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Immunoglobulin Heavy Chain Gene Mutations in Chronic Lymphoid Leukemia

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Abstract Chronic lymphoid leukemia (CLL) is the most common type of leukemia in adults in western countries and is a clinically and genetically heterogeneous disease. Although the disease usually follows a slow course, significant survival differences are observed depending on clinical and biological factors. Some patients with CLL do not need treatment for many years, while others need urgent treatment. It is noteworthy that staging systems are inadequate in patient follow-up and predicting the course of the disease. Therefore, parameters that determine prognosis in CLL independent of disease stage have been developed. In recent years, mutation status of Immunoglobulin heavy chain variable region (IgVH) genes has emerged as a strong marker for prognosis in CLL. Patients with CLL are divided into 2 subgroups with different clinical courses according to the mutation status in the IgVH genes: one refers to mutated IgVH segments with a more favorable clinical course and the other refers to non-mutated IgVH segments associated with a poor outcome. In this study, we will try to clarify the relationship between IgVH mutation status and CLL prognosis and survival.

Keywords: CLL, Mutation IgVH status, Somatic hypermutation

Introduction

CLL is a lymphatic system neoplasm characterized by the proliferation and accumulation of monoclonal B lymphocytes (Herishanu et al., 2011; Urbaniak et al., 2022). CLL is a heterogeneous disease with highly variable prognostic features. In some patients, the disease progresses very slowly and they can live their entire lives without any symptoms; in others, it progresses in an rapid form and they have a short survival (Motta et al., 2009). Rai and Binet staging systems, which are used as clinical staging systems in CLL patients, form the basis of prognosis evaluation (Moreno & Montserrat, 2008). According to these staging systems, the risk stratification of CLL patients is based on the measurement of the disease mass at the time of diagnosis, and the average survival time of patients in the advanced stage of the disease is approximately 1-2 years, while the average survival time of those in the lower stage is expressed as approximately over 10 years (Abbott, 2006). Although staging systems form the basis of evaluating prognosis, it has been reported that they are not effective in predicting patients with good prognosis (Mirzaei et al., 2018). Many biological and classical prognostic markers, including these systems, have been identified to determine prognosis (Moreno & Montserrat, 2008; Ivanescu et al., 2012). The main prognostic markers in CLL are; chromosomal abnormalities (17q13, 6q21, 11q23, 13q14, and 17p13), ZAP70 and CD38 expression levels, beta-2-microglobulin levels, IgVH mutation status, V3-21 gene usage, lymphocyte doubling time (LDT), peripheral blood lymphocyte count, morphology of lymphocytes in peripheral blood, BM histology, age, gender, serum thymidine kinase or soluble CD23 and TP53 mutations (Moreno & Montserrat, 2008; Mirzaei et al., 2018; Ivanescu et al., 2012). Among these prognostic markers in CLL, the mutation status of the immunoglobulin heavy chain gene variable region plays an important role in detecting differences in disease outcomes and guiding treatment decisions (Balla et al., 2024).

Immunoglobulin Genes and IgVH Mutation Status

The immunoglobulin (Ig) molecule is identified on the surface of all mature B cells, consisting of two homologous heavy (H) chains and two homologous light (L) chains linked to them by covalent bonds. Both heavy and light chains contain the N-terminal variable (V) region responsible for antigen binding and the C-terminal constant (C) region that decides the effector site (Tobin, 2005; Karan-Djurasevic & Pavlovic, 2017). The heavy chain consists of approximately 450-600 amino acid residues and the light chain consists of approximately 230 amino acid residues (Male, 2021). The heavy chain locus (IgH) is located on chromosome 14 (14q32.33), while the two immunoglobulin light chain (IgL) loci are located on chromosome 2 (2p11.3) kappa chain and chromosome 22 (22q11.2) lambda chain (Mikocziova et al., 2021). The IgH locus is estimated to be approximately 1250 kb in length (van Dongen et al., 2003). It occur of gene segment clusters containing almost 51 functional VHs, 30 diversity (D), 6 joining (JH) and 10 constant (C) genes, which are divided into 6 or 7 subgroups depending on sequence homology. The IgL locus is composed of VL and JL gene segments, but lacks D gene segments and contains 29-33 functional V(λ) and 36-40 functional V(κ) genes (Tobin, 2005; Tobin & Rosenquist 2005; Karan-Djurasevic & Pavlovic, 2017).

According to their various biochemical properties, immunoglobulins are divided into different isotypes or classes. Light chain isotypes come in two forms, kappa (κ) and lambda (λ). Heavy chain isotypes are γ, α, μ, δ, ε, and they are in related with kappa or lambda light chains. The name of a structurally complete imminoglobulin (Ig) isotype is determined by the heavy chain; Ig G, Ig A, Ig M, Ig D and Ig E molecules contain γ, α, μ, δ, ε heavy chains, respectively (Lodish et al., 2018). The heavy chain constant region, which defines Ig isotypes, is accountable for from fixing membrane-bound Ig to the plasma membrane of B cells. The variable region of each Ig chain occur of the three hypervariable complementarity determinant regions (CDRs) CDR1, CDR2, and CDR3, and the four relatively invariant framework regions (FRs) FR1, FR2, FR3, and FR4 (Karan-Djurasevic & Pavlovic, 2017). (Figure 1) While FRs are similar across various VH segments, CDRs vary considerably even within the same VH family. Moreover, CDRs express preferential target sequences of somatic hypermutations along the course of the germinal center reaction. Despite the fact that FRs are generally much less affected by somatic mutations, nucleotide changes can emerge in these regions, particularly in B cells under heavy mutational process (van Dongen et al., 2003). The heavy chain CDR3 region (VH CDR3) has great diversity potential and is the main determinant of the antigen specificity of the antibody (Arnaout et al., 2011).

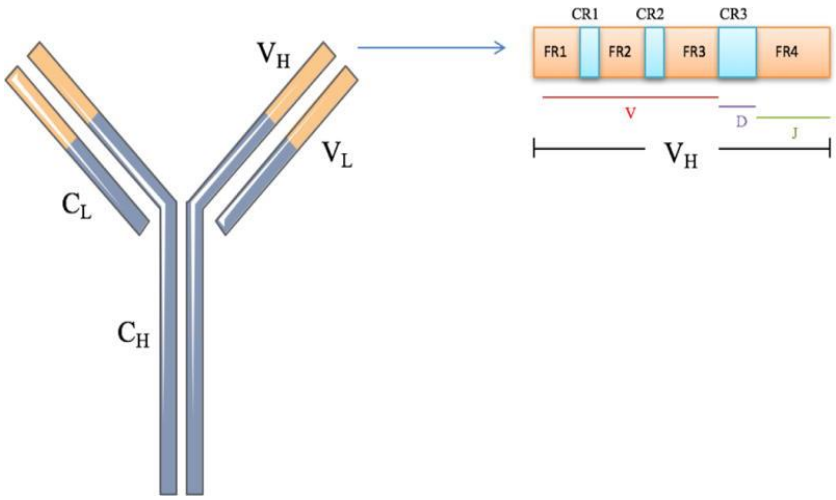

Figure 1. Schematic of an immunoglobulin molecule (Crombie & Davids, 2017).

B cells begin their development in the fetal liver and bone marrow and have the capacity to recognize a wide variety of antigens and make antibodies during their development (LeBien & Tedder, 2008). In the early developmental stage of B-cells, V, D, J genes recombine uniquely in the IgVH region and lymphocytes form a new VDJ genetic structure (Alkan, 2006). B lymphocytes that encounter the antigen undergo somatic mutation in the germinal center to provide the codes required for the immunoglobulin molecule in the IgVH gene segments. With point mutations in the nucleotide sequence, antibodies fully compatible with the antigen are synthesized and the Ig class changes (Meffre et al., 2000; Lu et al., 2020; Gupta et al., 2020).

In 1999, independent studies reported that IgVH mutation status differentiated CLL into two distinct clinical forms with different prognoses (Hamblin et al., 1999; Damle et al., 1999). The mutation status of IgVH genes defines depending on the cut-off value of 98% identity with the nearest germline IgVH genes; CLL cases with

≥98% identity are considered unmutated CLL (U-CLL), while those with <98% identity are considered mutated CLL (M-CLL). Somatic mutations of IgVH occur in about half of cases and have a favorable clinical course, require less treatment and have a longer treatment-free period than those without mutations, and have a significantly longer survival than those without mutations (Hamblin et al., 1999; Damle et al., 1999; González-Gascón Y Marín et al, 2014; Langerak et al., 2020). While CLL patients have positive results with a median survival of 10-20 years from the time of diagnosis; It is known that patients with unmutated IgVH have significantly worse outcomes, with an average survival time of 5-10 years (Kay et al., 2007). According to studies, it has been determined that the mutation status of IgVH genes is associated with a specific clinical response to chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab (FCR); fit M-CLL patients treated with FCR had longer sustained responses, progression-free survival, and substantial improvement in overall survival (OS) compared to U-CLL patients treated with the same therapy (Rosenquist et al., 2017; Thompson et al., 2016; Rossi et al., 2015; Fischer et al., 2016). It has also been reported that the risk of relapse after stem cell transplantation is quite high in patients with U-CLL (Ritgen et al., 2003).

Immunoglobulin heavy chain variable region gene repertoire: The repertoire of IgVH used in CLL is different from normal B cells. VH1, VH3 and VH4 gene families are common in B cells of CLL. Among B cells, the VH1 gene family is expressed more frequently than the VH3 gene family, and furthermore, these gene families exhibit a hierarchy of mutations among themselves; VH3 > VH4 > VH1 (Fais et al., 1998; Ghia et al., 2005). In most CLL studies, just 6-7 individual IgVH genes were used in more than half of the VDJ rearrangements. The most commonly used are IgVH1-69, IgVH3-7, IgVH3-23 and IgVH4-34, followed by a few other genes (IgVH3-30, IgVH3-30.3, IgVH4-59, IgVH3-48, IgVH1-2, IgVH4-39, IgVH1-3 and IgVH1-18), depending on the groups (Karan-Djurasevic, & Pavlovic, 2017). The frequency of somatic mutations is not the same among individual IgVH genes in CLL cells; IgVH3-7, IgVH3-23 and I IgVH4-34 show a high rate of somatic mutations, while IgVH1-69 may have few or no mutations (Fais et al., 1998; Ghia et al., 2005; Zhang & Kipps 2014).

Some IgVH genes may show different characteristics according to specific clinical features and different geographical regions, regardless of mutation status. The IgVH genes frequently used in Western patients are IgVH1-69, IgVH3-23, IgVH4-34 and IgVH3-07. The IgVH1-69 gene has been observed to be one of the most common rearranged genes in Western CLL patients and is mostly related with the U-CLL subset, but a very low frequency of IgVH1-69 usage has been reported in Asian cohorts. The IgVH3-21 gene has been reported to be more represented in CLL patients in northern European countries compared to the Mediterranean region and has been related with poor prognosis regardless of mutation status (Ghia et al., 2005; González-Gascón Y Marín et al., 2014; Stanganelli et al., 2013).

BCR stereotypy: Studies of VDJ recombinations of the Ig gene in CLL suggest that certain gene segments are very frequent in different patients, show stereotyped use of gene segments. A much higher ratio of unmutated CLL patients carry stereotypical VDJ recombinations that lead to alike CDRs (Jeyakumar & O' Brien, 2018). The antigen receptor on the surface membrane of the B cell (BCR) plays a significantly role in the progression and evolution of CLL (Vergani et al., 2023). In about 30% of CLLs, BCRs clustered into stereotyped subsets, each based on a distinct amino acid pattern in highly variable complementarity-determining regions (VH CDR3), some of which were named major because they were more common (Agathangelidis et al., 2012; Agathangelidis et al., 2021; Koehrer & Burger 2024). Just 6 of the IgVH genes; IgVH1-3, IgVH1-2, IgVH3-21, IgVH1-69, IgVH4-39, and IgVH4-34 constitute almost 80% of the major stereotyped subsets. It was stated that some IgVH genes, IgVH1-69, IgVH3-21, IgVH1-2, were highly represented, while IgVH3-7, IgVH3-23, IgVH3-30 were less represented (Koehrer & Burger 2024). Regardless of the mutation status of the IgVH3-21 gene, it is associated with an aggressive clinical course and poor overall survival; This indicates that the use of stereotypic IgVH genes affects prognosis (Tobin et al., 2003; Jeyakumar & O' Brien, 2018).

A consensus was reached in the ERIC (Europian Research Initiative on CLL www.ericll.org) structure for reliable and reproducible analysis of the IgVH gene mutation status in CLL, and the first recommendations on this subject were published in 2007 (Ghia et. al., 2007). As a result of increased knowledge and work, ERIC recommendations have been updated (Rosenquist et al., 2017; Langerak et al., 2011; Agathangelidis et al., 2022). IgVH mutation status is considered a strong prognostic factor in CLL and has been involved in the disease-specific International Prognostic Index (CLL-IPI) (International CLL-IPI working group, 2016; Rotbain et al., 2020). IgVH mutation status should be determined at the beginning of first-line treatment for its prognostic significance. It is routinely determined by Sanger sequencing and, unlike mutation burden, mutation status does not change over time. Unlike other types of mutations, repeated testing is not required for its evaluation (Pula et al., 2022). Recently, studies have been conducted with next generation sequencing (NGS) methods, which are reported to provide more accurate results than traditional methods (Crombie & Davids,

2017). Although Sanger sequencing is used as the standard method for IgVH mutation status, NGS is seen as the harbinger of a new era in medical diagnostic (Davi et al., 2020). The use of NGS to determine IgVH mutation status has not been validated for clinical routine testing due to absence of standardization and uncertain results; However, studies on the application of this methodology in CLL patients with additional applications are ongoing. (Pula et al., 2022).

Relationship between IgVH Mutation Status and Other Prognostic Markers

It has been stated that prognostic markers ZAP70, CD38, activation-induce cytidine deaminase (AID) mRNA, serum thymidine kinase, soluble CD23, lipoprotein lipase A and ADAM 29 are associated with IgVH mutation status (Gribben, 2008; Moreno &Montserrat, 2008; Pashaei et al., 2017). Among these, CD38 and ZAP70 are prominent markers.

CD38: CD38 is a glycoprotein with ectoenzymatic properties that is expressed in B, T, NK and other lymphoid and myeloid cells (Morandi et al., 2018; Pashaei et al., 2017). CD38 expression is related with neoplastic cells stating diffuse bone marrow infiltration, atypical morphology, elevated peripheral blood lymhocytosis and a less positive prognosis (Kostareli et al., 2008). High expression of CD38 has been reported to be related with unmutated IgVH (Damle et al., 1999; Hamblin et al., 2002; Thunberg et al., 2001). Although CD38 and IgVH mutation status are generally associated, CD38 expression changes have been reported to be observed in some patients throughout the course of the disease (Hamblin et al., 2002). This may limit the use of CD38 as a marker instead of IgVH mutation status. It is stated that CD38 can be a prognostic factor with its own biological and clinical value, independent of IgVH mutation (Kostareli et al., 2008).

ZAP70: ZAP70 (zeta transmitted protein 70) is a protein tyrosine kinase expressed primarily in T and NK cells (Guillaume et al., 2005). In CLL cells, a strong related between ZAP70 expression and unmutated IgVH genes, and patients positive for ZAP70 showed rapid progression, need for treatment in a short time, longer duration of treatment, and shorter survival rates (Wiestner et al., 2003; Crespo et al., 2003; Rassenti et al., 2004). It has also been suggested that determining ZAP70 expression at diagnosis is an important prognostic marker in the evaluation of disease progression in the early stages (Rassenti et al., 2004).

Conclusion

In conclusion, IgVH mutation status in CLL patients can be considered as an effective marker for the accurate determination of prognosis among prognostic markers. The IgVH mutation status determined at the start of treatment will provide accurate information about disease progression and survival. Accordingly, further studies on IgVH mutation status may lead to a new treatment strategy.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

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