# Targeted Therapies for Chronic Lymphocytic Leukemia

Subjects: Hematology

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The management of chronic lymphocytic leukemia (CLL) is based on symptom severity and includes various types of targeted therapies, including rituximab, obinutuzumab, ibrutinib, acalabrutinib, zanubrutinib, idelalisib, and venetoclax. These therapies rely on the recognition of specific peptides presented by human leukocyte antigen (HLA) on the surface of tumor cells by T cells, leading to an immune response. The therapeutic landscape for CLL is diverse and encompasses multiple therapeutic options, including chemotherapy, immunotherapy, radiation therapy, and stem-cell transplantation. There are several FDA-approved targeted therapies for CLL, including rituximab, ibrutinib, idelalisib, venetoclax, and acalabrutinib. Despite their high efficacy, the complex biology of CLL allows malignant cells to develop resistance mechanisms to these targeted therapies.

chronic lymphocytic leukemia BTK inhibitors tumor treatment strategy

## 1. Introduction

Tumor progression is a complex process that is regulated by a dynamic interplay between tumor cells and the host immune system [1]. Due to the selective pressure employed by the host immune system, tumor cells develop evading mechanisms to avoid detection and consequently elimination [2][3][4]. The host immune system relies on the recognition of antigens presented by human leukocyte antigen (HLA) class I molecules to monitor tumor cells. This function is predominantly facilitated by cytotoxic T cells (CTLs) via their T-cell receptors and by natural killer (NK) cells via their killer-cell immunoglobulin-like receptors (KIRs) [5]. The immune system has the capability to identify and destroy cancer cells by detecting and attacking tumor-associated antigens displayed on the surface of cancer cells. However, certain tumors can evade immune surveillance and persist by developing mechanisms of resistance. One such mechanism is the alteration in HLA expression, which can impair the presentation of tumor-associated antigens to immune cells [6].

## 2. Rituximab

Rituximab is a chimeric monoclonal antibody that specifically targets the CD20 antigen present on lymphocytes. It induces lymphocyte lysis with antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [7]. This therapy is widely used to treat various disorders, particularly malignancies such as non-Hodgkin's lymphomas (NHLs) and CLL [8][9]. Despite its effectiveness, the mechanisms of resistance to rituximab are not entirely clear, as its efficacy depends on the host immune response, which can be influenced by host

factors [10]. However, three primary mechanisms of resistance have been proposed. The first mechanism is that tumor cells may have developed ways to block CDC by expressing high levels of membrane complement regulatory proteins (mCRPs), such as CD46, CD55, and CD59. These proteins inhibit the activation of the complement cascade, thereby reducing the effectiveness of rituximab [11]. The second mechanism involves prolonged exposure to rituximab, leading to the downregulation of pro-apoptotic proteins Bcl-2 antagonist/killer (BAK) and Bcl-2 associated X (BAX), which can result in resistance to the therapy [12]. Finally, the most widely supported mechanism of resistance is the downregulation of the target antigen CD20. Studies have identified C-terminal deletions in the CD20 gene and decreased expression of CD20 mRNA in cells that become CD20-negative after rituximab exposure [13][14]. Rituximab is used in different phases of lymphoma treatment, including first-line, maintenance, and salvage phases, and ongoing research aims to develop strategies to overcome these mechanisms of resistance. Preclinical studies have demonstrated that neutralizing mCRPs with antibodies enhances the effectiveness of rituximab, indicating a potential therapeutic approach [15].

In CLL, the ratio of NK cells to malignant B cells affects the ability of NK cells to destroy cancer cells with antibody-dependent cellular cytotoxicity. Therefore, therapeutic interventions that enhance NK-cell activity may be beneficial for CLL treatment. Laprevotte et al. conducted a study to investigate the effects of recombinant human interleukin-15 (rhIL-15) on autologous NK cells in CLL samples [16]. The researchers demonstrated that rhIL-15 stimulated and expanded NK cells, leading to a reduction in malignant B cells. This effect was further enhanced in the presence of an anti-CD20 monoclonal antibody. Moreover, the study revealed a synergistic effect of promoting NK-cell growth exerted by rhIL-15 signaling and CD16 signaling, as obinutuzumab was found to be more effective than rituximab. The growth of NK cells in response to rhIL-15 was dependent on their contact with CLL cells, which was identified as an additional factor facilitating rhIL-15 transpresentation. These findings suggest that rhIL-15 can initiate NK-cell-mediated immunotherapy in CLL, highlighting the importance of NK-cell-mediated cytotoxicity in the treatment of this disease [16].

Furthermore, the administration of rhIL-15 may potentially reduce the immunosuppressive effects of transforming growth factor-beta (TGF-beta) in CLL models, leading to an increase in rituximab (RTX)-mediated antibody-dependent cell cytotoxicity (ADCC) [17]. Elevated levels of TGF-beta were observed in both in vivo and in vitro CLL samples, indicating its involvement in immune dysregulation in CLL [18]. Additionally, TGF-beta can inhibit the production of interferon gamma (IFN-gamma) mediated by CD16 and ADCC in NK cells in healthy individuals [19]. Khouri et al. conducted a study on post-transplant immunomanipulation with rituximab and donor lymphocyte infusion in 43 patients [20]. The researchers found that patients positive for HLA-A1, and negative for HLA-A2 and HLA-B44 (HLA-A1, non-A2, and non-B44) had a statistically significant improvement in complete remission (CR) rates and progression-free survival (PFS) relative to other HLA types. This combination of HLA allele characteristics was also associated with an improvement in response to immunomanipulation [20].

## 3. Ibrutinib

The signaling pathway mediated by the B-cell receptor (BCR) and its constituent, Bruton's tyrosine kinase (BTK), is implicated in the pathogenesis of various B-cell malignancies, such as CLL, mantle cell lymphoma (MCL), and

diffuse large B-cell lymphoma (DLBCL) [21]. The constitutive activation of the B-cell receptor signaling pathway in which BTK plays a crucial role has been associated with various B-cell malignancies. This persistent signaling leads to the activation of oncogenic NF-kB and other signaling pathways that promote the survival and proliferation of malignant B cells, leading to their accumulation in the bone marrow, blood, and secondary lymphoid organs [22] [23]. BTK is a significant contributor to the pathogenesis of B-cell lymphomas, as its phosphorylation is considerably increased in malignant B cells compared with normal B cells [24]. Ibrutinib was specifically developed to inhibit BTK and has been approved by the FDA for the treatment of several malignancies, including CLL, MCL, and DLBCL [25]. Woyach investigated the mechanism of resistance to ibrutinib in patients that showed relapse in CLL during the treatment period [26]. Their findings showed that resistance to ibrutinib is caused by mutations in the cysteine residue, where the drug binds. Furthermore, there are two additional mutations in BTK or downstream enzymes in the B-cell signaling pathway, such as PLCG2. Some studies have shown that mutations in BTK and PLCG2 are the most common mechanisms of resistance to ibrutinib in CLL, WM, and marginal zone lymphoma (MZL) [27][28].

A case study by Furman et al. investigated a case of a 49-year-old woman who had a diagnosis of CLL and developed progressive disease after 21 months post-ibrutinib therapy. RNA sequencing revealed a mutation of BTK (C481S) in the patients that was not present before the therapy [29]. Similarly, a study by Amin et al. identified 5 out of 48 CLL samples as more resistant to ibrutinib after relapse after chemotherapy [30]. The findings further revealed that three samples had acquired a del17p/TP53 mutation. The study also showed that CLL samples that had del17p/TP53-mutated cells demonstrated less sensitivity to ibrutinib-induced apoptosis [30]. Another study by Kanagal-Shamanna et al. sequenced mutations in 29 genes associated with CLL that developed resistance to ibrutinib/acalabrutinib [31]. They found mutations in *TP53*, *SF3B1*, and *CARD11* after disease progression [31]. Other mutations associated with ibrutinib include the deletion of the short arm of chromosome 8 (del(8p)), which leads to deficiency in a protein called TRAIL in combination with driver mutations in genes such as *EP300*, *EIF2A*, and *MLL2* [32]. Another mutation associated with ibrutinib resistance is a newly identified mutation in the BTK gene (*BTKT316A*), which activates a protein called PLCG2 in CLL [33]. These findings suggest that multiple genetic factors contribute to the development of ibrutinib resistance in CLL, and identifying these factors could help to develop new strategies for treating drug-resistant diseases.

Ibrutinib has been shown to decrease the expression of CD200 and BTLA molecules that cause immunosuppression in CLL cells [34]. In a recent study conducted by Long et al., the effect of ibrutinib and acalabrutinib therapy on the T-cell phenotype, immune function, and CLL cell immunosuppressive capacity was evaluated [34]. Their findings showed that in patients with CLL, the medication ibrutinib was found to significantly increase the number of CD4+ and CD8+ T cells, particularly in the effector/effector memory subsets. This may have been due to ibrutinib's inhibition of ITK, which appears to reduce activation-induced cell death. Both medications reduced the expression of PD-1 and CTLA-4 in T cells, which are proteins that suppress immune responses. The number of regulatory T cells (Treg) did not change, but the ratio of Tregs to conventional CD4+ T cells decreased with ibrutinib but not with acalabrutinib. Both medications also reduced the production of immunosuppressive molecules CD200 and BTLA, as well as IL-10, by CLL cells [34].

Manukyan et al. conducted a study to investigate the effects of short-term and long-term ibrutinib treatment on the expression of HLA-DR in CLL cells, T cells, and monocytes [35]. The study involved 16 patients with high-risk CLL who were treated with ibrutinib. The researchers analyzed the immune cells in their blood and observed that HLA-DR expression on CLL cells decreased, while the number of CLL cells increased after commencing ibrutinib treatment. Furthermore, when CLL cells were cultured with ibrutinib in a laboratory, a decrease in HLA-DR expression was observed at both the protein and mRNA levels. However, after one month of treatment, an increase in the number of CD4+ and CD8+ T cells, as well as CD4+ and CD8+ cells expressing HLA-DR, was observed. The decrease in HLA-DR expression on CLL cells was temporary and gradually increased by the 12th month of treatment. Long-term treatment with ibrutinib was found to be associated with an increase in the number of CD4+ cells expressing HLA-DR and an elevation of HLA-DR expression on all monocyte subsets [36].

## 4. Idelalisib

The PI3K signaling pathway plays a crucial role in the progression of many cancers, and targeting PI3K has emerged as a promising therapeutic approach [36]. However, the existence of four different PI3K isoforms with partially overlapping functions and varying toxic effects presents a significant challenge. Idelalisib, a selective inhibitor of the delta isoform of PI3K, has demonstrated impressive efficacy in treating B-cell malignancies with acceptable side effects and has been approved by the FDA for CLL, FL, and SLL treatment [37]. In vitro studies on CLL cells have identified that resistance to idelalisib is associated with increased expression of insulin-like growth factor 1 receptor (IGF1R). Furthermore, treatment re-sensitization was achieved with an IGF1R inhibitor [38]. Another study found that CLL cells developed resistance to idelalisib with increased and constitutive MAPK pathway activation, making communication between the PI3K and MAPK pathways that bypassed PI3K inhibition possible [39]. The study also identified that increased MAPK pathway activation was associated with mutations in KRAS, BRAF, and MAP2K1 [39]. Resistance to idelalisib has been primarily studied in solid tumors and has been attributed to alterations that increase the activity of PIK3CA, NRAS, or KRAS [40][41].

## 5. Venetoclax

Venetoclax is an FDA-approved drug that inhibits B-cell lymphoma 2 (Bcl2), a pro-survival protein that regulates the intrinsic apoptosis pathway [42][43]. The drug binds to Bcl2, allowing pro-apoptotic proteins such as BIM and BH3 to activate BAX and BAK, leading to apoptosis and inhibiting cell proliferation. The regulation of programmed cell death, or apoptosis, is governed by the intricate interplay between pro-apoptotic and anti-apoptotic members of the BCL2 protein family [44]. Anti-apoptotic proteins such as BCL2, BCL-XL, MCL1, and BCL-w exert their survival-promoting effects by countering the pro-apoptotic signals. The pro-apoptotic members can be classified into two subtypes based on their structure, namely, multidomain proteins, such as BAX and BAK, and BH3-only proteins, such as BID, BIK, NOXA, PUMA, BAD, and BIM. BH3-only proteins activate apoptosis by either inhibiting the anti-apoptotic proteins or directly activating the multidomain pro-apoptotic proteins [45]. Hence, the balance between pro- and anti-apoptotic proteins is a crucial determinant of cellular fate in response to apoptotic stimuli [46]. However, malignant cells can develop resistance to venetoclax with various mechanisms, including mutations in

the BH3 binding groove of Bcl2 or mutations in Bcl2 itself [46]. Patients with relapsed or refractory (R/R) CLL may also exhibit genetic aberrations in cancer-related genes that confer resistance to treatment. A study by Herling et al. sequenced eight CLL patients that developed resistance to venetoclax [47]. Their findings showed recurrent mutations in BTG1, CDKN2A/B, BRAF, and CD274 (PD-L1) [48]. To improve the clinical efficacy of venetoclax, combination treatment strategies with other agents, such as cytarabine, ibrutinib, rituximab, or bendamustine, have been developed, resulting in improved response rates. Ongoing studies are being conducted to identify optimal combination regimens for venetoclax [46].

Increased monocyte HLA-DR expression has previously been linked to improved cytokine response. A study by Svanberg et al. investigated monocyte and neutrophil phenotype functions in CLL patients who were treated with 420 mg for 8 weeks followed by venetoclax for 5 weeks [47]. The study involved nine participants, and their monocyte and neutrophil counts, as well as the distribution of mature and immature neutrophils, were initially found to be within the normal range. These measurements remained stable throughout the course of treatment. At baseline, the expression of HLA-DR on monocytes was found to be suppressed but significantly increased after combination treatment with ibrutinib and venetoclax ($p$ = 0.04). Furthermore, the HLA-DR expression on neutrophils was initially high and did not change after ibrutinib treatment (n = 8) but declined significantly after the addition of venetoclax (n = 7) ($p < 0.01$). The study also found that the LPS-stimulated production of TNF-α and IL-6 was initially suppressed. However, the IL-6 levels increased significantly upon ibrutinib monotherapy, and the levels of both TNF-α and IL-6 almost returned to normal upon the addition of venetoclax to ibrutinib treatment ($p$ = 0.02 for TNF-α and $p$ = 0.009 for IL-6) [47].

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