

The Traits and Treatment of Leukemia

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Abstract. Leukemia is a complex disease. Except some rare subtypes, leukemia can be classified to 4 types. They're Chronic Myeloid Leukemia (CML), Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia (CLL) and Acute Lymphocytic Leukemia (ALL). Roughly speaking, pathogenesis of 2 types of acute leukemia is not very clear. Other researches only discover some factors may cause the acute leukemia and the related genes. The therapeutic strategies for different types of leukemia are totally differentiated. First, the radiotherapeutic strategies are various. It's worth to notice that the '7+3' chemotherapies for Acute Myeloid leukemia. For other types of leukemia '7+3' therapeutic strategy is not applicable. Second, each leukemia has various novel therapies. As an illustration, Imatinib, or a more common name Gleevec, is an applicable targeting therapy medicine for CML patients. However, the patients with Acute Myeloid Leukemia have to accept intense chemotherapy. For CLL and ALL, they all have targeting therapies and immunotherapies can treat CLL and ALL.

Keywords: chronic myeloid leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, acute lymphocytic leukemia, treatment

1. Introduction

Leukemia is a serious blood disease. Many people call it 'blood cancer'. It's caused by a mutation in the hematopoietic system. The malignant tumor in the mutant hematopoietic system triggers an increase in white blood cell count. The majority of the cause of death of patients is infection, which is the responsibility of the disabled leukocyte [1]. The sort of leukemia is diverse. It can be differentiated into myeloid and lymphocytic through the location of the mutation. From the aspect of the speed of pathogenicity, it can be sorted into chronic leukemia and acute leukemia. Nowadays, there are a lot of therapies already. For example, there is traditional chemotherapy and radiotherapy; less harmful targeting therapy, and specific therapies for each type of leukemia. To sort each type of leukemia, it is important to find the corresponding therapies. This essay aims to conclude the major types of leukemia and therapies.

2. Chronic Myeloid Leukemia (CML)

Chronic Myeloid Leukemia is the rising of haemopoietic stem cells which occurs in the medulla ossium. From the aspect of genes, the origin of CML is the Philadelphia chromosome—the translocation of bcr and abl genes, finally triggering the formation of the bcr-abl gene. The

Philadelphia gene is necessary for CML. The corresponding bcr-abl protein forms the pathogenicity of CML. This protein triggers the proliferation of leukemia stem cells (LSCs) by inhibiting the tyrosine kinase inhibitors, resulting in the progression of CML from the chronic to the blast phase. There is still a biological question about how the CML transforms from the chronic phase to the blast phase, which is a more severe phase. Normally, the chronic phase is asymptomatic [2].

Targeted therapy is also a usable therapy for CML. It's mentioned in the essay of Quintás-Cardama et al that Imatinib is an appropriate medicine for curing CML. The statistical data shows that the use of imatinib noticeably increases the survival rate in seven years [3]. Nevertheless, the CML may not be cured completely after using Imatinib. First, there is a problem, which is recurrence. After the recurrence, hardly can the Imatinib be effective again. Furthermore, at first time using Imatinib, some patients show tolerance to Imatinib [3]. As a result, having more novel therapies is important for the cure of CML

For other therapies for CML, rather than traditional chemotherapy and radiotherapy, there are already a bunch of novel therapies mentioned in the article by Bhatia. Since the origin of leukemia is leukemia stem cells, it is possible to inhibit the activity of leukemia stem cells. Various mechanisms focusing on LSCs inhibition have been discovered already. In addition, the therapies have been invented too, based on this theory. As an illustration, JAK2 kinase inhibition. In CML, the STAT5 phosphorylation is unusual. The inactivity of STAT5 slows down the process of proliferation of leukemia stem cells. The inhibition of JAK2 kinase can inhibit STAT5. As a result, the leukemia stem cells decrease in this case [4].

3. Acute Myeloid Leukemia (AML)

The etiology of AML is not as clear as that of CML. Nevertheless, there are still many factors that affect the proportion of the answer shown in Deschler's article. First of all, genetics is a major factor. Children with Down syndrome have 10 to 20 times more possibility of developing AML, showing the relationship between AML and Down syndrome. It is worth noting that there is a subtype called acute promyelocytic leukemia (APL). It's a unique subtype with a characteristic morphology associated with distinct chromosomal and gene rearrangement aberrations. In addition, acquired clonal chromosome abnormalities increase the risk of patients developing AML. Some poor-risk patients face the loss of part of chromosomes 5 and 7. There is a '2-hit hypothesis' suggesting that both mutations in Fms-like tyrosine kinase (FLT3) and gene rearrangements involving hematopoietic transcription factors will trigger the phenotype of AML. The FLT3 mutation is associated with all subtypes of AML. Simultaneously, the harmful chemicals and viruses are capable of triggering the AML too [5].

The traditional therapies for AML are intense cytarabine + anthracycline-based chemotherapy. It's also called the '7+3' regimen. However, the survival rate is not appreciable with chemotherapy.

The major novel therapies used are FLT3 inhibitors. As mentioned above, the FLT3 associates with all subtypes of AML. Thus, to inhibit FLT3 seems to be a good option to inhibit AML. There are 2 types of FLT3 mutations. They are the Internal tandem duplication (ITD) mutation and the Tyrosine kinase domain (TKD) mutation. Several oral medicines have been invented to inhibit both mutations in FLT3. This therapy is necessary to coordinate with intense '7+3' chemotherapy to achieve better results [6].

The antibody therapies are also involved. Gemtuzumab ozogamicin (GO) is an illustration. This medicine focuses on the CD33 + relapse. However, some studies show that there is liver toxicity when using GO. It can also be cooperated with '7+3' therapy. Individual GO is appropriate for a gerontic patient [6].

4. Chronic Lymphocytic Leukemia (CLL)

CLL is the most common leukemia in the human body. The basis of CLL is the proliferation of B-lymphocytes. This process is caused by the inhibition of the anti-apoptosis mechanism. In many cases, the lack of the 13q14 gene triggers the loss of 2 cancer inhibition mechanisms. The first one is miR-15a/16-1. It underexpresses the BCL-2 gene, triggering the apoptosis of cells. In patients with CLL, the BCL-2 gene is overexpressed. In this case, the apoptosis is prevented, finally triggering the proliferation. The second one is DLEU7. The loss of DLEU7 triggers the lack of NF- κ B signal, promoting the survival and growth of the B-lymphocytic cells. (Pekarsky et al., 2010) There are 2 subtypes of CLL—Mutated CLL (M CLL) and Unmutated CLL (U CLL). They differ in the structure of the B-cell receptor. U CLL expresses higher amounts of BCR [7,8].

From several decades ago to now, the therapies of Chronic Lymphocytic Leukemia have changed from the chemotherapies, for example, fludarabine and cyclophosphamide (FC), to targeted therapies, including Bruton tyrosine kinase (BTK) inhibitors and BCL2 inhibitors. Both of them are signal pathways triggering proliferation. A typical therapeutic schedule for CLL is Ibrutinib (BTK inhibitor) + Venetoclax (BCL2 inhibitor). It's mentioned in the last paragraph. There are 2 subtypes. There are several therapies for both M-CLL and U-CLL patients [9,10].

5. Acute Lymphocytic Leukemia (ALL)

The pathogenesis is mysterious in ALL. However, there are some factors that are assumed to have relationships with the morbidity of ALL. Cameron K. Tebbi investigates various data about patients with ALL. Nowadays, many scholars believe that both inherited factors and environmental factors trigger the morbidity of ALL. The patients with several types of genetic conditions will show a high risk of ALL, including Down syndrome, Li-Fraumeni syndrome, Fanconi anemia, Bloom syndrome, Shwachman syndrome, etc. The genetic factor involves identical twins. If one of the identical twins shows the phenotype of ALL, the other one of the identical twins has a high possibility of contracting ALL. Same as AML, the 'two-hit hypothesis' exists in ALL, hypothesizing that both congenital genetic defect and environmental effect are necessary for the morbidity of ALL. The environmental factors include the harmful chemicals and radiation. Some types of viruses are capable of stimulating the morbidity of ALL [11].

ALL is hard to control. The only way to cure ALL completely is allogeneic hematopoietic stem cell transplant (AHSCT). Nevertheless, AHSCT is not appropriate for all patients. Except for traditional chemotherapy, immunotherapy is more commonly used in the fight against ALL. The CAR-T therapy is well utilized in this case. The B cell in the case of ALL can be detected by CD19, CD20, CD22, and CD79a antibodies. Rituximab and Ofatumumab are 2 typical examples of medicine based on immunotherapy [12].

The disadvantage of immunotherapy includes neurovirulence, which may become a means to kill patients with ALL. The challenge is to balance the use of medicine and intensity of ALL. In addition, in some cases, some patients may need to accept AHSCT. For some situations, the CD19 is invalid, forcing patients to have other drugs [12].

6. Discussion

Although many types of leukemia seem to have therapeutic strategies other than chemotherapy and radiotherapy, many patients face recurrence or a specific situation that triggers the patients not to have any medicine or therapy. Leukemia is an extremely complex cancer type. In most cases, the

surgery cannot solve the problem or even help to solve the problem. In the US, many patients are old, which is not acceptable for intense chemotherapy [13]. In addition, therapies for acute leukemia are still too lacking. Especially for AML, from the aspect of epidemiology, the majority of patients are children or elderly people [13]. It's so hopeless that the only therapy is chemotherapy, and the patients are not able to use it.

Furthermore, the cost of therapies for leukemia is enormous [14]. Many families cannot afford this enormous cost. As a result, many patients who are not hopeless cannot accept appropriate therapeutic strategies. The industry should focus on decreasing the cost to produce those medicines and the price of those medicines. The government can subsidize those who aim to decrease the cost of leukemia.

7. Conclusion

Leukemia, a complex and heterogeneous group of malignancies, is broadly classified into four main types: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). Each of these categories encompasses numerous molecular and cytogenetic subtypes, necessitating distinct therapeutic approaches. Among them, chronic leukemias (CML and CLL) generally offer more treatment options compared to acute leukemias (AML and ALL), largely due to their more indolent nature and better-understood pathogenesis.

Chronic Myeloid Leukemia (CML) stands out as the most treatable form, primarily because of the remarkable success of tyrosine kinase inhibitors (TKIs) like imatinib, which specifically target the BCR-ABL1 fusion protein. While imatinib has revolutionized CML treatment, some patients develop resistance or intolerance, necessitating alternative TKIs (e.g., dasatinib, nilotinib) or advanced therapies like allogeneic stem cell transplantation in refractory cases.

In contrast, AML presents a far more challenging clinical scenario. Its pathogenesis remains poorly understood, with high genetic heterogeneity contributing to treatment resistance. Currently, intensive chemotherapy remains the backbone of AML therapy, often combined with targeted agents (e.g., FLT3 or IDH inhibitors) or hematopoietic stem cell transplantation for eligible patients. Despite recent advances, relapse rates remain high, underscoring the urgent need for more effective treatments.

CLL, the most common leukemia in adults, has seen significant therapeutic progress with the advent of novel agents such as BTK inhibitors (ibrutinib, acalabrutinib), BCL-2 inhibitors (venetoclax), and monoclonal antibodies (obinutuzumab). These therapies have improved outcomes, particularly for high-risk or relapsed patients, shifting treatment away from traditional chemotherapy in many cases.

ALL, while sharing some pathogenic uncertainties with AML, differs in its treatment landscape. Pediatric ALL has high cure rates with intensive chemotherapy regimens, while adult ALL often requires multimodal approaches, including immunotherapy (blinatumomab, CAR-T cells) and targeted therapies for Ph+ ALL (e.g., ponatinib). However, relapsed/refractory ALL remains a major challenge.

Despite these advancements, many emerging therapies are still in experimental stages, requiring further clinical validation before becoming widely accessible. The full integration of precision medicine, immunotherapies, and gene-editing technologies (e.g., CRISPR) into standard care remains a future goal. To accelerate progress, pharmaceutical companies and regulatory bodies must prioritize rigorous yet efficient clinical testing to ensure both safety and efficacy, ultimately benefiting more patients.

Given that leukemia is not rare, early detection through routine blood tests—monitoring elevated white blood cell counts—could significantly improve outcomes. Early diagnosis allows for timely intervention, enhancing treatment success rates. Additionally, screening high-risk populations, such as children with Down syndrome (who have a markedly increased risk of developing acute leukemia), could facilitate preventive strategies or early therapeutic interventions.

In conclusion, while remarkable progress has been made in leukemia treatment, substantial challenges remain, particularly for acute leukemias. Future efforts should focus on accelerating drug development, improving early detection, and personalizing therapies to maximize survival and quality of life for all leukemia patients.

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