The application of Zanubrutinib in Chronic lymphocytic leukemia, Waldenstrom Macroglobulinemia, and Mantle cell lymphoma

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Abstract: The incidence of B-cell lymphoma is increasing year by year. The number of patients with diffuse large B-cell lymphoma over 75 years old in the United States is increasing at a rate of 1.4% per year. It had been ranked as the top 10th most common cancer-related cause of death. The growth factors that contribute to B-cell lymphoma have become central foci in clinical research. Zanubrutinib proves to be an effective drug in inhibiting BTK kinase. The phase I and phase II trial of Zanubrutinib was passed in 2014 and accepted accelerated approval at the beginning of 2020, December 2nd. Around the world, there are more than 20 clinical trials initiated and over 1000 patients receiving Zanubrutinib as a treatment to test its efficacy. After testing, the drug has been proven effective in treating the disease, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenstrom Macroglobulinemia (WM). For instance, a clinical trial has illustrated an 84% overall response rate from zanubrutinib therapy in patients with MCL specifically and is currently recruiting more members on clinical research. In fact, for Asian patients undergoing clinical trials aging from 19-90, Zanubrutinib has proven to increase the AUC for as well. In this paper, some of the advancements of BTK inhibitor and several vital parameters, including mechanisms of various diseases and various clinical trials data in each of the drugs treating the several diseases, will be discussed throughout this report.

1. Introduction

Nowadays, a wider variety of patients has been diagnosed with B-cell lymphoma. Take patients over 75 years old and diagnosed with diffuse large b-cell lymphoma; for instance, the number of these patients increased 1.4% per year in the US [1]. B-cell malignancy is commonly classified as a type of tumor that affects B-cells, often occurring in the lymph nodes. They are discovered in the aging population and patients with immune system impairment. B-cell malignancy includes Hodgkin's and non-Hodgkin's tumors and is classified as indolent and aggressive lymphoma. Under normal circumstances, indolent lymphoma is more sensitive to therapies and can be controlled with proper treatment, although it cannot be cured entirely. More aggressive lymphoma needs specialized treatment, and they have more possibilities of being completely cured. Before the advent of BTK inhibitors, regular treatments include radiotherapy and chemotherapy. Indolent tumors at an earlier stage can be inhibited but not completely cured, while aggressive lymphoma (non-Hodgkin) at an earlier stage had a cure rate of more than 50% [2].

Zanubrutinib is a Bruton's tyrosine kinase inhibitor that aims at inhibiting Bruton's tyrosine kinase signaling pathway [3]. It is an orally taken capsule aimed at treating various B-cell malignancies, including but not limited to chronic lymphocytic leukemia, Waldenstrom Macroglobulinemia (WM), mantle cell lymphoma (MCL), and non-Hodgkin disease. This paper will be primarily focus on the signaling pathway of Zanubrutinib, including how it blocks the BTK Kinase. Next, it will briefly discuss three types of diseases such as chronic lymphocytic leukemia, WM, and MCL, emphasizing its therapeutic effect and some essential properties of the drug well as clinical trials that are undergoing and recent progress.

2. The Signaling pathways of Zanubrutinib

The interactions between b-cell receptors and their corresponding cytokines that signal the whole pathway plays a vital role in the pathogenesis of B-cell cancer. Identifying the factors that influence cancer growth will drive researchers to inhibit tumor growth and proliferation successfully. In MCL, for instance, the tumor growth resulted from the mutant that occurs in the expression of the regulatory proteins. This protein is Bruton's tyrosine kinase, which plays a vital role in controlling the whole BCR signaling pathway. The inhibition of BTK or Bruton's tyrosine kinase, which resulted in the halt of the BCR pathway, has proven the vitalness of this protein, evidenced by previous drugs like ibrutinib [4]. This section will discuss how Zanubrutinib inhibits BTK kinase and hence stops the growth of B-cell cancer.

To begin with, B cells play an essential role in controlling and triggering the immune system, followed by the activated immune responses, such as producing antibodies and subsequent activation of Nk pathways, which leads the proliferation of effector cell. One part of such activity lies in the adaptive immune system. B-cell receptors, along with other vital receptors, are on the surface of the membrane barriers, including Toll-like receptors and chemokine receptors. The major signaling pathway is known as the B-cell antigen receptor pathway. Many responses may be triggered, such as producing antigen, activating Nk cells, labeling tumor cells followed by apoptosis. There are potential response signals in B cells, such as termination of cell activity, the spread of cell activity, and reproduction into memory B cells or antibody-producing B cells. Every B cell has a receptor that controls for a specific antigen. If the B cell never interacts with its antigen, the b-cell will enter another pathway engulfed by the lymphocytes. After B-cell binds to the antigen, an immune response will be triggered, and B cells will be activated and spread. In MCL, the mutant B cells undergo molecular proliferation due to the release of the BCR pathway [5].

The B cell receptor complex comprises membrane protein in the immune system. The membranes that interacted with each other are the heterodimers CD79a and CD79b. Within IgM, there are mainly two heavy immunoglobulin chains and two light chains. The cytoplasm region of CD79a and CD79b is called ITAM or the signaling molecule that resulted in the following signaling pathways. When a specific antigen binds to the receptor's active site, phosphate groups attach to ITAM, providing energy by the Src family kinase Lyn. This will result in the following biochemical reaction that binds to the SH2 domain of the tyrosine kinase Syk. Hence, Syk will keep on phosphorylating and activating PI3K, which converts PIP2 to PIP3. PIP3 will serve as a docking site for Bruton Tyrosine kinase and AKT to bind. BTK then activates C gamma two and C beta.

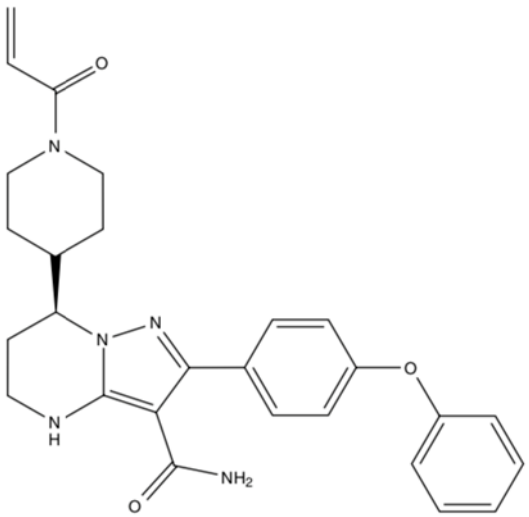

Figure 1. Chemical structure of Zanubrutinib [3].

The process of activating C-beta then phosphorylates IKK – a kinase that phosphorylates IKB. The phosphorylation of IKB. leads to the destruction of IKB. This frees the NFKB. transcription factor that

allows it to move freely toward the nucleus, driving tumor cell growth and proliferation4. Throughout the process, Zanubrutinib, as the second generation of the BTK inhibitor (figure 1), will inhibit the signaling pathway by preventing BTK from working, hence inhibiting the NFAT, Nk-kB, and MYC pathways. As Zanubrutinib is irreversibly bound to cysteine 481 in the binding pocket of BTK, BTK is inactivated. Traditionally, BTK can interact with four different parts: MYD88, protein adapter similar to MAL, IL-1R kinase one, and interferon-b, hence driving the transcription of NF-kB in the NF-kB pathway (figure 2). As BTK is inhibited, cell proliferation, antibody expansion, interferon activation factors are inhibited [5].

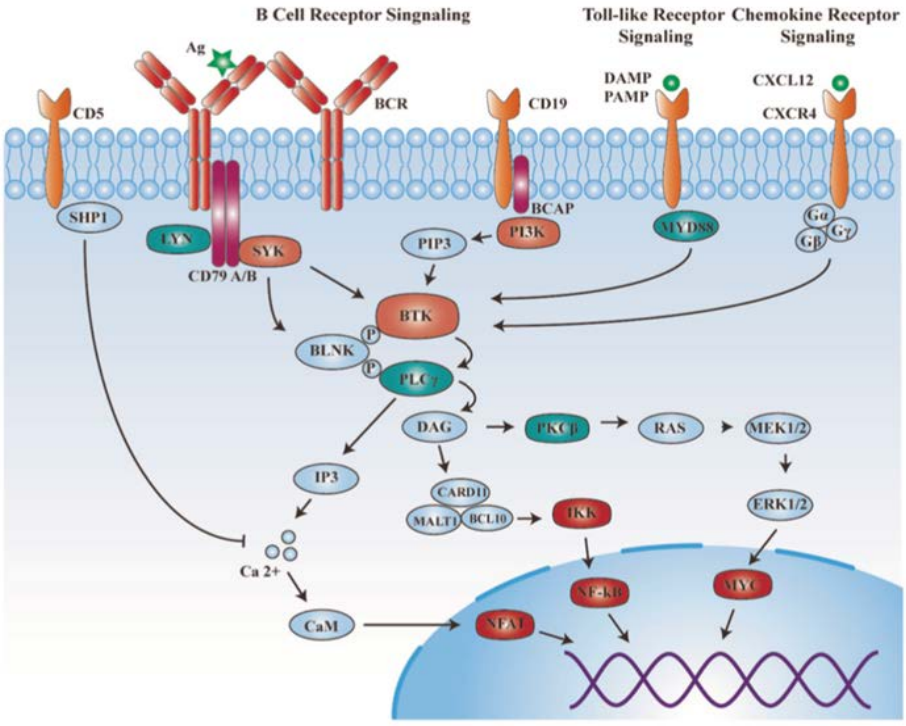

Figure 2. Zanubrutinib signaling pathway [5].

3. Chronic lymphocytic leukemia

3.1 Brief introduction of chronic lymphocytic leukemia

Research has shown that CLM has been found for 70 years for chronic lymphocytic leukemia. Essentially, cancer contained excessive lymphocytes that were made from bone marrow. The patients containing this disease usually have the symptoms of swollen lymph nodes and feeling extremely tired. Patients without treatment will even face severe bone marrow failures in the later stages. This disease is usually found in adults and rarely in children.

Recent research has indicated that the promoting factors in CLL included antigenic stimulation and interaction between accessory cells and cytokines. These jointly result in the tumor cell growth and development and prevent the tumor cell from apoptosis.

There are fundamental structural differences in b-cell receptors between patients and an average person, suggesting a strong correlation between the pathogenesis of CLL and the antigen-binding site. In particular, on the light chain of the cell-receptor, CLL patients exhibits special features on both D and JH structures. This, therefore, leads to the specialty in the antigen-binding sites of CLL patients. Unlike the ordinary person, the rearrangement and recombination have resulted in the oddity of the B-cell receptor. Statistically, virtually 10 percent of CLL patients' symptoms are triggered by the particular antigen-binding sites.

Another factor that contributes the CLL proliferation involves environmental antigens or autoantigens. Specifically, a possible explanation may be viruses or commensal bacteria that activates

b-cell receptors and their respective pathway. The activated b-cell will hence proliferate, cloning more impaired b-cells without apoptosis. In one particular model done in vitro, when an unfavorable prognostic marker is added, the binding affinity between antigens and b-cell receptor increases, expressing positivity of ZAP 70 and CD38+. B-cell receptors with IgD signaling, specific cytokines, and chemocytokines determine whether the activated B-cell will undergo apoptosis or survival and proliferation. When an excellent prognostic marker is added, the binding affinity between b-cell receptor and antigens decreases, making antigens more challenging to bind on the receptors. The B-cell will have a mutated V-gene expressing ZAP 70 and CD38 negative. These characteristic changes the shape of B-cell, hence making them less able to bind to antigens and have less possibility in apoptosis and proliferation [6].

In chronic lymphocytic leukemia, CLL cells keep on surviving and proliferating without apoptosis due to the reasons above. Hence, many blood stem cells are generated and cause abnormalities in lymphocytes or leukemia cells. As leukemia cells are unregulated in blood and bone marrow, there will be less capacity for white blood cells in healthy conditions, red blood cells, and platelets. Therefore, the resultant effect will cause less oxygen-carrying capability, less blood clotting ability, and fewer immune cells that could fight off harmful infections.

3.2 Clinical trials of Zanubrutinib for CLL

Among 90 patients with the CLL phase III trial, Zanubrutinib has illustrated significant effects. Zanubrutinib has illustrated an objective response rate of 92.2%, and the median time for the first response is averaged 2.79 months [6]. In clinical trials comparing the first generation of Bruton-kinase inhibitor with Zanubrutinib, the effect of Zanubrutinib has been proven to be effective.

In a clinical trial NCT03336333 where Zanubrutinib is compared against ibrutinib. At the 18th month of study, the total remission rate of Zanubrutinib reached 94.5%, and the progression-free survival event rate reached 90.6% [5]. However, there are still some adverse effects in the research that may hinder the development of Zanubrutinib. Most of the adverse events were classified as first or second graded. Some commonly identified events included but were not limited to contusion, diarrhea, upper respiratory tract infection, and so forth. Grade 3 and above A.E.s still occurred in 54.7% of patients [5]. Common phenomenon included anemia, myalgia, cellulitis, pleural effusion, and pneumonia. These statistics proved the effectiveness of the treatment. In particular, Zanubrutinib effectively remits and restricts the size of the tumor. Nonetheless, to enhance the drug's overall quality, the drug's side effects still require further research.

4. Waldenstrom Macroglobulinemia

4.1 Overview of Waldenstrom Macroglobulinemia

WM is a B-cell neoplasm. It includes the secretion of monoclonal IgM in the plasma cell. The secretion of IgM will lead to increase plasma viscosity in the blood. The increasing plasma viscosity will result in sluggish blood flow and hyperviscosity of the syndrome. The symptoms of WM include weakness, fatigue, and weight loss. Other symptoms involve coma and headache.

There are various somatic gene abnormalities and mutations identified in WM patients. The most common mutations occur at MYD88 and CXCR4. MYD88 is an adaptor protein for toll-like receptors. Once the ligand binds the receptor, a series of biochemical reactions are activated, leading to the activation of BTK kinase and adaptor protein TIRAP. This will be followed by the activation of MYD88, which will trigger the following pathway. However, another pathway will be induced when a point mutation in MYD88 occurs.

Specifically, when leucine is substituted to proline at position 265, there will be a gain of function when the cell avoids apoptosis. After testing, patients with WM. have illustrated having a mutation in MYD88, indicating the detection of proline in MYD88 as a possible way to diagnose the patients with WM.

CXCR4 is a G-coupled protein that plays a critical role in releasing cytokines and chemotaxis. The mutation of CXCR4 will result in the perpetual activation of CXCR4 by SDF-1a. Once mutated

CXCR4 is knocked down, the symptoms of WM are unseen, suggesting the significant correlation between CXCR4 and WM. The mutation of CXCR4 is identified at positions S344, S339, T311, and S338, respectively. In 27% of patients, this mutation is identified, indicating a strong correlation between the mutation of CXCR4 and this disease [8]. Another chemokine receptor, VLA-4, that interacts with CXCR4 plays a crucial role in preventing apoptosis of b-cell. Once VLA-4 is expressed, CXCR4 and VLA-4 will jointly activate AKT and MAPK pathway [8].

4.2 Clinical trials of Zanubrutinib for Waldenstrom Macroglobulinemia

Currently, there is no golden standard for WM to produce the best effect. Traditionally, available treatments include (Rituximab/Cyclophosphamide/dexamethasone), BR (Bendamustine/Rituximab), and VR (Bortezomib-rituximab ± dexamethasone). The primary response rate of these combination therapies is 60% to 80%, and the median progression-free survival time is between 3 to 6 years [8]. Approximately 10% (from 3% to 20%) of patients achieved complete response [8]. Although traditional methods already yield excellent results, relapse and refractory are inevitable. Other therapies like immunotherapy and chemotherapies may reduce relapse and refractory time, but the primary response rate has decreased to 40% to 50%, and the progression-free survival time is about 8 to 18 months [8].

The novel therapeutic approach that intended to enhance the drug's effectiveness was the first generation of BTK inhibitor: Ibrutinib. From the research conducted by Tam et al., the objective response rate is 93%, the primary response rate is 78%, and the complete response rate is 19% [8]. The estimated progression-free survival rate is 84% at 18 months. The therapeutic effect of the drug yielded good results. It also demonstrated effectiveness in relapsed and refractory circumstances, demonstrating an objective response rate of 90% and 73% [8]. On top of Ibrutinib, Zanubrutinib – the second generation of BTK inhibitor – was developed. It illustrated a higher objective response rate of 94% and a complete response rate of 28% [8]. Moreover, Zanubrutinib has also shown greater specificity by demonstrating less off-target effects. This significantly increases the potency of the drug [9].

The effectiveness of Zanubrutinib was cross-confirmed with other studies. In a phase III study whose code is NCT03053400 (an open-label, multicentre), Zanubrutinib has been proven helpful in patients with W.M Among 26 patients [9]. The objective response rate is 76.9%, the partial response rate is 53.8%, and the partial response rate is 15.4% [9]. The median time to the first significant response was 2.9 months in another phase III study comparing the effectiveness of ibrutinib and Zanubrutinib by the parameters like excellent partial responses, significant response rates, progression-free survival rate. For excellent partial responses, 28% of patients achieved this criterion under the treatment of Zanubrutinib, while 19% of ibrutinib patients achieved this criterion. For a significant response rate, Zanubrutinib achieved 77%, and Ibrutinib achieved 78% [9]. 84% of Ibrutinib patients and 85% of Zanubrutinib patients achieved a progression-free time of 18 months. This confirmed that Zanubrunib has a better effect in treating WM than traditional ways and the first generation of BTK inhibitor.

5. Mantle cell lymphoma

5.1 Overview of Mantle cell lymphoma

MCL is essentially a tumor inside the immune system. It is classified as non-Hodgkin (nodal and extranodal), B-cell, and aggressive lymphoma. The patient of MCL is usually younger and is treated to cure its root4. The median survival rate is usually about 1-2 years. MCL account for approximately 6% of the total lymphoma diagnosed [8].

MCL starts from the change in the location of chromosomes 11 and 14. The change in location of these two chromosomes has led to the up-regulation of the BCL-1 protein and the overexpression of cyclin D1, which leads to enhanced cell multiplication and cell cycle progression. In addition, chromosomal rearrangements and mutations in the untranslated regions will lead to shorter transcripts. This will result in a less AU-rich region and a less binding site for R.N.A.s, providing a more extended

transcription period, increasing the cyclin D1 protein level. This also proves to increase the aggressiveness of the tumor.

Apart from genetic alteration that results in the growth of tumors, the dysregulation of the signaling pathway is another important cause. For instance, BCR, BAFF-R, mTOR, WNT, and so forth are crucial pathways preventing apoptosis from transpiring. The evasion of apoptosis leads to the inevitable proliferation of b-cell by signaling different pathways.

5.2 Clinical trials of Zanubruitinib for Mantle cell lymphoma

Traditional treatment/protocol of MCL involves R-HCVAD/Mtx-ara-C108-110, R-maxi-CHOP, R-CHOP + auto-SCT R-CHOP, R-DHAP (four cycles) + auto-SCT, and so forth. In recent research, R-HCVAD had 97 patients participate. Results show that the objective response rate is 97%, and the median OSOS is around 10.7 years in the first treatment. For R-maxi-CHOP, the objective response rate is around 96%, and the median overall survival rate is 12.7 years [8]. For the combination therapy R-CHOP + auto-SCT R-CHOP, the objective response rate is 97%, and the overall median survival rate is around 9.7 years. R-DHAP (four cycles) + auto-SCT has an overall response rate of 89% and a median OSOS of 4 years [8].

Subsequently, new treatments such as Ibrutinib – the first generation of BTK inhibitor – has also been introduced in 2019. The combination of ibrutinib with rituximab was investigated in a phase 3 study involving 31 patients. Their overall response rate was 71%, the progression-free survival rate was around 86%, and the overall survival rate was 97% [10]. Zanubrutinib – as the second generation of BTK inhibitor – still contains limited data. Some research has shown that Zanubrutinib has a 90% Objective response rate and 20% complete response rate in the phase I trial in treating MCL [10]. This was cross confirmed by another study conducted in China, where the objective response rate is 81% with a PET-negative complete response rate of 58% [6].

In another study and therapeutic trials whose code is (NCT03206970), the monotherapy where the patient receives more than one phase II treatment, the result was profound. Among 86 patients, the overall response rate was 86%, the complete response rate was 59%, and the partial response rate was 24% [6]. The median response rate was around 17.1 months. The above results indicate that compared with traditional treatment methods, BTK inhibitors are more effective [11]. However, this is a new treatment method, and clinical data and prognostic follow-up data are still insufficient, and further research is still needed in the future [12].

6. Conclusions

Zanubrutinib - as a second-generation drug of Bruton tyrosine kinase inhibitor - has enormous clinical significance. For instance, in chronic lymphocytic leukemia, the objective response rate of 92.2% and the median time for the first response is averaged 2.79 months – significantly prolonged compared to the first generation of BTK inhibitor. Mechanistically, Zanubrutinib inhibits Bruton tyrosine kinase and inhibits the following signaling pathway, leading to the halt of the signaling functions and the proliferation of B-cells. Statistically, it demonstrated a high objective response rate, complete response rate, and long median overall survival rate in chronic lymphocytic leukemia, WM, and MCL, demonstrating the drug's effectiveness. Compared to traditional treatments, Zanubrutinib also demonstrated a better curing rate in multiple facets in treating the diseases above. However, due to the adverse events, such as anemia, diarrhea, fatigue, headache, rash, bleeding, and so forth, identified in the diseases, more research will be required in the foreseeable future.

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