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Review Article

Research Advance in Pathogenesis and Treatments of Chronic Lymphocytic Leukemia (CLL) of Adults

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Abstract

Chronic Lymphocytic Leukemia (CLL) is a type of leukemia with a chronic life-threatening condition not only causes thousands of deaths but also has a huge economic burden to families and the society every year. There is still no effective cure up to date, and the 5-year survival rate is 84.7%. With recent years' research advances, a load of discoveries and derivatives for CLL have been investigated, including genes attributed to CLL. With the new findings and various treatments are also invented. Meanwhile, studies are still underway to search for new mechanisms and develop novel effective treatments for CLL. In the current review, recent advances in the pathogenesis of CLL and new treatments for CLL have been summarized, which will be helpful for future investigation and treatment development for CLL.

Keywords: Mutation, Heredity, Environmental factors, BMT, Immunotherapy, Chimeric antigen receptor, Radiotherapy, Chemotherapy

Abbreviations

APOBEC: Apolipoprotein B mRNA Editing Enzyme, Catalytic Polypeptide; *BIRC3*: Baculoviral IAP Repeat Containing 3; BRAF: Serine/threonine-protein kinase B-Raf; CARM: Chimeric Antigen Receptor Macrophage Therapy; CARNK: Chimeric Antigen Receptor Natural Killer therapy; CART: Chimeric Antigen Receptor T-cell therapy; CD20: B-lymphocyte antigen CD20; CD22: Cluster of Differentiation-22; CD52: Cluster of Differentiation 52; *CHD2*: Chromodomain-Helicase-DNA-Binding Protein 2; CLL: Chronic Lymphocytic Leukemia; EBRT: External Beam Radiation Therapy; *FBXW7*: F-box and WD Repeat Domain Containing 7; FCR: Fludarabine, Cyclophosphamide and Rituximab; IRF4: Interferon Regulatory Factor 4; L265P: Leucine at Position 265 to Proline in MYD88; MYD88: Myeloid Differentiation Primary Response 88; Mir-16-1: MicroRNA 16-1; *NOTCH1*: Neurogenic Locus Notch Homolog Protein 1; *SF3B1*; Splicing Factor 3b Subunit 1; TBI: Total Body Irradiation; *TP53*: Tumor protein P53; *13q14*: Monosomy 13q14

Introduction

Chronic Lymphocytic Leukemia (CLL), is one of the most common types of Leukemia in adults. Many patients suffer for more than five or even ten years and pass painfully. Researchers have searched for possible treatments for CLL for many years, but the best way to treat CLL is to do a bone marrow transplant. Even if BMT is currently the best way, it is still challenging to find a proper donor, and the ten-year relative survival rate of CLL can't reach 66.66% (2 out of 3) [1]. Although there are different other types of treatments available, for example, targeting treatments, etc. These are still not widely available for all patients and effective for all CLL. The main reason for this is that efficient treatment methods are not still available yet [2].

Researchers recently have figured out most of CLL's possible causes and pathogenesis, e.g. radiation, chemotherapy, genetics, a blood disorder, exposure to chemical compounds, etc. But there does have some other risk factors that haven't been discovered yet. The research progress of the pathogenesis of CLL and the advance of treatment development were summarized in the current review. In light of providing info for further investigation and developing new treatment plans.

Pathogenesis of CLL Developments

Heredity and family gene mutations roles in the development of CLL, is its correlation or causation?

Genetics is one of the risk factors for CLL, around 10% of patients get CLL by heredity [3]. The following paragraphs will be talking about CLL causation that correlated with familial inheritance and genetics (Figure 1).

The abnormal expression of genes associated with CLL is likely to cause a disorder, and IRF4's SNP is usually associated with the low expression of interferon regulatory factor 4, and overactive Notch signaling, mice that lack this type of protein are likely to develop CLL [4].

New Zealand black mice have an allele at the *mir-16*-1 locus, the homologous gene to human's *13q14 gene*. The low expression of the *mir-16-2*, the allele is associated with the hereditary tendency of mice to get a similar B lymphocytic cell proliferative disease [4].

On the other side, research shows in a large-scale survey that APOBEC (cytidine deaminase family made up of eleven genes)'s mutation can cause somatic mutations, which might cause cancers including CLL [5,6]. To investigate this familial genetic mutation further, researchers found several CLL patients (N=65) and figured out that 1, 2, 3A, 3B, 3D, 4, and AID are in a state of hypo expression. APOBEC3F and 3G expressed hyper-expression. To find out if the APOBEC will indeed affect human beings and thus cause CLL,

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researchers transferred CLL cells to mice NSG. After the 4-14 weeks' transfer, the IGHV region was amplified, sequenced, and analyzed. The outcome isn't surprising that these data are unanimous to the hypothesis that the APOBEC gene family may promote the mutations out of the IG gene loci, and feasibly cause the aggressive CLL evolution [5].

Furthermore, CLL shows a prominent geographical diversity, this portion is almost 40 times different [7]. Caucasians have 4.14, they are the highest, followed by Afro-Caribbean, 3.03, Hispanics 1.94, Native Americans 1.44, and last, Asian 0.84. As time passed, the morbidity of CLL in the United States was relatively stable. Asian stay in the states' morbidity of CLL is similar to Asian stationed, which means that the environmental factor of CLL is not as significant as the hereditary factor [7].

Mutation

Researchers are initially trying to determine the relationship between Leukemia and gene conversion, thus Leukemic individuals can get better treatment. Due to morality and humanity, scientists were forbidden to use the Leukemic patient's model and tried to find a new way to do this experiment. In recent years, researchers have successfully found a way to imitate Leukemia's occurrence and found the gene that can cause Leukemia. This section provides 5 mutations that might cause CLL (Figure 1).

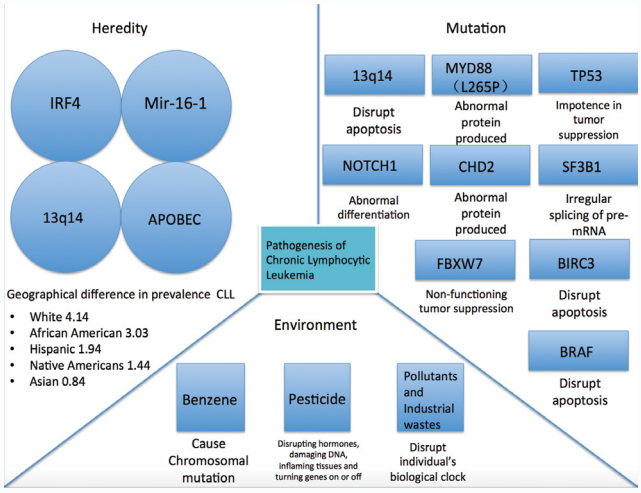

Figure 1: Illustration for Causes of CLL. The main classification of factors that induces CLL, includes heritable factors, autosomal mutations, and environmental factors.

A group of researchers has used the mouse model (the best-known model to study malignant B-cell) to imitate the human body organization and condition [8]. Investigations are based on the mice that generate MDR, this creates the first genetically "authentic" example of a model for investigators to study CLL, and they were not disappointed that it concluded the most common gene mutation for CLL, which is del (13q). "Deletion of *13q14* [del(13q)]. is the most common cytogenetic change (50%) in CLL, and it is a good prognostic factor if it is detected as a sole aberration by FISH" [8]. This further proves how this experiment helps us, whether to figure out how 13q deletion causes Leukemia or how hard it will be to treat Leukemia caused by 13q deletion.

Research a decade ago shows that *MYD88* mutation has a colossal effect on CLL development [9], *MYD88 L265P* mutation occurs in 30% of cases of diffuse large B cell lymphomas and 90% of Waldenstrom's macroglobulinemia, and it has been proved to be the activated mutation [10]. Researchers even found out that this could be the vital factor of M-CLL, which means that the *MYD88* mutation can cause M-CLL to large extent. It is worth mentioning that this is also the top ten factor of ALL, so its influenced area might be even bigger than we previously thought [10].

Abnormalities in *TP53* are associated with some other diseases and transformation of chromosomes, 17 out of 115 CLL patients detected deletion and *TP53* correlated protein [11]. Data shows that 5% of the CLL patients yet untreated with a treatment indication demonstrate *TP53* mutation without 17p deletion, these patients' survival rate is declining and their treatment so far has had no progression [12].

Analysis of Chronic Lymphocytic Leukemic Individuals' genome provides that the *NOTCH1* gene recurrently mutates when CLL is presented, in research, data shows that the *NOTCH1* gene mutation causes the rate of death to increase by 3.77 times, total survival period is also shortened [13]. The *NOTCH1* gene mutation is the most common gene in CLL, and these mutations often bring disastrous outcomes and difficulties in curing the disease, mutated CLL shows *NOTCH1*'s characteristic of triggered specific reaction form [14].

CHD2 is the most common mutant gene in CLL and MBL [15]. In recent years, researchers have figured out how genome transformation occurs in forming CLL, however, the molecule that manages chromatin remodeling is still opaque. Researchers have been doing experiments to examine how mutated *CHD2* takes place in the CLL formation, and the conclusion is evident, *CHD2* operate as a cancer-restrain gene in the human body [16], so once it is damaged, a particular disease can't be resisted, including CLL, ergo CLL cells are formed [15].

SF3B1 has been pointed out to be the most frequently altered gene and takes approximately 10% to 14% of CLL patients [17]. Researchers are trying to figure out how *SF3B1* is related to the pathogenesis of CLL, and they find two possible reasons for the occurrence of CLL, which are genetic solidity and epigenetic alternation. Their research outcomes are exceedingly conclusive, they conclude the analysis of CLL cell genes and their percentage of clonal frequency, and they include 149 samples in this experiment, the consequence shows that 53% (10 out of 19) patients have Subclonal CLL [18], and the others are clonal, which notifies us of two things, one. *SF3B1* gene mutation correlated with CLL, most of which is the subclonal evolution-caused disease [18].

12.2% to 15.1% of CLL patients got *NOTCH1* mutation [19], nevertheless, in the condition that *NOTCH1* alternation didn't occur, *NOTCH1* is still activated, 2% to 6% of CLL patients are found that negative regulator amended [20]. Researchers found that 36 out of 905 patients exist heterozygous *FBXW7* revised, and 78% of them are missense mutations [20]. The homozygous abridgment of *FBXW7* generates the escalation of CLL activity, thus promoting the transpiration of CLL [20]. It can be purported as the switch of *NOTCH1*, and *FBXW7* can trigger the *NOTCH1* without genetic alternation. The molecular regulator inside it is altered, which means the cell might perform some particular function errors, which leads to CLL.

BIRC3, from the clinical view, provides combativeness and it's less sensitive to chemotherapy, as evidence of it, *BIRC3* destruction

selectively materializes in 25% of the fludarabine-refractory CLL [21]. Fludarabine refractoriness of CLL can be generally analyzed as *TP53* abnormality, yet, around 60% of high-risk CLL didn't exhibit *TP53* mutation [21]. While *BIRC3* aberration just resolves 40% of it, if it contacts with *TP53* anomaly, it might even bolster the spectrum of biomarkers for previous recognition of chemotherapy-less-sensitivity cases [21].

BRAF mutation often causes melanoma and thyroid miscellaneous diseases [22], it usually blocks cancer cells from continuously dividing and after its mutation, there's a good chance of developing cancer and tumor [23]. The research was conducted to determine the role of *BRAF* mutation on CLL, researchers sequenced 138 CLL cases and 32 B-cell Prolymphocytic Leukemia (B-PLL) cases. Four out of 138 CLL patients are detected with an abnormality on *BRAF* exons 11 and 15 [23]. Analysis was done, and the result shows that *BRAF* mutation did not occur during the development of the disease. Further observation demonstrates that cells with *BRAF* mutation didn't induce apoptosis (cell programmed death) as the normal cell should [23].

Environments

CLL is a very convoluted disease; it's embodied not only in its symptoms but also in its pathogenic causes. Today, CLL is widely known as a gene issue; however, its causation is still sophisticated. The environment is one of the largest bases of CLL. This section will mainly be about how environmental factors shape the formation of CLL (Figure 1).

The most common factor that forms CLL is undoubtedly exposure to the compound benzene. An experiment from last century shows that benzene exposure can cause somatic cell chromosome abridgment [24]. The earliest benzene exposure cases can be traced back to the late nineteenth century, used for commercial use. Benzene exposure's effects can be varied due to its concentration of it, in most cases, which has a relatively low concentration of Benzene, did not affect workers, but in the relatively rare case, which had a high concentration of Benzene, the workers' erythrocytes, leucocytes, or thrombocytes (sometimes both leucocytes and thrombocytes) will be decreased [25]. According to research, the adjustment of leucocytes can cause leucocytes' abnormal proliferation, and increase the concentration of white blood cells, thenceforth, CLL cells are formed. It has been proved 200 years later that benzene had a colossal impact on the probability of getting CLL [25], especially for those working in a high-risking environment, e.g. Institute for Drug Control, a Chemical plant, or a laboratory. Furthermore, 238,000 people in the United States are occupationally contacting benzene [26], and calculation has indicated that these high-risking populations are five times more likely to have Leukemia than ordinary people.

Pesticide is one of the most common things in our life, it is used to kill insects, however, recent investigation shows that long-time exposure to pesticide is pernicious, and it presumably will cost malignant disease to happen. Research is done with 302 diagnosed cases and 1567 high-risking people (particular circumstances are excluded) [27], and the outcomes demonstrate that age, obesity, gender, hereditary abnormalities, race, and occupation may make pesticide exposure influential [27].

Researchers worked hard these years managed to solve these conundrums, meanwhile, some researchers found out that pollutants do have considerable repercussions on particular diseases [28], take CLL as an example, some industrial wastes will affect an organism's biorhythm, which is responsible for regulating procreation, production, and function, once these processes don't work fitly, that's when CLL starts to ensues. Contaminants mentioned above generally exist in mixtures with other matters, including tobacco mist, microplastics, benzene, and pesticides mentioned previously [28].

Treatment

CLL is recognized as a complicated disease, this can be embodied not only in its various types but also in its treatment method. As Figure 1 depicts, there are several customary ways to treat CLL, e.g. Chemotherapy, Bone Marrow Transplant, and Radiotherapy (Table 1). This part will mainly focus on these treatments and how can they cure CLL (Figure 2).

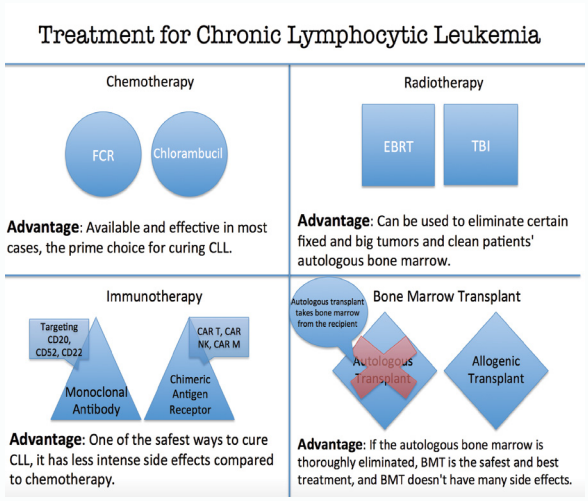

Figure 2: Illustration for therapy of CLL. The main classification of treatment that cures CLL, includes chemotherapy, radiotherapy, immunotherapy, and bone marrow transplant.

Chemotherapy

Chemotherapy uses a type of anti-cancer drug to disturb the development of cancer cells [29]. According to the research, the most significant advantage of chemotherapy is that it can be injected into the body and can be widely spread, it tends to kill the cancer cells that are spread imperceptibly in the body [29], and CLL is a clear example. Surgery and radiotherapy aren't the best option when the cancer cell is potentially transferred, in such condition doctors prefer chemotherapy (on the premise that the patient's health condition is stable) [30].

Chemo-drugs are cytotoxic, which means they can sometimes threaten the existence of the normal cells around the cancer cell. So, it does have a few side effects-for instance, hair loss, vomiting, and a bigger opportunity of getting infected. So, Chemotherapy is usually periodic, patients' doctors ought to give a 3-4 weeks rest period before the subsequent chemotherapy begins, to let the body recover [31].

In most cases, chemotherapy is the first-line (initial) treatment for CLL, the different drugs one takes depend on the phase, the development, and the patient's state of CLL. Initial treatment is usually an admixture of three drugs (fludarabine, cyclophosphamide, and rituximab), this is called FCR, regularly used by young patients due to their superior immunity. However, this treatment is only available in a certain stage and with certain gene mutations. Despite this treatment can work well in some cases, but this isn't suitable for everyone, in

Table 1: Conclusion and contrast of treatments.

	Definition	Advantages	Disadvantages	Types of therapy valid
Chemotherapy	A type of anti-cancer drug to disturb the development of cancer cells	Chemo drugs are relatively cheap, innumerable, and accessible, it's the most affordable way for normal patients.	Cytotoxicity of chemo-drugs made the drug attack all cells in an undifferentiated way, which lead to various side effects.	Fludarabine, Cyclophosphamide, Rituximab (FCR) & Chlorambucil
Radiotherapy	High-energy rays destroy malignant cells in the human body	Can be used to eliminate certain fixed and big tumors, and clean patients' autologous bone marrow.	Its limitation made it invalid in some cases, they can only affect a chosen region, and however, CLL is a blood disease.	External Beam Radiation Therapy (EBRT) & Total Body Irradiation (TBI)
Immunotherapy	Treatment plan mainly focuses on stimulating the human immune system to produce the substance needed to shrink or vanish the tumor to fight cancer.	It's expeditious and has slight side effects compared to other treatments.	Immunotherapy is expensive and time-consuming, and drugs are not ready-made in most cases.	Monoclonal antibodies & Chimeric Antigen Receptor (CAR) immunocyte therapy
BMT	Replace the leukemic bone marrow from the recipient with normal, CLL-free bone marrow.	BMT is the safest and best treatment, and it doesn't have many side effects.	BMT is also time-consuming, finding an unfamiliar valid donor is usually extremely hard, and there's a relapse chance using BMT.	Allogenic BMT

this case, consider using another workable treatment plan, such as chlorambucil.

This is the type of drug that has relatively fewer side effects; it is also portable, which makes the treatment convenient. For the one who is elder and can't deal with the severe side effects brought by the FCR or FCR treatment isn't useful in a particular case, and then trying chlorambucil is a better option. By the way, in recent years many more chemo-drugs are invented, for instance, bendamustin, pentostatin, and cladribine, this is something that patients are worth keeping tabs on [32].

Radiotherapy

Radiotherapy uses high-energy rays to destroy malignant cells in the human body, it can't be widely used as chemotherapy, when radiotherapy appears in a treatment schedule it is more likely to be an individualized program, for instance, radiotherapy can be used to shrink abnormal spleen (use to manage the quality of blood), lymph nodes and other body parts around that interact with the spleen as well. Radiotherapy is also useful when treating bone pain led by the erosion of affected lymphocytic cells [33].

The affected area and the intensity of radiation depend on the patient's type of disease, the patient's development, and most important symptoms and personal situation [34]. During the therapeutic process, other types of physiotherapy, e.g. chemotherapy might be needed to halt the remnant cancer cells. Also, the care team needs to maintain the normal count of the patient's blood, when homeostasis is imbalanced, necessary stimulations are needed, and so do the antibiotics [35].

The most effective therapy for CLL is External Beam Radiation Therapy (EBRT), EBRT is the example in the first paragraph, it serves the function of refraining from the development of infectious CLL tissue [35]. The main reason it is recommended to cure CLL is attributed to its effectiveness and speediness, so the fast development of CLL tumors can be expeditiously controlled. On the other hand, EBRT's side effects are relatively subtle, and most of them can be abated, treated, or spontaneously vanished [35].

Total Body Irradiation is a type of radiotherapy that aims at the entire body, it is utilized as a tool in the preparation phase of a bone marrow transplant because the high intensity of TBI can obviate the CLL cell [36]. Right before bone marrow transplant, tumor cells should be clear as much as possible, so the probability of relapse can be reduced. Also, TBI can restrain the immune system from eliminating the donated bone marrow, and infected bone marrow with Leukemia can be expunged, which makes space for donating healthy bone marrow [37].

Immunotherapy

Immunotherapy is a treatment plan that mainly focuses on stimulating the human immunosystem to produce the substance needed to shrink or vanish the tumor to fight cancer [38]. Because of the effectiveness of immunotherapy, it is one of the best ways to be used treat Chronic Lymphocytic Leukemia and other types of Leukemia as well. This section of the article will focus on different types of immunotherapy and their validity in different conditions.

Monoclonal antibodies: Monoclonal antibodies are the most effective and widely-spread immunotherapy that can be used to treat Chronic Lymphocytic Leukemia; it is a manmade version of an immune system antigen. Monoclonal antibodies are a way to induce the immunocytes to recognize CLL cells and respond normally and destruct the abnormal cell [39]. By the way, Monoclonal antibodies are one of the common treatment plans given by doctors, which again embodied their availability [40]. These monoclonal antibodies can be classified into various groups depending on what type of protein it creates.

Targeting CD20: Targeting CD20 is the first type of monoclonal antibody that will be discussed in this article; it is a protein that is detected on the surface of B lymphocytes [41]. Several drugs that can trigger the production of CD20 will be introduced; they are Rituximab, Obinutuzumab, and Ofatumumab [42]. Rituximab is the main treatment of CLL, it is often used with Chemotherapy and targeted drugs [43]. It will be used in the initiation of the whole treatment plan, also some second-line remedies [43]. Rituximab is noteworthy in that it can be used to treat patients with a bad health condition; it is usually referred to as the last hope for bad-situational individuals [44]. Obinutuzumab is a monoclonal antibody that can be either used with the chemotherapeutical drug chlorambucil or the targeted therapeutical drug ibrutinib [45]. Obinutuzumab is generally used in the first-line treatment of CLL, in some other conditions, it can be used when the patient relapsed or when other treatments don't

work well [46]. Ofatumumab is the last type of targeting CD20 that is informed, it is a drug that can be used itself, and it serves as a last resort that is used when other cures do not play a prominent role [47].

The side effect of targeting CD20 normally isn't as fierce, it's just like the other treatment, and the reaction to the drugs depends on the quantity of the drug that is provided and the patient's condition [48]. Subtle responses to the drugs involve itch, fever, headache, fatigue, etc. If the patients themselves have sensitive reactions toward the drug, including chest pain, hyper heart beating, coughing, etc., [48]. Also, these drugs can activate some liver problems, for instance, hepatitis B. Doctors can't provide the drugs if the patient shows awakening liver issues [49]. Infections after ceasing the drugs are common because the immunosystem gets activated by the drugs [50]. Rituximab is accused of causing an uncommon brain disease PML, which could cause headache, blindness, and even death. Other side effects might as well occur, it depends on the drug(s) provided [51].

Targeting CD52 and targeting CD22: CD52 is a protein found on the surface of CLL cells and most of the T lymphocytes, it is used when other treatments can't operate normally, or it can be used at the beginning of the treatment [52]. For instance, patients with irregular chromosome 17 under normal circumstances can be treated well by targeting CD52. However, standardized treatments regularly aren't efficacious enough to treat patients with abnormal chromosome 17, under this situation, patients would take rituximab (previously mentioned), and alemtuzumab (a type of targeting CD52 drug). By the way, Alemtuzumab seems like it doesn't work well in patients with swollen lymph nodes [53].

The side effect of targeting CD52 when injected include fever, chilling, vomiting, and rashes. When it comes to under skin injection, there are not many side effects [53]. Likewise, targeting CD52 cause a low account of white cells, which means old and new infections can be common while treating, so it is commonly used with antibiotics [54]. Also, there are some uncommon side effects, including the rupture of neck and head vessels and stroke [55].

CD22 is a protein found on the surface of B lymphocyte, and Lumoxiti is a derivative drug from CD22, it is a CD22 antibody with leukemic cell toxin, and it can directly lead the toxin to the leukemic cell and kills it [56]. CD22 is a special case because it is mainly used to treat hairy cell leukemia (a subtype of CLL that means there are too many lymphocytes in the patient's bone marrow and it typically progresses slowly) [57]. The side effect of CD22 is similar to the other treatments, comprising headache, vomiting, fatigue, swelling, constipation/diarrhea, a low account of red blood cells, and loss of electrolyte [58].

CAR immunocyte therapy:

CAR-T cell: Chimeric Antigen Receptor T cell (CAR-T cell) is a gene-modified T cell that is capable of recognizing and eliminating cancerous cells [59]. The cells are taken from the patient's blood at first, and then the gene that codes for chimeric antigen receptor protein is added to the target. After producing a considerable amount of modified T cells, it is mature enough to send back, and the chimeric antigen receptor of the T cell will bind to the cancer cell and releases a cytotoxic substance that can perish cancer cells [60]. CAR-T therapy is usually used to treat certain types of blood cancer, noteworthy, researchers are managing to use CAR-T in other types of cancer as well [61]. This section will mainly focus on the various types of CAR-T therapy and its effectiveness on CLL.

Axicabtagene ciloleucel is the first type of CAR-T therapy that will be discussed today, it is used when the first-line chemotherapy & immunotherapy is impotence or the patient relapses within 12 months. Its mechanism has barely different from other CAR cell treatments, Axicabtagene ciloleucel binds to a protein on the surface of lymphoma cells and leukemic cells called CD19 and helps the immune system damage cancerous cells as much as possible [62]. Other CAR-T cell drugs include Brexucabtagene autoleucel, Ciltacabtagene autoleucel, Idecabtagene vicleucel, etc., [63]. Nevertheless, according to their definition by National Cancer Institute, they're pretty much drugs that have a different composition that serves the same function [59], so these drugs' further discussion will be omitted due to their redundancy. The common side effects of those drugs mentioned above include nausea, fatigue, fever, headache, and chills. However, serious side effects of CAR-T cells include severe issues in the vessel, the heart, lungs, kidneys, and other organs as well [64].

CAR-NK and CAR-M cell: Furthermore, there're two types of cells in the CAR treatment, CAR-NK and CAR-M. Natural Killer (NK) cells are one type of white blood cell in the human body, it serves the function of killing cancerous cells and viruses due to the enzyme that it carries [65]. Macrophage (M) serves the function of surrounding and killing microorganisms that enter the organism's body, removing dead cells, and activating the immune system cells [66]. Both cells were first taken from the patient's or the donor's body and then modified to get the specificity that allows it to eliminate CLL cells after that cells are produced in considerable amounts and sent back to the patient's body [67]. The possible difference between the cells that are used in their behavior after entering the body, the chimeric antigen receptor works as a navigator to locate cancerous cells for NK cells after they found the cells, NK cells will serve their function to destruct the cell, chimeric antigen receptor works the same in CAR-M cells, instead of eliminating the cancerous cell in the same way as NK cells, the macrophage will deal with its way, which is to swallow it.

Bone marrow transplant

BMT is a very effective way to treat CLL, its basic mechanism is to replace the leukemic bone marrow from the recipient with normal, CLL-free bone marrow [68]. Regularly, patients need to receipt radiotherapy (usually total body irradiation, doses & types vary from an individual due to different body conditions) to ensure the elimination of sick bone marrow is thorough enough that after the bone marrow donation the percentage of relapse can be lower [69]. There are two types of BMT: autologous & allogeneic, the difference between these two types is the donor, autologous is taken from the patient, and allogenic is taken from other healthy individuals [70]. In this case, the answer is obvious CLL use allogenic BMT rather than autologous BMT in normal condition.

Even though BMT is a nice way to treat CLL, however, it isn't easy to find a donor other than family members. Also, there are possibilities that CLL will relapse, but the good news is the possibility of relapse will decrease over time.

Drugs combination

Researchers are developing various kinds of drugs. They aimed to eliminate the cancerous cell by specific proteins located in CLL cells. This led to the appearance of drugs targeted on tumor markers such as CD20 [71], BTK [72], PI3K [73], and BCL-2 [74]. This section will mainly discuss a new drug makeup that is used.

BCL-2, a protein found on the surface of CLL cells, allows CLL cells

to survive while they supposed to be eliminated [74], Venetoclax is a drug target of BCL-2 [75]. It is used with a drug called obinutuzumab, which targets CD20 (previously mentioned). This combination is used since 2019 [76].

However, it might cause serious side effects called tumor lysis syndrome. This happens when a tumor is eliminated rapidly, and some substance inside the tumor will leak into the bloodstream, which disrupts the homeostasis of chemicals in the vessel. Patients with this syndrome demonstrate organ destruction, for instance, kidney, liver, and heart [77].

There are still many drugs under development, including lenalidomide (Revlimid), ublituximab (TG-1101), umbralisib (Ukoniq), and ABP-798 [77].

Conclusion and Prospective

Everything nowadays about Chronic Lymphocytic Leukemia is being increasingly less opaque, for instance, its pathogenesis; however, there are a few enigmas that we expected. The future direction of development would be more mutations that are found responsible for the formation of CLL and environmental factors that cause CLL (Chemical substances, industrial wastes, etc).

Many different reasons can cause different types of leukemia, and various types of leukemia need different types of treatment, so a common treatment plan came up as an idea, which has relatively slight side effects, high effective for most patients, is convenient, and is affordable to most patients.

Recent research has prominently demonstrated shortages in each treatment plan. These shortages make the treatment of CLL synthetical (referred to as the usage of many drugs and various other treatments), e.g. chemotherapy combined with immunotherapy, radiotherapy combined with a bone marrow transplant. It's usually very exhausting for the patient; many patients are tortured by multifarious side effects brought by the individualized synthetical treatment. New ways that have relatively fewer side effects, and are simpler yet effective will help. Additionally, the convenience of the treatment can be considered to add, so they can focus on other things rather than accept treatment every week, it's time-consuming and often causes disturbance in life.

Authors' Contributions

HM and XF conceived the idea, initiated and wrote the manuscript. HM conducted the literature search designed and illustrated figures. HM and XF read and approved the final manuscript.

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