5000$  B lymphocytes/ $\mu$ l in the peripheral blood for duration of at least 3 months.
- $\leq 55\%$  prolymphocytes in the peripheral blood.

PB flow cytometry showing co-expression of CD5 and B-cell surface antigens CD19, CD20 and CD23, low levels of sIg, CD20, CD79b and kappa or lambda light chain restriction.

A definition of a precursor form of CLL –MBL (monoclonal B lymphocytosis) has also been proposed by Rawstron *et al.* and Shanafelt *et al.*<sup>[3,4]</sup>

## Advances in pathobiology of chronic lymphocytic leukemia and their prognostic relevance

A detailed discussion on pathogenetic mechanisms in CLL is beyond the scope of this article and has been adequately covered by Zenz *et al.* and Burger *et al.*<sup>[5,6]</sup>

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### **B cell receptors signaling**

Antigenic drive (autoantigen or polyreactive antigen) and triggering of B cell receptors (BCR) leading to activation of various intracellular signaling pathways such as Syk, Btk, PI3k and Lyn kinase. These pathways are now being successfully exploited as therapeutic targets.

### **Sequencing of immunoglobulin heavy chains mutation status**

Sequencing of immunoglobulin heavy chains (IGHV) has led to stratification of CLL into clinically relevant prognostic subgroups – Somatic hyper mutations - Mutated (M-CLL) and unmutated (U-CLL). The former with better survival and clinical course than the latter. It should be noted, however, that CLL patients with IGHV 3.21 gene usage are exceptions as they do poorly, irrespective of mutational status.

### **ZAP70 and CD38 status**

Expression of 70-kD zeta-associated protein (ZAP70) on CLL B cells is an oncogenic event leading to enhancement of calcium flux and intracellular signaling. Expression of CD38 in chronic lymphocytic leukemia B cells favors B-cell growth and survival through interactions between CD38 and CD31 and between CD100 and plexin B1 (PLXNB1). A higher expression of zap-70 and CD38 by CLL B cells correlates with worse clinical outcomes.

### **Specific chromosomal aberrations**

It has been known that CLL lymphocytes do not readily go into metaphase, therefore conventional banding techniques based on cytogenetic studies were not useful. However, fluorescent in situ hybridization technique (FISH) has provided important data on chromosomal abnormalities in CLL. Defects such as del13q14, del11q22-23 (ATM gene), del17p13, TP53 pathways, Trisomy 12 are seen in more than 80% cases.<sup>[7]</sup> Each of the genomic aberrations is associated with different genetic defects. TP53 mutations and del17p have emerged as a unique risk category in CLL associated with resistance to chemotherapy and poor outcomes. Most common is del13q14 (55% cases) associated with micro RNA's miR-15a and miR16-1 associated with good prognosis and better response to chemotherapy. Deletions of ATM gene involved in DNA damage check point pathway are associated with del11q22-23 and bulky lymphadenopathy. Trisomy 12 (possibly involving MDM2 an inhibitor of p53 gene) has an intermediate prognosis. Trisomy 12 also has higher expression of CD20. Very recently, whole genome sequencing of CLL reported Notch 1 mutations in CLL.<sup>[8]</sup> Recurrent chromosomal translocations are rare in CLL.

### **Microenvironmental interactions**

This is currently among the hottest area of translational research in CLL. CLL microenvironment comprises T cells,

CLL B cells, monocyte-derived nurse-like cells, CXCR4-CXCL12 axis and various other chemokines and cytokines which together support CLL cell growth, angiogenesis and survival. CLL cells, have tissue-specific microenvironmental niches (lymph nodes, marrow, blood and spleen), which provide a safe haven to leukemic cells. Lymph node microenvironment has been proven to be an active site for CLL proliferation as compared to bone marrow in having a different gene expression profile.<sup>[9]</sup> Further studies are ongoing to understand the intricate mechanisms involved.<sup>[10]</sup>

### **Monoclonal B cell Lymphocytosis**

Monoclonal B cell Lymphocytosis (MBL) has been defined as an asymptomatic condition where absolute monoclonal B-cell count is less than 5000 per  $\mu\text{L}$ .<sup>[3]</sup> It is proposed as a precursor to CLL. This can occur in 4-5% of healthy adults. Most cases of CLL can be preceded by MBL while only 1-2 % individuals with MBL can develop CLL every year. Studies are underway for identification of common cellular pathways in MBL and development of CLL.

### **Prognostic factors in CLL**

Advances in our understanding of various pathogenetic mechanisms in disease progression helped in developing guidelines incorporating newer, reliable and clinically relevant prognostic markers in CLL. These factors can help in characterizing disease, overall survival (OS) and time to first treatment (TTFT). [Reviewed in detail in<sup>[11]</sup>].

### **Poor prognostic factors in CLL**

Surrogate markers for assessing poor prognosis in CLL which are now recommended for evidence-based clinical practice.

- Advanced Rai and Binet clinical stages.
- del (11q) ATM gene and del (17p) using interphase FISH.
- Higher expression of ZAP-70 (>20%) and CD38 expression (>30%) on CLL B cells. #
- Unmutated IGVH genes (<2%).
- Short lymphocyte doubling time (LDT) <6 months (only when lymphocyte counts above 30,000/ $\mu\text{L}$ ) with poor outcomes.
- Elevated serum markers such as  $\beta 2$  microglobulin.
- VH3.21 gene usage (independent of IgVH mutation status).
- Fludarabine refractoriness (failure to achieve partial response or relapse within 6 months of treatment)

### **Word of caution**

All flow cytometry reporting and procedure to stain the cells should be standardized among various centers and core labs. Hematologists and oncologists should be aware of the potential misdiagnoses based on flow cytometry reports – for example a precise gating strategy will determine the accuracy of the report. % of CD38

and Zap-70- should be obtained on CLL B cells (CD5 and CD19 double positive population). Zap-70 is an intracellular molecule and this staining procedure involves permeabilization steps which are different from surface expression of CD38.

Minimal residual disease (MRD) is residual disease at the end of the treatment that is below the sensitivity described by traditional response criteria. MRD negative CR rates are looked for as end points in clinical trials. MRD is detected using 4 color flow cytometry and allele-specific oligonucleotide PCR for clonality of IGHV (0.01% sensitivity).

Recently an attempt has been made in delivering a multivariate model-based nomogram independently predicting for TTFT. A shorter TTFT was associated with three involved lymph node sites, size of cervical lymph nodes, del17p or del11q by FISH, increased LDH in serum and U-CLL status.<sup>[12]</sup> This may help in identifying patients for early intervention trials.

#### To summarize the risk categories in CLL includes

- Low Risk – Mutated CLL
- High Risk – Unmutated CLL, del11q, VH3.21 and elevated serum  $\beta$ 2-microglobulin
- Ultra High risk – del17p with/without TP53 mutations and fludarabine refractory disease.
- “Accelerated CLL” – Expanded lymph node proliferation centers with High Ki67 per proliferation center >40% or high mitosis counts.<sup>[13]</sup>

#### Advances in therapy of CLL

As explained above remarkable heterogeneity exists among CLL patients in terms of disease course and prognosis, ranging from indolent to an aggressive disease. Improvement in our knowledge of pathogenetic mechanisms in CLL has helped in developing a risk stratified treatment approach. This approach depends on age, Rai or Binet clinical stage, chromosomal aberrations, IGHV mutation status, CD38, Zap-70 status and serum  $\beta$ 2-microglobulin. The decisions for selecting the type of therapeutic regimen should be based on each patient's presenting features and the iwCLL guidelines but not solely on anyone of a single prognostic marker.

#### Chemoimmunotherapy- (Frequently used first-line therapy)<sup>[14]</sup>

Fludarabine, Cyclophosphamide with Rituximab (FCR) was initiated by MD Anderson Cancer Center (MDACC) by Dr Michael Keating and associates. Single arm results of FCR were reported in about 300 untreated CLL patients.<sup>[15]</sup> Grade  $\frac{3}{4}$  neutropenia was seen in 52 % courses. After 6 years follow-up overall survival rate of 77% was observed. In this trial two-thirds patients achieved no detectable MRD assessed by flow cytometry.

German CLL8 Trial<sup>[16]</sup> randomized FCR vs FC as - F 25 mg/m<sup>2</sup> IV and C 250 mg/m<sup>2</sup> IV on (days 2-4 in first cycle and days 1-3 in cycles 2 to 6) are given every 4 weeks for 6 cycles. Rituximab is given before chemotherapy at a dose of 375 mg/m<sup>2</sup> day 1 in first cycle and increased to 500 mg/m<sup>2</sup> on day 1 for cycles 2 to 6. We, however, recommend the use of 375 mg/m<sup>2</sup> throughout the six cycles. Results of CLL8 trial were 72% and 44% OR and CR rates and 87% 3-year survival, respectively, with FCR. Although patients with poor risk cytogenetics (del17p) had lower response to FCR.

Bendamustine (B) is being used with rituximab as BR (B 90 mg/m<sup>2</sup> days 1 and 2 and R 375 mg/m<sup>2</sup> day 1 every 4 weeks for 6 cycles in previously untreated CLL patients.<sup>[17]</sup> OR rates were 90.9 % and CR rate 32.7% with grade  $\frac{3}{4}$  neutropenia in 6.5% of all cycles. Median PFS was not reached at the time of publication of these results. At present a trial by German CLL study group is comparing BR with FCR in frontline setting and the results are expected by 2013.

#### # Word of caution

These trials are based on patient data from western countries and prospective randomized studies are needed in CLL from Asian populations such as in India and China in order to effectively assess the tolerability and efficacy of these regimens in local population.

[Detailed discussion on various other chemotherapy regimens and relapse refractory disease is beyond the scope of this review – reviewed in detail in<sup>[18]</sup>]

#### Treatment algorithm

##### Selection of treatment regimens (2012) first line

Asymptomatic early stage (Rai 0-II) – wait and watch (except clinical trials).

Symptomatic disease (any stage) – with good P.S. and no del 17p, Age <70 years (or older patient without significant comorbidities) - FCR is standard of care; other regimens are (FR, BR, Pentostatin with cyclophosphamide and rituximab - PCR).

Symptomatic disease (any stage) – with poor P.S. and no del 17p, single agent chlorambucil, oral fludarabine (F) and other agents such as bendamustine (aim of therapy is symptom control).

Symptomatic disease (any stage) – with good P.S. and del 17p, Alemtuzumab or fludarabine with alemtuzumab (FA) followed by Allo SCT (if appropriate).

#### Newer therapeutic agents in CLL

With an upsurge in advances in pathogenesis of CLL





favorable safety profile. A remarkable shrinkage in lymph nodes was observed accompanied by a shift of lymphocytes to peripheral blood. This drug also has a dual mechanism of action on signaling and inhibition of cross-talk in CLL microenvironments.<sup>[26]</sup>

### Immunomodulatory drugs

Agents belonging to this class have been shown to affect various defects and components of CLL microenvironments – cytokines, chemokines, angiogenesis, and T-cell cytoskeleton and immune synapse formation. However, the exact mechanism of action is still under active research.

### Lenalidomide

This is an immunomodulatory drug. It possibly acts in the CLL microenvironment by various mechanisms -inhibiting TNF, altering cytokine secretion and enhancing T-cell immunological synapse formation with CLL B cells. Lenalidomide has shown efficacy in relapsed refractory setting in two trials with different dosing schedules. In one trial an oral dose of 25 mg/day was given on days 1-21 of a 28-day cycle. ORR in this trial was 47%. Tumor flare reaction was observed in 58% patients with features of painful swelling of lymph nodes, fever and rash **1**. Another trial at MDACC used low dose of 10 mg orally daily with 5-mg increase every 28 days up to 25 mg/day. OR rate was 31% (including in poor risk CLL) and reduced toxicity with low dose was observed.<sup>[27]</sup> In frontline setting, in elderly patients, lenalidomide was started as 5 mg/day and escalated to 25 mg/day. Grade  $\frac{3}{4}$  myelosuppression was observed in 34 % of patients. ORR was 65% and CR was 10%.<sup>[28]</sup> An increase in serum immunoglobulin levels with reduction of CCL3 and CCL4 was noted. It was well tolerated in this subgroup of patients. This trial was important as elderly cohort of CLL is poorly represented in most of the trials. Careful monitoring of patients and prophylactic allopurinol therapy is needed. Myelotoxicity is another major toxicity associated with lenalidomide therapy. Further trials in combination with rituximab are ongoing. It is now studied for maintenance as well. This drug has a potential to be used in high-risk cases unfit for chemoimmunotherapy and in maintenance.

### Others agents in pipeline are<sup>[18]</sup>

- *Flavopiridol* (Alvocidib) – pan cyclin-dependant kinase (cdk) inhibitor drug.
- *Obatoclax, navitoclax (ABT-263)* (BH3 mimetic inhibits Bcl2 and Mcl-1).
- *Dasatanib* – dual Src- and Abl-kinase inhibitor.
- *ROR1 Oncofetal antigen* - The receptor tyrosine kinase-like orphan receptor 1 (ROR1) is identified as a highly expressed gene in CLL, but not normal B cells, suggesting it may serve as a tumor-specific target for therapy.
- Perifosine (Akt pathway inhibitor)

- Plerixafor (CXCR4 antagonist)

Finally, it is essential to discuss the most recent advance in CLL therapy. Chimeric antigen receptor –T cells directed toward CD19 (CART-19).<sup>[29,30]</sup> Chimeric antigen receptors combine an Ag recognition domain of a specific antibody (CD19) with an intracellular domain of the CD3- zeta chain or FcγRI protein into a single chimeric protein and CD137, a co-stimulatory molecule. Autologous T cells from a CLL patient were collected. Lentiviral vector expressing a CAR for CD19, coupled with CD137 and CD3 zeta was designed. On day 4 after chemotherapy -  $1.5 \times 10^5$  cells/kg bwt) of autologous chimeric antigen receptor–modified T cells were reinfused (D1-D3). Tumor lysis syndrome was noted on day 22 post-infusion. Evidence of a dramatic CR in a relapsed and refractory CLL patient was noted. This response was reported to have lasted for more than 10 months after infusion along with expansion of CART-19 cells for > 6 months.

## Conclusions

These recent advances in CLL have not only paved way for newer developments in risk-stratifying the disease but also improved outcomes while minimizing toxicity. Large scale clinical trials and international collaborations have shown to have excellent results. However, the disease remains incurable. We hope that with the current pace of developments in our knowledge in pathogenetic mechanisms, international scientific collaborations will now become possible and thus result in further improvements in the treatment of CLL.

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