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Research Progress on Zanubrutinib and Chlorambucil for CLL Therapy

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Abstract: Chronic lymphocytic leukemia (CLL) is a bad type of disease that keeps getting worse in adults all around the world. Some things make people get CLL, like genes, immune system problems, bad stuff in the environment, and radiation. Many doctors find it hard to treat CLL because it grows slowly, and normal cancer medicine does not work well on it. Two medicine types, called Chlorambucil and Zanubrutinib, can help treat this disease. Chlorambucil works by making DNA mess up. It sticks purine and pyrimidine parts together, so DNA breaks and cancer cells cannot copy themselves. Also, this medicine makes something called p53 work differently, which makes cancer cells die or stop growing. When doctors give Zanubrutinib to patients, it stops something called BTK from working right. BTK is very important for B-cells. This medicine sticks to a special part of BTK called cysteine 481. After that, B-cells cannot grow anymore, and cancer stops getting bigger. Zanubrutinib works better than Chlorambucil because it sticks to BTK in a special way. These two medicines work in different ways to fight CLL. The first one messes up DNA, and the second one makes B-cells stop working right by stopping BTK. Both medicines can help sick people, but maybe Zanubrutinib is better because cancer cells cannot learn to fight against it so easily.

Keywords: CLL Therapeutics, BTK, Chlorambucil, Zanubrutinib

1. Introduction

Chronic lymphocytic leukemia (CLL) belongs to the chronic myeloid leukemia family, which mostly occurs in middle-aged and old people. The main feature of this sickness is that mature B lymphocytes grow into clonal tumors. When someone gets CLL, they often show signs like too many lymphocytes in the blood, a bigger liver and spleen, and swollen lymph nodes. Sometimes, organs not related to the lymph system can also be affected. The bone marrow might stop working well at different times during the disease. CLL looks very much like small lymphocytic lymphoma (SLL) when doctors check their pathology and immune cell types, but they appear in different places - CLL mainly shows up in blood, while SLL starts in lymph nodes.

CLL is the most common type of leukemia in the West, accounting for 25-35% of all leukemias. The incidence rate of middle-aged people in Europe and the United States is 4-5 per 100,000, and the ratio of men to women is 1.2-1.7:1, while Asian populations experience significantly lower CLL/SLL rates, approximately one-tenth of those in Europe and the United States, as indicated by population registries in Japan, South Korea, and Taiwan. The median age of CLL/SLL onset is high, ranging from 70-75 years in Europe and the United States and 65 years in China.

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Chronic lymphocytic leukemia usually has no symptoms in its early stages and is usually diagnosed by chance during routine blood tests. Some patients may present with painless lymphadenopathy, mainly in the neck, which may resolve sporadically but rarely completely. In later stages, symptoms such as fatigue, night sweats, anorexia, mild fever, and weight loss may occur. In addition, patients with CLL may exhibit acquired immune deficiency that leads to the development of recurrent infections or immune-related disorders such as autoimmune hemolytic anemia, immune thrombocytopenia, or pure erythrocyte hypoplasia. Insect bite dermatitis is also a more common one.

1.1. Physical signs

1). Lymph node enlargement: there can be superficial lymph node enlargement, which is more common in the neck and armpit, abdominal lymph node enlargement, and mediastinal lymph node enlargement. It can fuse and become a large mass.

2). Splenomegaly: it often exists at the same time as lymphadenopathy. A few patients with megalosplenia may have left upper abdominal pain due to splenic infarction.

3) Hepatomegaly: it can be present.

4) Waldeyer's ring swelling: oropharyngeal ring constriction can be seen, which can be caused by tonsil enlargement or lymphocyte infiltration in the submucosa. It can cause sleep apnea and dysphagia.

5) Skin lesions: leukemic skin infiltration may be present, which requires pathological diagnosis. Paraneoplastic syndromes such as pemphigus and angioedema can be present.

6) Other organ involvement: a small proportion of patients had nephrotic syndrome. In the terminal stage, Richter's transformation can occur, that is, transformation into large cell lymphoma. Secondary tumors such as acute myeloid leukemia, myelodysplastic syndrome, skin cancer, lung cancer, gastrointestinal cancer and melanoma can occur.

1.2. Diagnostic criteria

The absolute value of monoclonal B lymphocytes in peripheral blood was ≥5×109/L for at least 3 months. The diagnosis can also be made if the absolute count of monoclonal B lymphocytes is less than 5×109/L and there is cytopenia caused by lymphocyte infiltration into the bone marrow.

2. The morphology of peripheral blood leukemia cells was normal, with mature small lymphocytes, and the immature lymphocytes were less than 55%.

3. Typical immunophenotypic lymphocytes were derived from B lineage, CD20+, CD5+, CD19+, CD23+. sIg, CD20, CD22 and CD79b were weakly expressed. The expression of Kappa or Lamda light chain (κ:λ>3:1 or <0.3:1) was restricted in leukemic cells, or sIg was negative in >25% of B cells.

At present, the cause of chronic lymphocytic leukemia is still a mystery and may be related to immunological, radiological, chemical, and genetic factors. Advances in treatment have increased the median survival of CLL patients by 5-7 years. In China, the incidence of CLL is increasing every year, and hematopoietic stem cell transplantation is often advocated as a treatment. However, there are still challenges in matching donors and managing post-transplant rejection, which can lead to complications and can affect treatment outcomes.

2. Chlorambucil

Advances in modern medicine have led to the emergence of new therapeutic agents for chronic lymphocytic leukemia, including Bruton tyrosine kinase (BTKi) inhibitors and the anti-apoptotic protein Bcl-2 inhibitor venetoclax (Ven). These developments have led to a change in CLL treatment paradigms, from chemoimmunotherapy (CIT) based on regimens such as FCR (fludarabine +

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cyclophosphamide + rituximab) and BR (bendamustine + rituximab) to continuous treatment with small-molecule targeted drugs. However, challenges such as limited depth of remission (especially BTKi monotherapy), economic burden, patient compliance, and drug-resistance-associated target gene mutations limit the effectiveness of monotherapy in the new drug era. Therefore, a limited course of treatment has become the focus of future CLL treatment strategy exploration. Chlorambucil is a member of the anti-metabolite class in alkylating agents, which comes from aromatic nitrogen mustard. This cytotoxic drug has dual functional alkylation activity, and as a cell cycle non-specific drug, it has the greatest effect on the M and G1 phases. Its main action mode involves the formation of highly reactive ethylene imine groups, which can cross-link the two helical strands of DNA. This disrupts the internal helix structure of DNA, preventing replication and ultimately preventing cancer cells from growing and proliferating, achieving the desired therapeutic effect.

Guidelines rarely recommend the clinical use of chlorambucil. Conversely, for CLL patients who did not have the del(17p)/TP53 mutation and were in poor health, they preferred ibrutinib, Zanurutinib, and Clampicillin combined with rituximab/Binutuzumab. For relapsing/refractory patients with similar conditions, irutinib, Zarutinib, and orutinib are preferred.

BTK is a non-receptor tyrosine kinase that is expressed in B cells, mast cells, and megakaryocytes but not in T cells. The protein structure of BTK consists of 659 amino acids divided into five distinct signaling domains. These domains allow BTK to conduct and enhance signals delivered by surface molecules, making it an important part of the BCR signaling pathway. Antigen interaction with BCR activates BTK and initiates a downstream signaling cascade, which is essential for B cell survival, proliferation, and differentiation. BTK inhibitors, especially covalent inhibitors, are small molecules that covalently bind to BTK, blocking its activity. This binding targets the conserved non-catalytic residue C481 and prevents the autophosphorylation of Y233. This process disrupts the recognition of its phosphorylation state by the Src Homology 2 (SH2) domain, preventing BTK from being able to locate the phosphorylation sites of other proteins.

BCR signaling, an important process against tumors, gets stopped in this way. The use of small molecule targeted drugs like BTK inhibitors (BTKi) has made the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) totally different from before. BTKi gives patients a way to avoid chemotherapy. Young patients with good exercise ability and immunoglobulin heavy chain variable region (IGHV) mutations can benefit from the FCR treatment plan, but this method does not work well for a long time if patients have bad factors like abnormal TP53 and unmutated IGHV. BTKi shows good results for both relapsed/refractory CLL and untreated CLL cases and can solve some of these problems. Because of this, BTKi makes CLL/SLL treatment much better than before, because it attacks cancer more directly and causes less damage to patients.

Chemical immunotherapy used to be the main way to treat chronic lymphocytic leukemia (CLL). But now, irutinib, which is a first-generation BTK inhibitor, brings fresh hope and better options for patients with CLL, particularly those who face high risks. Many research works like ALLIANCE, iLLUMINATE, resonance, and E1912 have shown that irutinib works great by itself or with other medicines to fight CLL. Looking at data from these research works, patients who took irutinib lived longer without their disease getting worse (PFS) and had better overall survival rates (OS). Still, irutinib is not perfect and can cause some troubles for patients. People who take it might have problems like bleeding, atrial fibrillation, getting sick more often, and stomach issues, including diarrhea. When talking about how irutinib works, it stops BTK enzyme from working properly. BTK enzyme is really needed for B cells to work right and for B cell receptor signals to happen normally. Even though irutinib does a good job at treating CLL by targeting specific things in the body, it can also mess with other kinases it's not supposed to affect, which is why patients sometimes get side effects they don't want.

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Bad side effects are making many patients stop irutinib treatment - nearly 50% of cases mention this reason for quitting. The treatment only shows good results when patients keep taking it without stopping. When patients take breaks or quit, the medicine becomes less useful in fighting disease. Patients should carefully check what kind of problems this drug might cause them and talk to their doctors about dealing with these problems. They need to follow doctor's orders about taking medicine even if it's hard. Though side effects can be really bad sometimes, irutinib still helps a lot in treating chronic lymphocytic leukemia. This medicine gives better chances to patients, especially those who have high-risk condition.

3. Zanubrutinib

Zanubrutinib, a BTK inhibitor made by Chinese company Beigene, reached a big milestone by getting approval in the USA, making it the first cancer drug from China to do so. The research team at Beigene worked very hard to test zanubrutinib in two Phase 2 clinical trials in China. These trials checked how well it worked for patients who had relapsed/refractory mantle cell lymphoma (MCL) and chronic lymphocytic lymphoma (CLL). The drug research also got enough patients signing up for another Phase 2 clinical trial that looks at treating Waldenstrom macroglobulinemia (WM). Right now, Beigene is busy running many phase III clinical trials in different places around the world. These trials are checking if zanubrutinib works well by itself or when mixed with other drugs to treat different types of B-cell lymphomas.

Zanubrutinib works as a second-generation BTK inhibitor by focusing on Bruton's tyrosine kinase in the B-cell receptor signaling pathway. In some quite strange ways, this pathway connects with different kinds of B-cell bad diseases. When zanubrutinib finds cysteine residue 481 (C481) at the active site of BTK, it sticks to it and stops those molecules below from being activated. Such effect helps stop bad B cells from growing too much and spreading around the body. Because zanubrutinib blocks cell growth like antimetabolic drugs do, it shows good effect on B cell growth and change process. This characteristic makes doctors think it can maybe help treat chronic lymphocytic leukemia.

Zanubrutinib can stop cancer cells from growing by blocking cell growth and making B-cells die, which makes it good for treating cancer. The drug also affects the immune system, making it work better to fight tumors. Research shows that this targeted drug works really well for people with chronic lymphocytic leukemia (CLL) and lymphoma. In CLL, about 85% of patients have changes in their B-cell receptor signaling pathway, and BTK problems are linked to getting CLL. Because zanubrutinib blocks BTK, it helps stop CLL from getting worse. This drug works in many different ways to fight B-cell cancers. Since it attacks the main things that cause CLL and similar diseases, zanubrutinib could become a very important medicine for treating these kinds of cancer, which might help many sick patients get better.

Zanubrutinib can be used to treat non-Hodgkin lymphoma (NHL), with good results seen in B-cell lymphoma patients. This type of NHL happens most often. The problem in B-cell lymphoma starts when some changes happen in B-cell receptor signaling pathway - these changes make the cancer cells grow and spread without control. When patients take zanubrutinib, it stops BTK from working, which makes those bad B cells stop growing so fast in NHL. Because zanubrutinib was made to attack only NHL cells, many doctors think it will work better than some older cancer drugs.

During zanubrutinib use, some problems like digestive troubles, liver issues and high blood pressure may happen. Patients might face heart rhythm changes and feel tired. Because zanubrutinib makes the immune system weak, they can get sick more easily. Doctors need to check blood test results often to find infections early. When sick feelings or weird symptoms show up, patients should talk to doctors right away and not wait too long.

Zanubrutinib works by stopping B cell growth through BTK blocking in B cell receptor pathway. The drug shows good results when treating chronic lymphocytic leukemia (CLL) and lymphoma.

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However, patients should pay attention to side effects and take action fast if any problems happen. The changes in the immune system also need checking. Patients need to talk with doctors about how to use medicine in the right way based on their situation. The medicine gives new chances to CLL and lymphoma patients, but they must follow the doctor's guidance and watch their body condition all the time.

Recent research has made good progress in the area of Bruton's tyrosine kinase inhibitors (BTKi), which looks like a good choice to treat B-cell leukemia and lymphoma. Some new BTKi drugs have finished Phase I clinical trials and shown they are safe to use - these include tirabrutinib, GDC-0853, vecabrutinib, and CC-292. The medical community got some nice news at the 61st Annual Meeting of ASH, where they shared middle-stage results from a worldwide Phase I-II study about LOXO-305. This drug helped patients get better even when other treatments did not work before. China's indigenous BTKi Obrutinib also showed encouraging results in a preliminary Phase II study presented at the ASH annual meeting. At a median follow-up of 6.3 months, the treatment of patients with relapsed and refractory CLL showed an impressive 88.5 percent objective response rate, as well as improved safety compared to first-generation BTKi drugs. The efficacy of single-agent BTKi therapy is well established, especially in patients with high risk or intolerance to CLL. Research into BTKi combination therapy is gaining momentum, with studies such as HELIOS showing promising results.

Patients taking irutinib combination regimen showed better progression-free survival when their minimal residual disease (MRD) was negative, compared to those with MRD above 0.01%. According to iLLUMINATE study results, the risk of disease progression or death dropped by 77% in patients using combined ibrutinib treatment, with 35% of patients reaching MRD-negative status. Such data shows how combined targeted therapy can work better for CLL treatment, particularly in MRD-positive cases. Several good treatment options exist now - doctors can mix stable kinase inhibitors with chemical immunotherapy, use MRD levels to guide treatment or stop treatment after patients become MRD-negative. New BTKi drugs being made now will make combination treatments work even better, giving more choices to patients whose CLL comes back or does not respond to other treatments.

4. Conclusion

Recent studies show that zanubrutinib, a new type of BTK inhibitor, works well and is safe for CLL patients who do not get better with other treatments. Using this drug can have fewer side effects than old treatments. Some doctors start to combine zanubrutinib with other drugs, which seems to help patients get better and maybe stop treatment after uMRD. But doctors still need to check if this works for a long time and if it stays safe. One big problem is that CLL can still get worse even when using BTK inhibitors. This means doctors need to find ways to make drugs work better. The next steps in the research will look at new types of BTK inhibitors that work differently from current ones and also other drugs that can block the BCR signaling pathways. These new drugs might help when current treatments stop working. All these new treatments could make big changes in how doctors treat CLL and help patients live better.

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