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Review Article

Recent advances in chronic lymphocytic leukemia

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Abstract

Chronic lymphocytic leukemia (CLL) was largely considered to be a disease of slow progression, standard treatment with Chlorambucil and having almost similar prognosis. With the introduction of molecular methods for understanding the disease pathophysiology in CLL there has been a remarkable change in the approach towards the disease. The variation in B-cell receptor response and immunoglobulin heavy chain variable region (IGHV) mutation, genetic aberration and defect in apoptosis and proliferation has had an impact on therapy initiation and prognosis. Early diagnosis of molecular variant is therefore necessary in CLL.

Key words: Ataxia Telangiectasia Mutation, immunoglobulin heavy chain variable region, somatic hyper mutation, Zeta associated protein

Introduction and Background

Chronic lymphocytic leukemia (CLL) is defined as a malignant lymphoproliferative disorder of small, mature-appearing monoclonal B-lymphocytes in the blood cells, bone marrow and lymph nodes. Small lymphocytic lymphoma (SLL) is a lymph node counterpart of CLL. The cell morphology, course and prognosis of the disease are almost similar.^[1]

Epidemiology

CLL is the commonest form of leukemia in Europe and North America, mostly in the elderly male population averaging above 70 years. The incidence in the USA is about 3.9 per 100,000 per year with the frequency in men twice as high as that in women.^[2] The incidence in the UK is much higher, up to 6.5 per 100,000 per year, as per the research fund data study.^[3] The incidence in white Americans is higher than

African Americans (3.9 vs. 2.8 per 100,000 per year), in contrast the American people of East Asian origin have an incidence about five times lower.^[4] CLL in Jewish people is twice as common compared to the non-Jewish North Americans.^[6]

Looking at the above facts it was also studied that CLL runs in the family as first-degree relatives are three times more likely to develop the disease.^[5-7] Monoclonal lymphocytosis is normally up to 3.5% of white cells in healthy individuals above 40 years of age.^[8] Prevalence in first-degree relatives of patients with familial CLL is between 13.5–18%, suggesting that monoclonal lymphocytosis can progress to CLL in due course.^[9,10] There is no consistent evidence to link CLL with environment exposure to radiation or chemicals except in cases of agriculture workers and herbicides.^[11]

Diagnosis

CLL can be diagnosed if: the clonal B-lymphocyte count is >5,000/cuml of blood (duration of lymphocytosis >2 months). If the lymphocyte count is less than 5,000/cuml in asymptomatic individuals, without organ involvement, it is designated as 'monoclonal B lymphocytosis'.^[12]

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-Bone marrow lymphocytes >30%

The immunological profile of CLL lymphocytes is defined by:

- Weak surface membrane immunoglobulin (Ig) levels (most often IgM or both IgM and IgD)
- Monoclonal: expression of either Kappa or lambda
- B-cell antigens CD23, CD19 and CD20 (weak), with co-expression of CD5
- Negative for cyclin D1 and CD10 expression,
- No or weak expression of FMC7, CD22 and CD79b.^[13,14]

Differential diagnosis of CLL includes

- Mantle cell Lymphoma
- Follicular lymphoma
- Splenic marginal zone lymphoma
- Hairy cell lymphoma
- B Prolymphocytic Leukemia.

These can be differentiated on the basis of CD markers as shown in the flowchart [Figure 1]

Staging at diagnosis (Rai system)

0. Lymphocytosis
1. Lymph node enlargement
2. Spleen enlargement
3. Hemoglobin < 11 g/dl
4. Platelets < 100,000/ μ l

Staging at diagnosis (Binet system)

1. Lymphocytosis
2. Lymph node enlargement in > 3 areas
3. Cytopenia: Hemoglobin < 10 g/dl or platelets < 100,000/ μ l

Pathophysiology of chronic lymphocytic leukemia

Most of the CLL cells are inert *in vitro*. Recently, the understanding of the patho-biology in CLL has divided this disease into subgroups and this has had a profound impact on prognosis and treatment.

The three major subdivisions are based upon:

Figure 1: Differential diagnosis of CD19+ lymphocytosis^[15] (With permission from: Chronic Lymphocytic Leukemia. *Lancet*; Vol. 371, 1017-29).

- 1) B-cell receptor response and the IGHV mutation,^[16-19]
- 2) Genetic aberration/gene mutation,^[20-24]
- 3) Defects in apoptosis and proliferation.^[25-29]

B-cell receptor response

The B-cell receptor (BCR) is composed of two immunoglobulins (Ig), heavy and light chains (variable and constant region) and CD79a and CD79b. These contain intracellular activation molecules (SYK and LYN) that transmit signals to intracellular tyrosine kinases [Figure 2]. The ability of these kinases to activate downstream pathways varies in CLL subgroups and is correlated with:

- Ig heavy chain variable region (IGHV) mutational status,
- ZAP-70 and
- CD 38 expression.

These pathways can be targeted by small molecule inhibitors, the most promising of which might be SYK inhibitors.

B-cell receptor response and the IGHV mutation [Figure 3]

The B cell response to antigenic stimulation is mediated through the BCR in normal and malignant B-cells.

Each B-cell displays a distinct BCR that is formed through variable combinations of V, D and J segments for the Ig heavy chain and V and J gene segments for the light chain.

CLLs have mutated IGHV genes and unmutated IGHV genes (unmutated IGHVs showing poorer survival).

Figure 2: CLL pathogenic mechanisms and examples of targeted treatment options (With permission from NPG, "From pathogenesis to treatment of chronic lymphocytic leukaemia"; *Nature Reviews Cancer* Dec 2009)

Figure 3: CLLs with unmutated or mutated IGHV genes show markedly different biological and clinical behaviours (With permission from NPG, "From pathogenesis to treatment of chronic lymphocytic leukaemia"; *Nature Reviews Cancer* Dec 2009.)

(IGHV genes = immunoglobulin heavy chain variable region)

Folding and glycosylation defect of the μ and CD79A chains (not of the CD79B chain).

Poor expression of the CD22 molecule in B-cell chronic lymphocytic leukemia cells was also as a result of folding defect arising in CD79A.^[30]

Most B-cell chronic lymphocytic leukemia cells express CD5 and IgM/IgD due to which they have a mantle zone-like phenotype of naive cells that, ..., express unmutated immunoglobulin genes normally.^[31] Somatic mutations of IGHV genes are seen in Fifty to seventy percent of cases of chronic lymphocytic leukemia,^[32] appearing as if they had matured from a lymphoid follicle.

Mutational status of IGHV genes has a profound effect on the prognosis of CLL showing markedly different biological and clinical behaviors.^[33] BCR surface expression is usually weak in CLL. Low expression of the B-cell receptor is the typical presentation of lymphocytes in CLL^[34] (mechanisms remain elusive).

ZAP70 (Zeta-Associated Protein)

Low expression of the B-cell receptor correlates with defective intracellular calcium mobilization and tyrosine phosphorylation due to reduced induction of protein tyrosine kinase activity.^[35] High protein tyrosine kinase activity associated with ZAP70-a receptor (not found in normal circulating B-cells) is usually found in T-cells and natural killer cells detected

in most patients with un-mutated chronic lymphocytic leukemia.^[36]

ZAP70 expression is associated with advantageous survival of CLL cells because of enhanced access to proliferation centre and increased sensitivity to chemokine migratory signals^[37] (presence of ZAP70 is an oncogenic event in CLL, concentrated particularly in lymph node lymphoid cell).

CD38

CD38, which is associated with poor prognosis, predominates in patients with unmutated IGHV genes.^[16]

In chronic lymphocytic leukemia, expression of CD38 on B cells favors —. its growth and survival through sequential interactions between CD38 and CD31 and also between CD100 and plexin B1 (PLXNB1).^[38]

Genetic abnormalities

Dohner and colleagues^[39] in a series of 325 patients with chronic lymphocytic leukemia showed that chromosomal aberrations can be detected in interphase cells by fluorescence *in situ* hybridization (FISH) technique in 82% of cases. According to them the most frequent aberrations are:

- Deletion on Chromosome 13q (55%), Trisomy 12 (18%), A deletion on Chromosome 11q (16%), Deletion on chromosome 17p, affecting the TP53 protein, is seen less frequently (7%).

Deletions in band 13q14

'Deletion on Chromosome 13q' is the most frequently found genetic structural aberration in CLL and confers a favorable course.^[22,39] No inactivation of candidate genes by mutation has been demonstrated. Two microRNA genes, mir-15a and mir-16-1, located in the crucial 13q14 region have been implicated in CLL pathogenesis.^[20,21,40] A mouse model with a targeted deletion of the mir-15a-mir-16-1 locus recapitulates many features of CLL. This suggests that miR-15a and miR-16-1 have a direct pathogenetic role in CLL.

Deletions at 13q14 occur at high frequencies in other lymphomas and solid tumors, and a recent study has implicated miR-15a and miR-16-1 in the pathogenesis of prostate cancer through their targeting of cyclin D1 and WNT3A, which promote survival and proliferation.^[41]

Deletions of ATM (11q22–q23)

Although they are rarely found in early-stage disease, approximately one-quarter of patients with advanced CLL have 11q23 deletions. Correspondingly, patients who have 11q23 deletions have a more rapid disease

progression and extensive lymphadenopathy.^[39,42-44] In studies that aimed to delineate the 11q23 deletions in CLL, all aberrations affected a minimal consensus region in chromosome bands 11q22.3–q23.1 which also harbors the ataxia telangiectasia-mutated (ATM) gene in almost all cases.

ATM mutations have been shown to be present in 12% of all patients with CLL and in approximately one-third of the cases with a 11q23 deletion.^[45] The ATM protein kinase is a central component of the DNA damage pathway and mediates cellular responses to DNA double-strand breaks (DSBs). ATM deficiency leads to ataxia-telangiectasia, which is characterized by extreme sensitivity to irradiation, genomic instability and a predisposition to lymphoid malignancies.^[46] ATM activates cell cycle checkpoints, can induce apoptosis in response to DNA breaks and functions directly in the repair of DNA DSBs by maintaining DNA ends in repair complexes.^[47]

Trisomy 12

Trisomy 12 is among the more frequent aberrations in CLL (10–20%), the genes implicated in the pathogenesis of CLL with Trisomy 12 are unknown. A previously described association with poor outcome has not been confirmed.^[42,44] Incidence of Trisomy 12 does not increase with advanced stage or progression to refractory disease.

Deletions in band 17p13 or TP53 mutations

Deletion of 17p13 is found in 4–9% of CLLs at diagnosis or at initiation of the first treatment.^[22,39] 17p13 deletion usually encompasses most of the short arm of Chromosome 17p, the deletion always includes band 17p13, where the tumor suppressor TP53 (which encodes p53) is located. Among CLL cases that have monoallelic 17p13 deletions, the majority show mutations in the remaining TP53 allele (>80%). Among cases without 17p13 deletion, TP53 mutations are much rarer^[48] [Figure 4].

TP53 mutations in chronic lymphocytic leukemia

TP53- tumor suppressor gene, is a transcription factor activated by strand breaks in DNA which can trigger apoptosis or cell cycle arrest.

The Genetic lesions associated with deletions of the short arm of Chromosome 17 (del17p13), encodes the TP53 —. gene. The long arm of Chromosome 11 (del11q23), which encodes the ataxia telangiectasia mutated (ATM) gene can also result in a loss of function of TP53.

Patients with a 17p13 deletion or TP53 mutation

Figure 4: TP53 mutations in CLL (With permission from NPG, “From pathogenesis to treatment of chronic lymphocytic leukaemia”; *Nature Reviews Cancer* Dec 2009.)

have a poor outcome and are candidates for experimental strategies with novel agents and stem cell transplantation.^[49] 17p13 deletion is invariably associated with loss of TP53 as confirmed by fluorescence *in situ* hybridization (FISH) (‘+’ in Figure 4 denotes a TP53 deletion). Multiple genomic aberrations target the p53 pathway in CLL.

Recurrent translocations

Recurrent translocations are rare in CLL in contrast to other types of leukemia or B-cell lymphoma in which specific and recurrent Ig locus-associated translocations deregulate known oncogenes. However, IGHV-mutated CLLs, in which the precursors were exposed to SHM (Somatic Hyper Mutation) and, in a fraction of cases, also had undergone class switching. The lack of Ig-associated translocations may support the notion that CLL is derived from post-GC B-cells, in which SHM and class switching are silenced.^[50]

Microenvironment

CLL cells interact with and seem to shape their microenvironment, which consists of T-cells, stromal cells and soluble factors.^[51] CLL cells rapidly undergo apoptosis when they are removed from patients.^[52] This process can be prevented by adding a number of cytokines or other cell types to the CLL cell culture.

In the lymph node, the microenvironment provides anti-apoptotic signals and proliferative stimuli, resulting in the formation of proliferation centers of CLL cells (pseudo follicles) that are not found in other lymphomas.

CLL cells seem to recruit accessory cells^[53,54] and thereby create a microenvironment that supports their own survival.

There is an increase of CD3+ T-cells, most of which are CD40L+CD4+, and cluster in and around pseudo follicles.^[27] CLL cells that are in close proximity and in contact with activated CD4+ T-cells show expression of the cell surface marker CD38. This is of interest because CD38 has been linked to the proliferation of CLL cells. The presence of high numbers of CD38+ CLL cells in the blood is associated with a poor prognosis.^[16]

High-risk features for chronic lymphocytic leukemia^[55]

1. CD38 expression in > 30% of lymphocytes
2. ZAP70 expression in > 30% of lymphocytes
3. Unmutated (germ line) IgVH gene
4. High-risk cytogenetic abnormalities
 - a. 14q changes
 - b. 11q changes
 - c. 17p depletion
 - d. Trisomy 12
5. Rai Stage 3 or 4 or Binet Stage C
6. Doubling time of lymphocyte count <12 months
7. Elevated beta-2 microglobulin
8. Elevated serum thymidine kinase
9. Presence of large-cell transformation (Richter's syndrome)

Clinical management, therapy and prognosis

CLL is not necessarily treated at diagnosis. However, early intervention trials are currently selecting high-risk subgroups of CLL based on biological and clinical criteria to reassess early intervention. Transitions are noted from single-alkylating agent based therapies to nucleoside analogues, and combinations of both alkylators and nucleoside analogues and, most recently, chemo-immunotherapy. Complete response rates have improved from 7% to a maximum of 70%.^[42,56]

The goal of this early intervention approach should be a genotype (or risk factor)-adapted therapy in all patients.

The major prognostic factors in CLL includes: age, "Binet or Rai stage", serum markers^[57] and genetic factors (such as genomic aberrations,^[39] IGHV mutation status,^[16] ZAP70,^[58] and TP53 mutations).^[48]

Current and Emerging Treatments for Chronic lymphocytic leukemia

Chlorambucil with or without corticosteroids had been the mainstay of treatment in CLL for a long time. More recently purine nucleoside analogues (PNAs) have been introduced (e.g. fludarabine, cladribine and pentostatin) which have shown superior overall response (OR) and complete response (CR) rates in patients

treated with PNAs primarily.

PNAs and cyclophosphamide taken together have produced better response rates, including CR and molecular CR, compared with PNA as monotherapy.

Currently, with the advent of monoclonal antibodies (mAbs) like Rituximab which targets CD20 antigens, and Alemtuzumab, an antibody against CD52, significant improvement in the course of CLL has been noted.^[59]

Rituximab plus PNA can increase the rates of OR and CR, compared with PNA or Rituximab alone, with acceptable toxicity.

New mAbs, agents targeting the antiapoptotic bcl-2, the anti-CD20 molecule, lumiliximab and anti-CD40 mAbs are also in research.

Hematopoietic stem cell transplantation (HSCT): The role of HSCT in the management of CLL patients as regular practice is still undefined. HSCT has been utilized mainly in patients with high-risk CLL or those who did not respond to standard therapies.

Genotype-specific therapy

The first risk-adapted treatment for patients with CLL has been developed for patients with 17p13 deletions who have a very poor prognosis with alkylator- and purine analogue-based chemo-immunotherapy.^[42,44,60] There are evidences that several 'biological' agents, such as alemtuzumab, corticosteroids, lenalidomide and flavopiridol act independently of functional p53 in CLL, therefore the current treatment approaches in clinical trials use these agents before going for allogeneic stem cell transplantation.

Translating biological insights into treatment

The clinical course is generally indolent in the majority of patients and therefore clinical endpoints are reached slowly. In spite of this, the growing number of approaches that act differently from classical chemotherapy show great promise and some of them are particularly promising for CLL (for example, SYK inhibition).^[61]

Conclusions and perspectives

CLL can be divided into subtypes (IGHV-unmutated and mutated) that have distinct biological and clinical characteristics. IGHV-mutated CLLs derive from post-GC B-cells, and that IGHV-unmutated CLLs stem from B-cells that have been activated by antigens. The dependence and interaction of CLL cells with the microenvironment is of pivotal importance and is being

used as a drug target in preliminary studies.

Specific aberrations (11q23 and 17p13 deletions) and gene mutations (TP53 and ATM) help to define distinct biological and clinical subgroups of CLL. The most common genetic lesion—deletion 13q14—may serve as a model of how deregulated non-coding RNAs contribute to cancer initiation, and this may become a ‘druggable’ target in the future.

Overall, CLL may serve as a model for how microenvironmental stimuli, antigenic drive and genetic deregulation are combined in cancer pathogenesis. Importantly, there are a growing number of agents that act on specific biological targets and therefore open new therapeutic horizons.

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