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CLINICAL FEASIBILITY OF IMMUNOTHERAPY FOR ACUTE LEUKEMIA – *A REVIEW*

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Abstract – *Leukemia is a malignant cancerous condition of hematopoietic stem cells associated with increased number of white blood cells within the blood circulation and bone marrow. We aimed to assess the clinical feasibility of immunotherapy for treating acute leukemia. The innate immune response provides the first line of defense for the body; whereas, adaptive immune response is recognized as a separate aberration, associated with the cancer cells. The process of immunotherapy is divided into seven different types of therapies including; monoclonal antibody therapy, vaccination, chimeric antigen receptors, radio-immunotherapy, cytokine therapy, donor lymphocyte infusion, and stem cell transplantation. However, the general treatment of leukemia involves allogeneic bone marrow transplantation, post-induction therapy, and autologous bone marrow transplantation. The study has concluded that immunotherapy depicts promising outcomes in treating acute leukemia.*

KEYWORDS: *Clinical Feasibility, Immunotherapy, Leukemia, Malignant, Transplantation, White blood cells.*

INTRODUCTION

The cancer of blood and bone marrow is known as leukemia. Clinically, leukemia is defined as a malignant disease of hematopoietic stem cells, which is correlated with increased number of white blood cells in the peripheral blood and bone marrow[1]. On the basis of cell type and rate of growth, leukemia is classified into four groups by American Cancer Society as follows.

Acute Lymphocytic Leukemia (ALL)

Acute lymphocytic leukemia (ALL) is considered as a serious malignancy of lymphoid cells, which is directly associated with the 80% of prevalence among pediatric population and 20% prevalence among adult population[2]. World Health Organization has stated that there are two diagnostic entities for such malignancies, which include precursor B-cell ALL and precursor T-cell ALL. Some of the common symptoms mainly include fever, pallor, hepato-spleno-megaly, lymph node swelling, and hemorrhage[3]. The common symptoms associated with ALL include: hemorrhage, swelling of the lymph nodes, pallor, fever, and hepato-spleno-megaly[3]. However, this condition is diagnosed through physical examination, serum biochemical profiles, peripheral blood counts, and investigating morphology of the bone marrow[4]. The patients are treated on the basis of appearance of specific symptoms.

Chronic Myeloid Leukemia (CML)

Chronic myeloid leukemia (CML) is another chronic malignancy, which has the tendency to affect the myeloid cells. Blood tests have shown an increase in the number of white blood cells[5]. Some of the common clinical symptoms of this malignancy include fatigue, tiring easily, weight loss, and a sense of fullness in

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the upper abdomen from an enlarged spleen. Imatinib (Gleevec) therapy is identified as the most significant therapeutic modality for addressing the complications of CML. In the case of CML, increased number of white blood cells can be identified in the blood test. It is characterized as clonal disorder of hematopoietic stem cells that increase the number of erythroid and myeloid cells within the bone marrow[6-8].

CML is a form of chronic leukemia that is classified as one of the myelo-proliferative disorder, and it progresses to a more acute form. The leukemic cells in later stages loose ability to mature, which results in building up of blast cells in the blood and bone marrow. The three distinct phases of CML include:

- Chronic phase (at the time of diagnosis) – Few blast cells are present in the blood and bone marrow, but this condition shows none of the symptoms of leukemia. This condition might last from several months to several years.
- Accelerated phase – The number of blast cells in the blood and bone marrow increase.
- Blast phase – More than 30 % of blood and bone marrow comprise of blast cells. The blast cells are made from tumors in the bones and lymph nodes at the blast phase. The clinical symptoms experienced by patients in the blast phase include; fever, an enlarged spleen, weight loss, and generally feel unwell.

After almost 3-5 years of the diagnosis, a condition known as blast crisis occurs, that is similar to aggressive acute leukemia. However, this condition is difficult to treat[6]. This condition is likely to cause fatigue and weight loss among the affected individuals. Moreover, these patients also complained about headaches, fever, bone tenderness, and pain. Splenomegaly is the most common abnormality that is observed during physical examination. According to Sawyers et al[9], the progression of CML starts from chronic phase, and finally results in blast crisis within time period of 3-5 years. The patients are administered to control the multiplication of blast cells. However, at advance stage, when the patient is unable to tolerate imatinib, the patient is advised for allogeneic bone marrow transplant (BMT). The success rate of BMT is very low and around 30 % of the patients die after receiving the treatment. Leukemia may spread to other organs, which would result in the impaired functioning of cells. Leukemia can be treated using different treatments, but the present study has evaluated the effectiveness of immunotherapy. Immunotherapy is a kind of biological therapy, which has the ability to boost the immune system of affected patient, remove the malignant cells, and recognize the tumor-associated antigens[10,11].

ImmunoSystem

The immune system comprises of cells, tissues, and organs that keep the body away from foreign particles (virus and bacteria) by working together (Figure 1). The organs associated with immune system are known as lymphoid organs as they are present in the center to the lymphocytes [12]. The production of blood cells is controlled by bone marrow, which is a soft tissue structure in the hollow center of bones. Blood vessels have been identified as the mode of transportation for lymphocytes as indicated by Otto[12]. The cells have capability to travel through the lymphatic vessels that are parallel to the body's veins and arteries. Moreover, spleen has been identified as a flattened organ in the abdomen, where specialized compartments are present. Such compartments are mainly used for the collection of immune cells. Immune system has the capability to recognize viral and bacterial presence in the human body. However, it is difficult to recognize tumor cells as they are similar to the healthy cells.

The pathogens entering the body through intestinal tract are intercepted at Peyer's patches that are located in the wall of intestine and appendix and attached to cecum (large intestine)[13]. Surface proteins are present on every cell that are known as distinctive proteins. The immune system is well-aware about these proteins, and do not destroy or harm these proteins. However, immune system is efficient in recognizing virus and bacterial cells as they are different from the normal healthy cells.

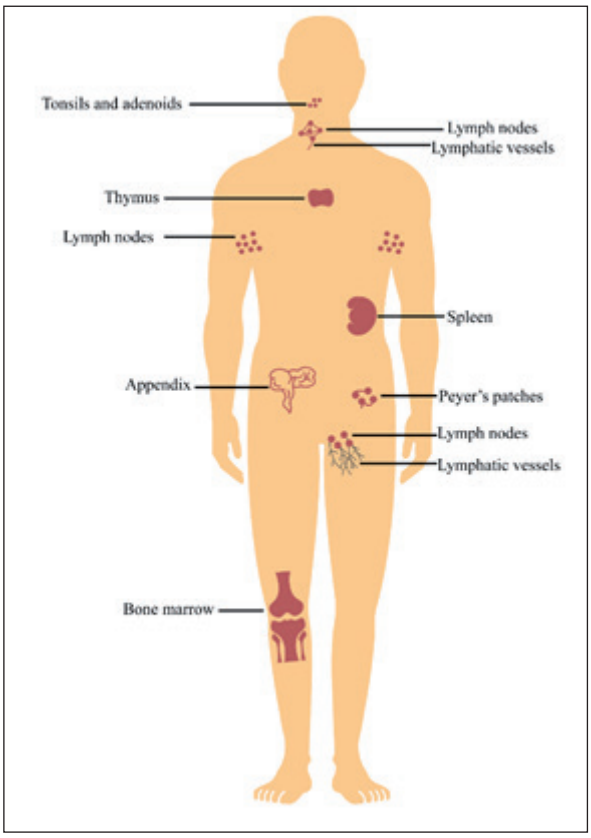

Fig. 1. Organs of the Immune System.

Tumor is not destroyed by the immune system because the cells are similar to the normal body cells, which make it difficult for the immune system to deal with the tumor cells. Therefore, human body experiences much difficulty in perceiving tumor cells as foreign bodies.

Innate and adaptive immune responses in cancer

Immune system has two major responses[14], which work together for exposing and demolishing the cancer cells:

- Innate immune response
- Adaptive immune response

The activation of innate immune response protects human body against the infestation of viruses and bacteria. Moreover, specific aberration on the cancer cells is recognized by the adaptive immune response that differentiates them from the cells, naturally presents within the body[14]. Innate immune response is always considered as the first line of defense for the human body. The major function of this response is to protect the body from the initial infestation through viruses and bacteria. Natural killer (NK) cells play a major role in carrying out innate immune system in an effective way. Adaptive immune response has the capability to recognize specified aberration related to the cancer cells, which results in the differentiation of cells in the human body. This response takes longer time frame for the activation. B and T cells work as a part of adaptive immune response. B cells are produced in the bone marrow; however, they mature in the lymphoid tissues. B cells are similar to body's warlike intelligence system, which is helpful for seeking their targets and sending defenses to lock those [14]. T cells play a major role in recognizing and eliminating abnormal cells, which mainly includes viral, bacterial, or parasitic infections or malignant cells.

IMMUNOTHERAPY

Monoclonal antibody therapy

According to Ansar and Ghosh[14], monoclonal antibodies (MAbs) are characterized as immunological tools that are linked with domains of biochemistry, immunology, applied biology, and biotechnology. Lymphomas and solid tumors can be treated easily with antibody-drug conjugates. This therapy can be utilized against the cancer cell-specific antigens as it causes immunologic response against the target cancer cell. The improved diagnosis of lymphoma and leukemia is possible through MAbs, which are responsible for distinguishing immune cell antigens.

Vaccines

Vaccines contain antigens of a disease, producing signs and symptoms that are not strong enough. However, these antigens tend to produce antibodies that is responsible for preventing infections, attacking a person later[15,16]. The two major reasons for targeting antigens for immunotherapy include;

- On the cancer cells, these antigens are overexpressed;
- Immune response is elicited by the antigens that attack the cancer cells;
- A reprogram to establish interaction between immune system and tumor cells is possible through cancer vaccines and other immunotherapies[17].

Chimeric Antigen Receptors (CARs)

The involvement of patient's own immune cells to recognize and attack the malignant tumor is known as Chimeric Antigen Receptors (CARs) that have shown efficient results among the patients, suffering leukemia. CARs improve cells genetically that contain sequences encoding antibody-based recognition domains, associated with the signaling sequences[18]. In case of patients suffering from blood cancer, this method shows promising results. T cells are extracted from the blood of the patient and engineered genetically by introduction of DNA, which helps in the production of 'CARs'. CAR T-cell therapy is associated with the recognition and binding of receptors to specific target on the cancerous cells[19] (Figure 2). The synthetic receptors comprise of antigen binding domain from B cell receptor that fuses with the signaling receptors of T cells[20].

Radio-immunotherapy

The technique of radio-immuno therapy is associated with the production of specific type of energy that is responsible for killing and shrinking of tumor malignant cells. However, it may even harm the normal cells of the body[21]. This therapy utilizes monoclonal antibody to deliver high energy radiation to the tumor cells. Radioactive emissions are produced by radio nucleotides that are favorable for targeting antibody because they are tumoricidal. Certain body parts are capable of absorbing isotopes on the basis of radioactive material that is used for the treatment[22].

Cytokine therapy

The connections and interaction between the cells are determined by the proteins, known as cytokine that carry signals across the cells. They play a significant role in the functioning of immune system. Communication between different immune cells is facilitated by the cytokine therapy. Moreover, it also helps in the launching of immune responses.

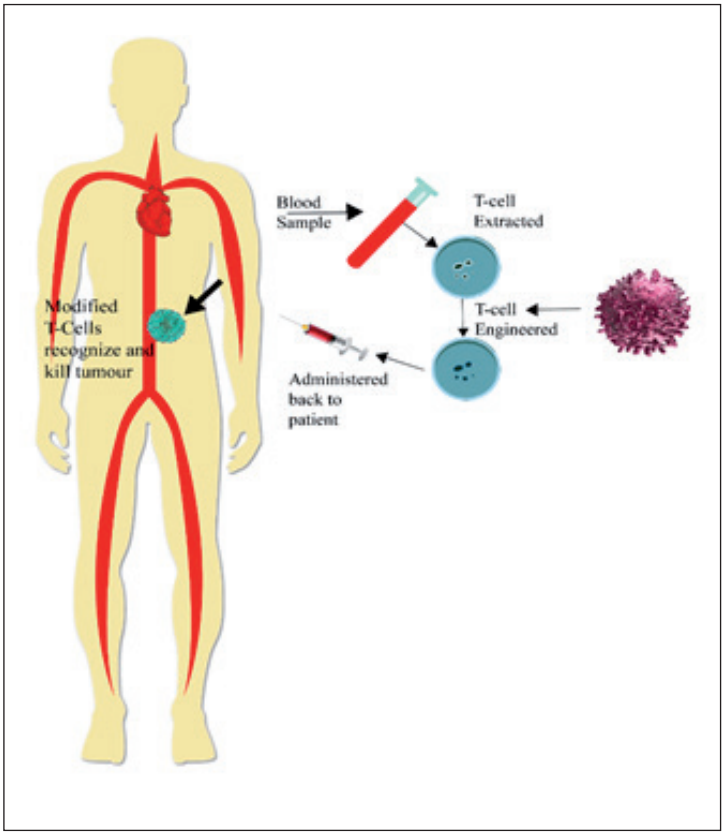

Fig. 2. CARs therapy.

This therapy mainly focuses on the substances that promote immune system responses, while fighting against cancer. Interleukin and interferon are included in the cytokine therapy (Figure 3).

Donor lymphocytes infusion

A significant type of immunotherapy, known as donor lymphocyte infusion, is characterized as a collection of lymphocyte cells from the blood of donor and implanted in the affected individual. The lymphocyte cells are conducted as attack targets by the donor[23]. The infusion facilitates in increasing the immune responses that protect the body against infection and kill the abnormal cells [24]. This technique is used for the patients, suffering relapsed chronic myeloid, chronic lymphocytic leukemia, relapsed acute leukemia, and Hodgkin lymphoma (Figure 4).

Stem cell transplantation

The patients prepared for low intensity stem cell transplantation undergo the reduced intensity allogeneic stem cell transplantation[25]. The transplantation procedure involved low density cultivation that depends on graft *vs.* tumor and donor cells. It enables the donated stem cells to destroy the existing cancer cells.

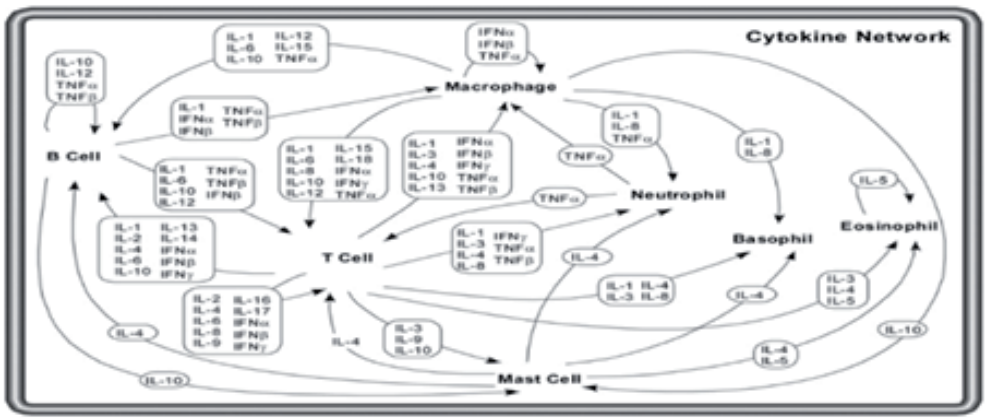

Fig. 3. Procedure of Cytokine Therapy.

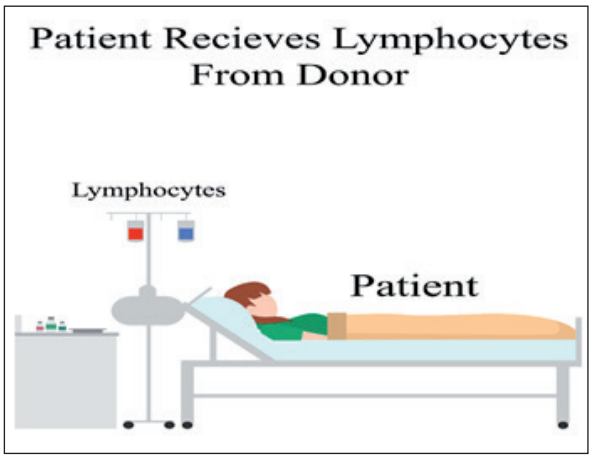

Fig. 4. Procedure of Donor Lymphocytes Infusion.

General treatment for leukemia

The general treatments of leukemia that are implemented to prevent relapse are as follows.

Allogeneic bone marrow transplantation

Allogeneic bone marrow transplantation is considered as the most active anti-leukemic treatment that decreases the risk of relapse among patients in first complete remission. These patients have initially received HLA-matched transplant from a blood relative.

Autologous bone marrow transplantation

In recent years, myeloablative treatment supported by autologous stem cell transplantation has been used broadly.

Post-induction therapy

This therapy is essential for preventing relapse of the disease. This therapy involves autologous bone marrow transplantation, allogeneic bone marrow transplantation, and chemotherapy[7].

CONCLUSIONS

Leukemia is considered as a malignant disorder of hematopoietic cells that is linked with increased number of white blood cells. The prevalence of cancer is increased since the past decade. We may conclude that the condition of leukemia is associated with abnormal production of white blood cells that compete with the normal cells after entering the bloodstream and alter normal functioning of the healthy cells. Moreover, the study may also conclude that unlike the chemotherapy and radiation therapy, immunotherapy is not a harmful treatment. The study has concluded that immunotherapy has depicted promising results in treating cancer effectively.

Supplementary Materials:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of Interest:

The authors declare no conflict of interest.

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