

# **Leukemia: A Comprehensive Study for Understanding and Treating the Disease.**

**Submitted By**

Zajiba Sadia Islam

Student ID: 501279357

**Submitted for**

Program: MEng in Biomedical Engineering

Course: Anatomy/Physiology for MedPhys

BP8114, Winter 2024

Date: 04-22-2024

## Table of Contents

Introduction .....	4
Process of Production of White Blood Cells .....	4
The Role of Cytokines and Growth Factors in White Blood Cell Production.....	5
Maturation and Activation of White Blood Cells .....	6
The Different Types of White Blood Cells .....	6
Development Process of Leukemia .....	8
Genetic Mutations .....	8
Effects on Blood and Bone Marrow .....	8
Types of Leukemia.....	8
Symptoms of Leukemia .....	9
Diagnosis Method of Leukemia .....	10
Initial Assessment and Medical History .....	10
Blood Tests .....	10
Bone Marrow Aspiration and Biopsy .....	10
Cytogenetic Analysis .....	10
Molecular Testing .....	11
Imaging Studies.....	11
Lumbar Puncture (Spinal Tap).....	11
Diagnosis and Subtyping.....	11
Treatment Methods .....	11
Chemotherapy .....	11
Targeted Therapy .....	12
Immunotherapy.....	12
Stem Cell Transplantation .....	12
Radiation Therapy.....	12
Supportive Care .....	12
Advances in Treatment of Leukemia .....	12

Targeted and Personalized Therapies .....	13
Genetic and Molecular Profiling.....	13
Immunotherapy.....	14
Gene Editing Technologies .....	14
Clinical Trials .....	14
Challenges and Considerations .....	15
The Crucial Role of Clinical Physicists and Radiation Therapists in Leukemia Treatment ..	15
Ensuring Accurate Delivery of Radiation Therapy.....	15
Minimizing Side Effects .....	15
Monitoring Patient Response to Treatment .....	16
Importance of Staying Updated with Advancements in Radiation Oncology .....	16
Conclusion.....	16
References .....	17

# Introduction

Leukemia is a type of hematological condition. More specifically, it is a complex form of cancer that affects the blood and bone marrow. Leukemia is characterized by the abnormal proliferation of white blood cells. Originating from the genetic mutations in bone marrow, it disrupts the normal process of blood cell formation. This unusual growth of cells can spread to other organs through the bloodstream and affect the body's ability to fight infections. It can cause a wide range of symptoms to appear. Leukemia can be a very challenging disease since it is very difficult to diagnose and treat.

The focus of this study is to understand the root causes of leukemia, and to know about the various types and symptoms of the disease. In addition, this study explores the latest advancements in leukemia research and aims to provide a comprehensive overview of the latest advances made in treating leukemia. The scopes and limitations associated with the treatment methods has also been a focal point of the study.

## Process of Production of White Blood Cells

Hematopoiesis is the process of production of normal blood cells in the human body. It occurs in the bone marrow. White blood cells are also produced in the bone marrow from hematopoietic stem cells (HSCs). HSCs are multipotent cells capable of producing all blood cell types, including white blood cells, red blood cells, and platelets. HSCs are found in the bone marrow, where they can self-renew and differentiate.

Under the influence of various growth factors and cytokines, HSCs contribute to the generation of white blood cells. For this purpose, the HSCs are differentiated into two main progenitor cell types: myeloid and lymphoid progenitors.

- **Myeloid Progenitors:** Myeloid progenitors give rise to several types of white blood cells, including neutrophils, eosinophils, basophils, monocytes, and macrophages.
- **Lymphoid Progenitors:** Lymphoid progenitors differentiate into lymphocytes. Lymphocytes are further categorized into T cells, B cells, and natural killer (NK) cells.

## The Role of Cytokines and Growth Factors in White Blood Cell Production

The creation of white blood cell progenitors is strictly controlled by a network of cytokines and growth factors. Some of these signaling molecules include interleukins, colony-stimulating factors (CSFs), and erythropoietin. For instance,

- Interleukins (ILs): IL-3, IL-6, and IL-7 are essential for the proliferation and differentiation of various white blood cell lineages.
- Colony-Stimulating Factors (CSFs): Granulocyte colony-stimulating factor (G-CSF) stimulates the production of neutrophils, while macrophage colony-stimulating factor (M-CSF) promotes the differentiation of monocytes into macrophages.

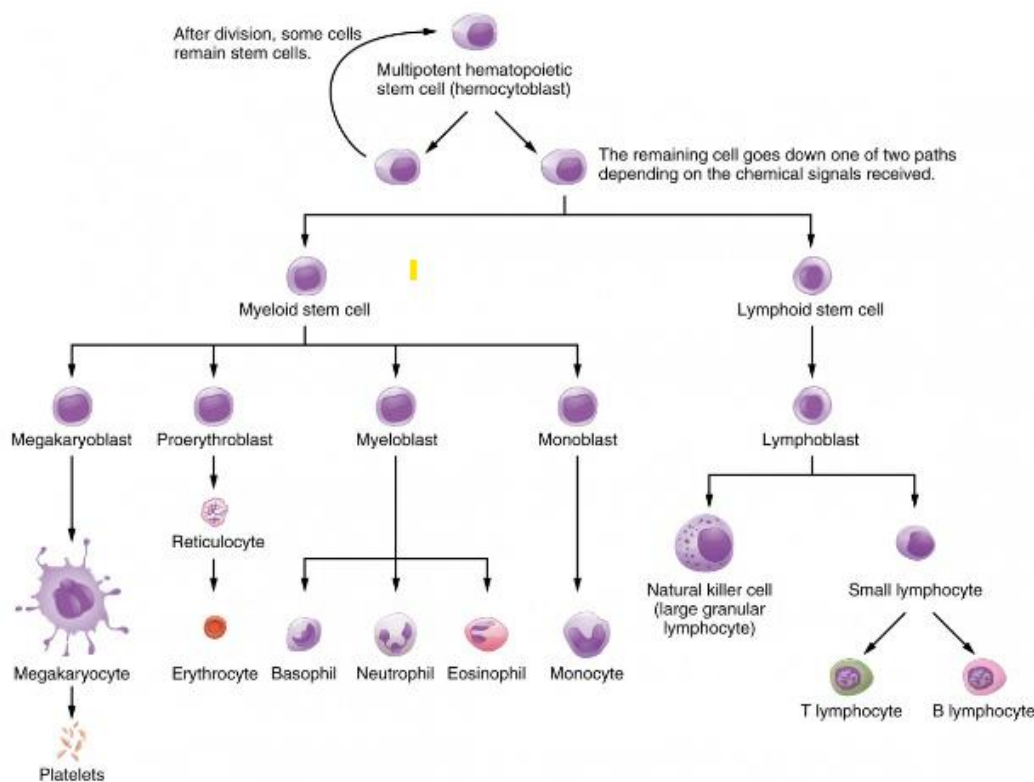


Figure: Production process of white blood cells (and other blood elements) by hematopoiesis.  
(Image Source : <https://courses.lumenlearning.com/suny-ap2/chapter/production-of-the-formed-elements/>)

## Maturation and Activation of White Blood Cells

White blood cells undergo maturation once differentiation is completed. They acquire specialized features that allow them to perform respective immune functions effectively. For example, neutrophils develop phagocytic capabilities, while T cells train to recognize self from non-self antigens.

The production of white blood cells is regulated to meet the body's immune needs. Pro-inflammatory cytokines and other mediators can be released to combat infections or other challenges that require the rapid production of specific types of white blood cells.

## The Different Types of White Blood Cells

### **Neutrophils**

Neutrophils are the most abundant type of white blood cell and are known for their rapid response to infections. They have a multi-lobed nucleus and are filled with granules containing enzymes and antimicrobial substances.

Function: Engulfing and destroying bacteria, fungi, and other foreign invaders.

### **Eosinophils**

Eosinophils have a bi-lobed nucleus and contain granules that stain red orange with acidic dyes.

Function: Responding to parasites and allergic reactions. They release toxins to destroy parasites and help regulate inflammation.

### **Basophils**

Basophils have a bi-lobed nucleus and contain large, dark-staining granules.

Function: Releasing histamine, which causes blood vessels to dilate and become more permeable.

### **Monocytes**

Monocytes are the largest type of white blood cell and can differentiate into macrophages or dendritic cells. They have a kidney-shaped nucleus.

Function: Phagocytosis and the immune response to pathogens.

### **Macrophages**

Macrophages are large cells with a kidney-shaped nucleus and abundant cytoplasm.

Function: Engulf and digest pathogens, dead cells, and debris. They also play a role in antigen presentation and the activation of other immune cells.

## Dendritic Cells

Dendritic cells are antigen-presenting cells that play a critical role in initiating and regulating the adaptive immune response. They have long, branching projections called dendrites and are found in tissues that are in contact with the external environment, such as the skin and mucous membranes.

Function: Capturing antigens and presenting them to T cells to generate an immune response.

## Lymphocytes

Lymphocytes are a diverse group of white blood cells that play a central role in the adaptive immune response. There are three main types of lymphocytes: T cells, B cells, and natural killer (NK) cells.

- T cells: T cells help regulate the immune response and are involved in cell-mediated immunity. They can directly kill infected cells and help activate other immune cells.
- B cells: B cells are involved in humoral immunity and produce antibodies that can neutralize pathogens and target them for destruction by other immune cells.
- Natural Killer (NK) cells: NK cells are cytotoxic lymphocytes that can recognize and destroy infected or cancerous cells without prior sensitization.

The different types of white blood cells can be summarized in the figure below:

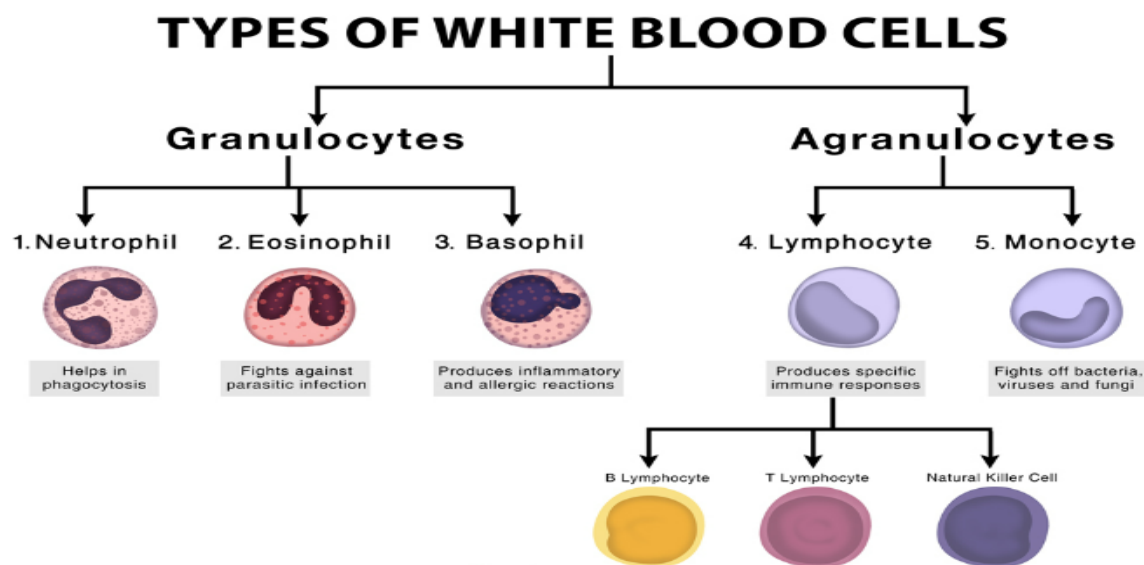


Figure: Different types of white blood cells.

(Image Source : <https://www.sciencefacts.net/types-of-white-blood-cells.html>)

# Development Process of Leukemia

The normal process of hematopoiesis is destroyed in leukemia, which leads to the uncontrolled production of immature white blood cells. This condition may arise from genetic mutations in the stem cells that produce blood cells. These abnormal cells, known as leukemia cells, do not function properly and overshadow the normal blood cells. The abnormal white blood cell production can lead to a variety of symptoms and complications.

## Genetic Mutations

**Stem Cell Mutation:** Leukemia typically begins with a mutation in the DNA of hematopoietic stem cells (HSCs) in the bone marrow. These mutations alter the normal growth and division of stem cells.

**Oncogenes and Tumor Suppressors:** Mutations can affect genes known as oncogenes, which promote cell growth, and tumor suppressor genes, which inhibit cell growth. When these genes are altered, they can disrupt the normal balance of cell growth and division, leading to cancer.

## Effects on Blood and Bone Marrow

**Bone Marrow Infiltration:** The abnormal white blood cells accumulate in the bone marrow and affects the other blood cells. It might lead to a decrease in the production of red blood cells and platelets, causing anemia and bleeding problems.

**Immature Cells in Blood:** The presence of immature white blood cells, known as blasts, in the bloodstream is key mark of leukemia. These cells are not able to perform their normal functions and are the key causes of the symptoms of the disease.

## Types of Leukemia

Leukemia can be classified as acute or chronic, based on how quickly it progresses and the maturity of the abnormal cells.

- **Acute Leukemia:** The abnormal blood cells are immature and unable to carry out their normal functions. This leads to a rapid increase in the number of abnormal cells in the bone marrow and blood.
- **Chronic Leukemia:** It progresses more slowly, and the abnormal cells are more mature. These cells may be able to perform some of their normal functions but not fully.



Leukemia can also be classified based on the type of white blood cell affected. The main types include:

- Lymphocytic Leukemia: Affects lymphoid cells, which are responsible for producing lymphocytes.
- Myelogenous Leukemia: Affects myeloid cells, which give rise to red blood cells, white blood cells, and platelets.

Each subtype has unique characteristics, requiring different treatment approaches.

## Symptoms of Leukemia

Leukemia can present a variety of symptoms. These symptoms often develop gradually and may be mild at first. This makes them easy to ignore. However, early detection is crucial for effective treatment. The key symptoms associated with leukemia can be classified as follows:

### Fatigue and Weakness

Persistent fatigue, weakness, and shortness of breath are the most common symptoms of leukemia. This is often caused by anemia, since the production of red blood cells are disrupted.

### Frequent Infections

Leukemia can suppress the immune system. This can cause frequent or severe infections that take longer to resolve, such as pneumonia, bronchitis, or skin infections. Recurrent fevers or flu-like symptoms may also be due to leukemia.

### Easy Bruising and Bleeding

A decrease in the number of platelets can lead to easy bruising and bleeding. Individuals with leukemia may bruise easily, bleed more than usual from minor cuts or injuries, or experience frequent nosebleeds or gum bleeding.

### Swollen Lymph Nodes

Swollen lymph nodes, particularly in the neck, armpits, or groin, may be a sign of leukemia.

### Unexplained Weight Loss

Unexplained weight loss can be a symptom of leukemia. This weight loss may occur due to a loss of appetite, a result of the cancer affecting the body's metabolism.

### Bone Pain or Tenderness

Pain or discomfort in the bones, often described as a deep, aching pain can be caused due to leukemia. This pain may be more noticeable at night or during physical activity and is caused by the abnormal accumulation of leukemia cells in the bone marrow.

#### Other Symptoms

Other symptoms of leukemia can include swollen or bleeding gums, frequent headaches, enlarged spleen or liver, and night sweats.

## Diagnosis Method of Leukemia

The diagnosis typically involves a combination of medical history review, physical examination, and laboratory tests.

### Initial Assessment and Medical History

The diagnostic process may begin with a review of the individual's medical history and physical examination. Inquiries are made about symptoms, family history of cancer, exposure to toxins or radiation, and any relevant medical conditions.

### Blood Tests

A complete blood count (CBC) assesses the number, and types of blood cells present. Individuals with leukemia often have abnormal levels of white blood cells, red blood cells, and platelets. The presence of immature white blood cells in the bloodstream can be indicative of leukemia.

### Bone Marrow Aspiration and Biopsy

A small sample of bone marrow and bone is taken from the hipbone or breastbone and examined under a microscope. This helps determine the presence of leukemia cells, their characteristics, and the extent of bone marrow involvement.

### Cytogenetic Analysis

Cytogenetic analysis involves examining the chromosomes of leukemia cells for any abnormalities. This helps classify the leukemia and predict its prognosis. Fluorescence in situ hybridization (FISH) and karyotyping are common techniques used in cytogenetic analysis.

## Molecular Testing

Molecular testing is used to detect specific genetic mutations or changes in leukemia cells. Polymerase chain reaction (PCR) and next-generation sequencing (NGS) are common molecular techniques used to identify mutations that may guide treatment decisions.

## Imaging Studies

Imaging studies such as X-rays, CT scans, MRI scans, or PET scans may be performed to assess the extent of leukemia and detect any complications, such as enlarged lymph nodes or organ involvement.

## Lumbar Puncture (Spinal Tap)

In some cases of leukemia, a lumbar puncture may be performed to collect cerebrospinal fluid from the spinal canal. This helps assess if leukemia cells have spread to the central nervous system.

## Diagnosis and Subtyping

Based on the results of these tests, the healthcare provider can confirm the diagnosis of leukemia and determine its specific type and subtype. This information is crucial for developing an individualized treatment plan.

## Treatment Methods

Leukemia typically requires a tailored treatment approach based on the specific type, subtype, and characteristics of the disease. Treatment methods for leukemia aim to eliminate cancerous cells, restore normal blood cell production, and prevent the recurrence of the disease. Some of the usual methods of treating leukemia are discussed below in detail:

### Chemotherapy

Chemotherapy is the primary treatment for many types of leukemia and has been proven to be effective in the treatment of leukemia for the past 50 years <sup>1</sup>. Chemotherapy involves the use of powerful drugs to kill cancer cells or stop them from dividing. It may be given orally, intravenously, or through injections. Combination chemotherapy, which uses multiple drugs, is often more effective than single-agent therapy. Combination therapy can cure certain leukemias completely if detected in the early stage <sup>2</sup>.

## Targeted Therapy

Targeted therapy drugs are designed to specifically target cancer cells while minimizing damage to normal cells. These drugs regulate specific molecules involved in cancer cell growth and survival. Examples of targeted therapy drugs used in leukemia treatment include imatinib, dasatinib, and rituximab.

## Immunotherapy

Immunotherapy uses the body's immune system to fight cancer. Monoclonal antibodies, such as alemtuzumab and rituximab, can target and destroy leukemia cells. Chimeric antigen receptor (CAR) T-cell therapy is another form of immunotherapy that involves modifying a patient's own T cells to better recognize and attack cancer cells.

## Stem Cell Transplantation

Stem cell transplantation is also known as a bone marrow transplant. This method may be practiced for certain types of leukemia, especially when chemotherapy alone is not effective. This procedure involves replacing diseased or damaged bone marrow with healthy stem cells from a donor or from the patient.

## Radiation Therapy

Radiation therapy uses high-energy radiation to kill cancer cells and shrink tumors. It may be used in combination with chemotherapy or as a standalone treatment for leukemia that has spread to other parts of the body.

## Supportive Care

Supportive care plays a crucial role in leukemia treatment. This includes managing symptoms such as pain, fatigue, and nausea, as well as providing emotional support and guidance throughout the treatment process.

## Advances in Treatment of Leukemia

Leukemia treatment has come a long way, but there is still a lot of room to improve outcomes and reduce the toxicity of current therapies. Research in leukemia treatment is now focused on developing more targeted and personalized therapies based on the genetic and molecular

characteristics of individual tumors. Improvements in utilizing immunotherapy and gene editing technologies are promising for revolutionizing the treatment of leukemia.

## Targeted and Personalized Therapies

One of the most effective and promising developments is the emergence of targeted therapies, which offer a more precise and effective approach to combating the disease <sup>3</sup>. Targeted therapies aim to exploit the weaknesses of cancer cells, while sparing normal cells and thus reducing side effects.

Two main types of targeted therapies have shown promise in the treatment of leukemia:

1. Tyrosine Kinase Inhibitors (TKIs): TKIs are drugs that target specific enzymes, called tyrosine kinases, which play a crucial role in the growth and survival of cancer cells. By blocking these enzymes, TKIs can effectively inhibit the growth of leukemia cells. A study showed that the inhibition of BCR-ABL with kinase inhibitors is an effective in targeted therapy of chronic myeloid leukemia (CML) <sup>4</sup>. Examples of TKIs used in the treatment of leukemia include imatinib, dasatinib, and nilotinib.
2. Monoclonal Antibodies: Monoclonal antibodies are antibodies made to target specific proteins on the surface of cancer cells and marking them for destruction by the immune system. Studies find this technique to be effective in selectively destroying malignant cells while sparing the normal cells from toxicity. Rituximab and alemtuzumab are examples of monoclonal antibodies that have been used in the treatment of leukemia <sup>3</sup>.

Personalized therapies are more advanced in that it provides tailored treatment to the unique genetic and molecular characteristics of an individual's tumor. This approach can increase efficiency while decreasing the toxicity associated with treatment. Studies have found that when combined with precise clinical diagnosis and detailed risk assessment, targeted new drug therapy has made unprecedented progress in treatment of patients with AML <sup>1</sup>.

## Genetic and Molecular Profiling

Advances in technology have made it possible to analyze the genetic and molecular profile of leukemia cells with greater precision and speed. Studies have found links between biomarkers and prognosis of the disease <sup>5</sup>. This information can also help identify specific mutations or

abnormalities of cancer cells which allows the development of targeted therapies that can precisely utilize the vulnerabilities.

## Immunotherapy

Immunotherapy is a rapidly evolving field that harnesses the power of the immune system to fight cancer. This approach can be particularly effective in leukemia, as it can target cancer cells that may be resistant to other treatments. CAR-T cell therapy, for example, involves genetically modifying a patient's own T cells to better recognize and attack cancer cells. This approach has shown remarkable success in treating certain types of leukemia. Studies show breakthrough result in treatment of AML by using immunotherapy, especially in patients who are not eligible for intensive chemotherapy <sup>6</sup>.

## Gene Editing Technologies

Gene editing technologies, such as CRISPR-Cas9, offer new possibilities for treating leukemia. These technologies allow researchers to precisely edit the DNA of cancer cells, potentially correcting genetic mutations that drive cancer growth or enhancing the immune system's ability to target cancer cells <sup>7</sup>.

## Clinical Trials

Clinical trials are an effective and important mean for improving the leukemia treatment. Through clinical trials, researchers understand how effective the various therapies are, identify potential side effects, and determine the best method for individual clinical treatment. Some examples of successful clinical trials are found:

- A phase III clinical trial evaluating the use of TKI imatinib in patients with chronic myeloid leukemia (CML) showed significantly improved survival rates and fewer side effects compared to standard chemotherapy. In fact, the prognosis of 5-year survival rate has gone up from 20% to more than 90% <sup>8</sup>.
- Another clinical trial investigating the use of a monoclonal antibody in patients with acute lymphoblastic leukemia (ALL) demonstrated high response rates and prolonged remission periods. Monoclonal antibodies selectively target leukemic cells and minimize toxicity in normal cells. This, in combination with chemotherapy rituximab increases cure rates of adults with Burkitt leukemia from 40% to 80% <sup>9</sup>.

## Challenges and Considerations

While the future of leukemia treatment looks promising, there are challenges that need to be addressed. New strategies are required to be developed constantly since resistance to targeted therapies can develop over time. Chemotherapy is effective in the treatment of leukemia, but it has not been able to show improvement in aspect of increasing life expectancy <sup>1</sup>. Finding donors for stem cell transplantation can be challenging <sup>6</sup>. Studies have shown that BCR-ABL kinase inhibitors does not kill leukemic stem cells (LSCs) efficiently and is not effective in curing CML. Developing targeted therapies requires a deep understanding of the genetic and molecular mechanisms driving leukemia <sup>4</sup>. Moreover, these specialized therapies involving new technology and strategies can be expensive and may not be accessible to all patients. Hence, ensuring access to these advanced therapies for all patients will be essential for improving outcomes and reducing disparities in care.

## The Crucial Role of Clinical Physicists and Radiation Therapists in Leukemia Treatment

Clinical physicists and radiation therapists are some of the most important factors in the treatment of leukemia patients. It is their expertise and skills which ensures the accurate delivery of radiation therapy, minimizes side effects, and monitors the patient's response to and adjusts treatment.

### Ensuring Accurate Delivery of Radiation Therapy

Clinical physicists play a crucial role in ensuring the accurate delivery of radiation therapy to leukemia patients. They are responsible for planning the treatment, including determining the optimal radiation dose and the precise location and shape of the radiation beams. They are responsible for creating detailed treatment plans using advanced imaging techniques like MRI and CT scan, that ensures maximum efficiency of treatment while causing minimum possible side effects.

### Minimizing Side Effects

Radiation therapists work side by side with clinical physicists to deliver the radiation therapy according to the treatment plan. Their expertise in positioning patients and operating the radiation equipment is essential for ensuring that the radiation is delivered precisely to the intended target

area. The radiation therapists help minimize the risk of side effects and ensure that the maximum dose of radiation is delivered to the leukemia cells by following the treatment plan.

## Monitoring Patient Response to Treatment

Throughout the course of treatment, clinical physicists and radiation therapists monitor the patient's response to radiation therapy. The treatment plan may be adjusted based on imaging studies and patient's response to treatment to ensure that the leukemia cells are being effectively targeted. For monitoring this, regular follow-ups and imaging studies are essential.

## Importance of Staying Updated with Advancements in Radiation Oncology

Since the field of radiation oncology is highly specialized and complex, it is evolving rapidly. New technologies and treatment techniques are constantly being developed. It is essential for clinical physicists and radiation therapists to stay updated with these advancements so that they can provide optimal care to leukemia patients. Only by staying informed can the professionals provide the best and most effective possible treatment solutions to their patients.

## Conclusion

Leukemia is a complex disease, and it requires a multidisciplinary approach for effective management. Although the mechanism of developing leukemia has been the scope of recent research, determining the exact cause behind leukemia can be challenging. Leukemia can be classified into different categories, which require different treatment methods. Treatment of the disease has come a long way, and prognosis for leukemia patients has increased greatly with various treatment modalities in recent times. However, various challenges continue to exist for the different treatment modalities and there is increasing need of research. Target therapies have emerged as promising treatment process, with increased life expectancy of the patients. However, these treatments still face some limitations, which are the scopes of continuous research and improvements. In this regard, clinicians and radiation therapists play a crucial role. They are at the heart of providing effective treatment while constantly working to improvise and provide crucial information to researchers. Despite the challenges, the treatment of leukemia holds a promising future.



## References

1. Yu J, Jiang PYZ, Sun H, et al. Advances in targeted therapy for acute myeloid leukemia. *Biomark Res.* 2020;8(1):17. doi:10.1186/s40364-020-00196-2
2. Pomeroy AE, Schmidt EV, Sorger PK, Palmer AC. Drug independence and the curability of cancer by combination chemotherapy. *Trends in Cancer.* 2022;8(11):915-929. doi:10.1016/j.trecan.2022.06.009
3. Kim JA. Targeted therapies for the treatment of cancer. *The American Journal of Surgery.* 2003;186(3):264-268. doi:10.1016/S0002-9610(03)00212-5
4. Sullivan C, Peng C, Chen Y, Li D, Li S. Targeted therapy of chronic myeloid leukemia. *Biochem Pharmacol.* 2010;80(5):584-591. doi:10.1016/j.bcp.2010.05.001
5. Murakami N, Okuno Y, Yoshida K, et al. Integrated molecular profiling of juvenile myelomonocytic leukemia. *Blood.* 2018;131(14):1576-1586. doi:10.1182/blood-2017-07-798157
6. Aureli A, Marziani B, Sconocchia T, et al. Immunotherapy as a Turning Point in the Treatment of Acute Myeloid Leukemia. *Cancers.* 2021;13(24):6246. doi:10.3390/cancers13246246
7. Montaña A, Forero-Castro M, Hernández-Rivas JM, García-Tuñón I, Benito R. Targeted genome editing in acute lymphoblastic leukemia: a review. *BMC Biotechnol.* 2018;18(1):45. doi:10.1186/s12896-018-0455-9
8. Jabbour EJ, Cortes JE, Kantarjian HM. Tyrosine kinase inhibition: A therapeutic target for the management of chronic-phase chronic myeloid leukemia. *Expert Rev Anticancer Ther.* 2013;13(12):1433-1452. doi:10.1586/14737140.2013.859074
9. Jabbour E, O'Brien S, Ravandi F, Kantarjian H. Monoclonal antibodies in acute lymphoblastic leukemia. *Blood.* 2015;125(26):4010-4016. doi:10.1182/blood-2014-08-596403