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METHODS OF TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKAEMIA

V. M. M. DEEPAK[*1] AND PALANISWAMY R[2]

1: Department of Biotechnology, School of Biological Sciences, CMS College of Science and Commerce, Chinavedampatti, Coimbatore

2: Dr. N.G.P Arts and Science College, Kalapatti Road, Coimbatore

***Corresponding Author: Vadakkum Madathil Mohandass Deepak: E Mail: vmmdeepak@gmail.com**

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ABSTRACT

Acute Lymphoblastic Leukemia (ALL) is a type of cancer that beings in lymphocytes, especially the white blood cell (WBC). The bone marrow synthesizes plenty of underdeveloped lymphocytes called lymphoblasts. The lymphoblasts in large numbers crowd out other blood stem cells, normal blood cells platelets, and WBC causing the blood to malfunction. The treatment and diagnosis of ALL depend on age, gender, symptoms, signs, and other factors. ALL is found in bone marrow, blood, and organs such as the testicles or the Central Nervous System (CNS). This paper concentrates on the different methods used for a long time and other novel treatment modalities used for ALL. The ALL-treatment techniques can be categorized into three phases. The major techniques used for treatment are chemotherapy, enzyme therapy, steroids, plant alkaloid therapy, radiation therapy, targeted therapy, immunotherapy, and stem cell transplants. Each modality of treatment is different based on the characteristics of the disease. For instance, chemotherapy targets the cells, enzyme therapy targets the asparagine amino acid, steroids, and plant alkaloids target the cell cycle, targeted therapy affects Tyrosine kinase inhibitor, immunotherapy targets CARs (Chimeric Antigen Receptor) and CDs, and stem cell therapy improves the immune system and avoids relapse of the disease ALL.

Keywords: ALL (Acute Lymphoblastic Leukemia); Tyrosine Kinase Inhibitor (TKI) Therapy, stem cell transplant, Plant alkaloid therapy; steroids; Philadelphia chromosome

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a malignancy of B or T lymphoblasts. They are differentiated with unconstrained growth of abnormal and immature lymphocytes and their progenitors. These malignancies are most common in childhood, with persistent fever, bruising, fatigue, and recurrent infections. Haematologic abnormalities are found in the spleen and liver and in the mature B cells. The malignancies are more common in children of age 19 or younger; it is quite frequently found in men and affects more white people than black. Thus, leading to the replacement of bone marrow elements and lymphoid organs. The patients with ALL have typical symptoms such as thrombocytopenia, anemia, neutropenia, and cranial neuropathy disorders **[1, 2]**. Fortunately, the survival rates have increased over the past few decades from 50% in the 1970s to 90% in the 21st century. The advances in the treatment have allowed biological risk stratification in children **[3]**.

The cause of a disease and its abnormal conditions are still under research. The reason behind ALL could be the exposure to ionizing radiation, benzene, or exposure to radiotherapy and chemotherapy, which causes mutations in the genetic material or DNA. Polymorphic variants of genes ARD5B, IKZF (the genes encoding Ikaros protein) in the somatic cells are associated with a high risk of ALL **[4, 5]**. The rare germline mutations in the genes of ETV6 (translocation-Ets-leukemia virus) and p53 (gene that produces a protein responsible for cell division and cell death) are predisposed to the development of leukemia. ALL is not a heredity disease, and there are no tests available that can be performed prior to the birth of the fetus. The epidemiology of ALL is predominantly found in children with ataxia-telangiectasia, neurofibromatosis type 1, Bloom syndrome, and trisomy 21 (Down syndrome). The diagnosis in infants lesser than one year is not very favorable **[6, 7]**.

Philadelphia Chromosome (Ph+) is a fusion gene that is formed when pieces of chromosomes 9 and 22 break off and switch places. The ABL gene from chromosome 9 joins to the BCR gene on chromosome 22, to form the BCR-ABL fusion gene. The changed chromosome 22 with the fusion gene on it is called the Philadelphia chromosome. This BCR-ABL fusion gene is found in most patients with ALL. It is more prevalent in the adult ALL rather than paediatric ALL. The symptoms are similar to that of standard ALL, such as fevers, weight loss, enlargement of the liver or spleen, bone pain, enlarged lymph nodes,

bruising and abnormal blood cell counts **[8, 9]**. Once the patient is diagnosed with ALL they further undergo special tests to understand the genetic mutations in the specific genes of cancer cells. The Ph+ is one of the most typical genetic mutations identified in the diagnostic tests. However, the Ph+ ALL is identified only after 2 weeks of confirmation of ALL **[10]**. Treatment for patients below 18 years who are diagnosed with Ph+ ALL mostly fails and leads to death. Tyrosine kinase is an enzyme that is involved in many activities for the normal functioning of the cell. However, some dysregulation may lead to the progression of cancers. By inhibiting the activity of tyrosine kinase, the cancer cells are destroyed. Tyrosine kinase inhibitors are widely used in targeted therapy such as dasatinib (Sprycel) or imatinib (Gleevec) for the treatment of people with this abnormal chromosome; especially more promising on children younger than 12 years. Research is still on to identify the treatment failure for paediatric Ph+ ALL **[11, 12]**. Improvements in medications and new drug therapy are still on close watch. This paper concentrates on the treatments and the recent novel methods used for the treatment of ALL.

TREATMENTS FOR ALL

According to the National Comprehensive Cancer Network (NCCN) guidelines for patients on ALL when concentrating on treatment, the response depends on each individual and their remission towards the treatment. When a treatment is given for ALL, and there are no signs of the disease does not mean that ALL has been completely cured **[13, 14]**. The patient must be further diagnosed for the lymphoblasts count. When the count is 20% or lesser, it is considered safe; however, it is likely that there will be the presence of 2/10 lymphoblasts in the bone marrow. When the count is below 10%, the patient is closely watched until the recommended treatment completely destroys the blast cells **[15]**.

There are three phases of treatment offered to the patients. The first phase would be the induction, where the patient spends a couple of days in the hospital receiving the multidrug combination chemotherapy with steroids treatment. The target is to reduce the blast cell count below 5%. If the treatment fails, the patient is put on a bone marrow transplant which is the only alternative to keep the patient alive. After several bone marrow tests with PCR and flow cytometry the treatment enters into the second phase **[16, 17]**. The second phase of treatment is consolidation. The remaining cancer cells (below 5%) will be treated with the prescribed drug. The treatment depends on the severity of cancer, age, and the reaction towards the drug

given to the individual. The third or the last phase is maintenance chemotherapy which is a long-term treatment that aims to stop the reoccurrence of cancer **[18]**.

The chances of recovery factors of some regimens during the induction phase may include the patient age, cyclophosphamide, L-asparaginase or a higher dose of methotrexate or cytarabine (ara-C) drugs **[19]**. Considering the age factor, the dose of the drugs for the induction treatment is invariably the same. However, the doses might vary under special cases. The major hurdle in the induction treatment is to stop the leukaemia cells from spreading to the CNS by a treatment called the prophylactic CNS treatment. If the cancer has already spread, then an intrathecal chemotherapy injection is directly intercalated into the CSF. Mostly the drugs include cytarabine or a steroid such as prednisone which can be administrated via lumbar puncture or intravenous therapy. If the chemotherapy with the above-mentioned drug regimen does not lead to remission of the leukaemia cells, the next option for survival would be stem cell transplant (SCT). But, the only risk behind this procedure is that a good donor match will always be the patient sibling (allogenic stem cell transplant). If the patient does not have a sibling, then rarely autologous SCT works. Even though the risks are high, this could be the only option **[13, 14]**.

Chemotherapy

Chemotherapy is the first and foremost treatment given to any patient with ALL. It is well comprehended that the treatment involves the use of several combination drugs to kill the lymphoblasts and stop the cells from further division. There are different modes of administration of the drug, and often, it is given orally as pills or in the liquid form, which is usually given at home. Sometimes depending on the observation by the physicians, the drug is subjected subcutaneously, intramuscularly, intravenously, or directly into the CSF fluid, otherwise called intrathecal chemotherapy, which is suggested for the patients whose brain and spinal cord is with leukaemia cells **[13, 14]**.

There is another method in chemotherapy using alkylating agents where the DNA is damaged using chemicals or drugs and the most commonly used drug is cyclophosphamide. Anthracycline is another class of drug used in cancer treatment which has its own limitation since it causes cardiotoxicity. Other kinds of drugs which are used for the treatment are daunorubicin and docorubicin. The antimetabolites drugs prevent the building blocks of DNA, most

common drug used here is cytarabine, fludarabine and clofarabine **[18, 19]**.

Enzyme therapy

Enzyme therapy is one the widely used treatment method for ALL. The two major enzymes used are Asparaginase and Pegaspargase. The interesting fact about human cells is that it needs the enzyme Asparagine Synthetase (ASNS) to survive, the white blood cells in our body produces its own amino acid called the asparagine **[20, 21]** which helps for the survival of normal cells. The cancer associated WBC do not produce ASNS. Here, the asparaginase enzyme is introduced into the blood stream which works quickly on asparagine and hydrolyses the asparagine causing the cancer cells to breaks down easily or leads to death.

Pegaspargase is another enzyme which is often used in enzyme therapy. Pegaspargase is the modified form of the enzyme L- asparagine amidohydrolase, which converts asparagine into aspartic acid and ammonia. Enzyme therapy is more useful as it can avoid the side effects of chemotherapy such as muscle wasting, vomiting, body pain and exhaustion. It is considered better than radiation therapy since it can avoid the scar tissue breakdown **[22 - 24]**. Here, the patient recovery is much faster than other therapies.

Steroids

Steroids are used for the treatment of ALL, especially with a class of steroid hormones called corticosteroids. Steroids reduces the inflammation and suppress the immune system **[13]**. Glucocorticoids work through Glucocorticoid receptors to arrest growth and induce apoptosis in lymphoid tissue. Glucocorticoids are amazingly effective in this role, and have been deployed as the cornerstone of lymphoid cancer treatment. They are naturally made by our bodies in small amounts produced in the adrenal glands which control many functions. Methylprednisolone, prednisolone and dexamethasone are few types of steroids used for the treatment of ALL **[14]**, despite an incomplete understanding of the mechanism of action of glucocorticoids, it is clear they are of great clinical value in the treatment of lymphoid.

Plant alkaloid therapy

Plant alkaloids are chemicals derived from the plants. They are cell-cycle specific as they have the ability to stop the cell division of cancerous cells. They play a role in every stage of the cell cycle but works more efficiently during the synthesis and mitotic stage. Alkaloids bind to the microtubule proteins during metaphase causing a mitotic arrest which causes the cells to inhibit cell division and lead to cell

death. Vinca alkaloids, taxanes and epipodophyllotoxins play a significant role and are the most commonly used plant derived drugs **[25, 26]**.

Radiation therapy

This therapy uses high energy x-rays to kill the cancer cells. It destroys the DNA of the cancer cells and prevents them from further growth or reproduction **[13]**. The major side effect is that they kill the healthy cells as well. Recent studies have proved that upon minimizing the scattering effect towards the healthy cells, kills only the targeted cancer cells. Radiation therapy is not the sole plan of treatment. It forms a part of the treatment of stem cell transplant or chemotherapy as it is used to ease the body aches or discomfort of lymph-nodes or enlarged liver or spleen **[14]**.

External radiation therapy is mostly focused on the high energy x-ray beams on the external body of the patients with ALL. Most of the radiation machines use photon beams which can reach deep tumours at various angles on the body, but generally at lower doses since it can damage healthy cells also. Few cancer centres use proton beam radiation which is made up of positive charges that can minimize the damage to the healthy cells. The organs do not sustain much damage and can be recovered soon. The external radiation therapy is given when the physician suspects the spread of cancer cells towards the brain, spinal cord or even testicles. This therapy is named as the prophylaxis treatment or palliative therapy and is mostly given to relieve symptoms and improve the quality of life of the patients **[27]**.

Targeted therapy

It is a novel method as it targets the cancerous cells throughout the body with minimal side effects. This therapy studies the reasons and ways the cancer cells grow, divide and move around the body. They even target the cancer cells and destroys the molecule which assists them to grow **[28]**.

Tyrosine kinase inhibitor (TKI) drugs are commonly used in targeted cancer therapy. They block the signals which is used for the growth of cancerous cells and stops the spread of cancer cells throughout the body. This therapy is usually given alone or in combination with chemotherapy. Tyrosine kinase are proteins which are very crucial for many cell functions. However, when it undergoes mutation, it may stimulate the cells to undergo malignancy. They are made of BCR-ABL1 gene which produces a protein leading to uncontrolled division of cells. The TKIs block this reaction by inhibiting the transfer of phosphate group to the protein which subsequently inhibits the cell signalling cascade thereby preventing the

unlimited cell division. Generally, the TKIs therapy is not given to patients who already have lung and heart disorders or other unpredictable mutations, as it may cause toxicity and may not be of any help when treated. Common TKIs which are used for the treatment are Bosutinib (Bosulif), ponatinib, (islusig), Imatinib (Gleevec) etc.

There are 3 generations of drugs which has improved over the years and can be used to target specific types of mutations. This certainly means the fourth-generation drugs will be more specific, effective and faster in their treatment regimen. The drug Imatinib which is a first-generation drug has a very low intensity with reference to toxicity when compared with second-generation (dasatinib, nilotinib, bosutinib) and third-generation TKIs (ponatinib) **[13]**. Therefore, this drug can be certainly used for the ALL patients who are older and have other major health issues. The dosage will be planned accordingly for every individual based on several factors which can be termed as personalized or tailor made **[29]**.

If a patient is under a TKIs treatment he/she should avoid the intake of herbal supplements since it may induce drug interactions which would affect the treatment process or the working ability of the prescribed drug. These supplements include turmeric, green tea extract and gingko biloba. An antacid or an antidepressant stops the ability of TKI drugs to carry out its function effectively **[30]**.

Immunotherapy

After prolonged use of stem cell transplant and small molecule inhibitor the cancerous cells still survive. Immunotherapy is found to improve the high incidence of relapse for patients who have hemotological malignancies because the treatment is not a conventional one. There are studies which have been done to check the immunological features such as antibody – drug conjugate, unconjugated antibodies, NK cells, chimeric antigen receptor (CARs) and bi specific antibody.

For decades immunotherapy was given to the patients to improve their health and the immune system but recent discoveries showed the benefits of immunotherapy against cancer cells. The bi specific antibodies like blinatumomab binds to CD19 (Cluster of Differentiation) during B cell differentiation and neutralize B cell malignancies. There are notable potency when the CD3-CD19 bi specific T-cell engage blinatumomab and when the B-cell acute lymphoblastic leukemia (B-ALL) engage with (CARs) targeting CD-19 in the treatment of immunotherapy there were impressive effects. The other targets are CD22 which is promising for

immunotherapy of (B-ALL). However, there is not much information currently on the effects of the same with the toxicity studies when CD-22 is targeted on the CAR -T cells **[31- 33]**.

Blinatumomab (Blincyto)

It is a unique monoclonal antibody which has two completely different proteins where one part attaches to the CD-3, a protein which is found to be on the immune cells and another attaches to the CD-19 protein which is found on the B cells that includes the lymphoma cells. When these two proteins bind to the immune cells and the cancer cells they are brought together and hence they fight with the cancer cells. This treatment is given to the patients intravenously for 28 days which could have life threating or other serious side effects. Some of them include passing out, confusion, headache, low potassium levels and low white blood cell count.Inotuzumab ozogamicin (Besponsa) **[34]**.

Some leukaemia cells have CD-22 on their surface protein. This particular drug is an Anti-CD-22 antibody linked to the chemotherapy drugs. When the cell division is about the happen there is a signal called homing signal which is passed. This brings the targeted cancer cells and chemodrug together and destroys them. This treatment is safer than the other one as it gives some common side effects. But more serious ones are lowering the blood cells count and high bilirubin levels in the blood causing liver damage.

Rituximab (Rituxan)

It works against the CD20 protein found on the surface of B cells and blood cells with cancer. It helps in the recognition of the cancer cells by our immune system and destroys it. It also destroys the cancer cells by itself. It is also involved in suppression of the immune system of the skin causing some side effects.

CD19 Targeting CAR T-cell therapy

The T cells are separated from the patient's blood and they are altered genetically in vitro which is later known by the term Chimeric Antigen Receptors (CARs) is introduced back into the patient's blood system. Now the receptors attach itself to the protein part of the leukaemia cells, multiplied and reinfused back to the blood where it can search for leukaemia cells to attack them **[35, 36]**.

Tisagenlecleucel (Kymriah)

This particular treatment is mostly given to the children or patients below 25 years to treat the B cells of ALL. The drug is infused intravenously and could cause serious side effects. It is given to patients who are already undergoing chemotherapy treatment **[31, 32]**.

Stem cell transplant

Here, the healthy bone marrow stem cells are introduced or transplanted into the patient who has ALL. Thus, it triggers new stem cells to grow and retain in the patient's body and improve the immune system. There are two major types of stem cell transplants namely, autologous and allogenic stem cell transplants. In autologous stem cell transplant, the stem cells are collected from the patients by harvesting their blood, frozen and stored until needed. This is generally used when the patient has undergone a chemotherapy **[33]**. In allogeneic stem cell transplant, it is carried out when the stem cells have been harvested from a matching donor's blood. The patient has to undergo a Human Leukocyte Antigens (HLA) test and they are matched with the blood and tissue samples of the donor.

Before the stem cell transplant treatment, the bone marrow cells will be destroyed and this procedure is called conditioning. It creates a room for the new healthy donor stem cells. This can also weaken the immune system so that the body does not attack the transplanted cells. Chemotherapy or radiation therapy are used for the conditioning procedure. Soon after this treatment, the healthy stem cells will be transfused intravenously. This procedure can take several hours thus, from this point the new healthy blood cells grow in the bone marrow and this procedure is called engraftment which takes 2 to 4 weeks depending on the individual.

Soon after the transplant the patient is closely monitored to check for the needs of platelets and RBC transfusions. If the patient has minor to serious side effects, the patient is kept sterile and given antibiotics to avoid infection as the immunity is low. Until the cells are engrafted the patient is generally tired and weak.

The allogenic transplant has an advantage as the healthy cells from the healthy donor has been transplanted but finding a matching donor is a challenge. Hence, autologous transplant has been suggested **[13]**. Another major disadvantage is that the donated cells attack the patient's cells and tissues if there is a failure during grafting of cells. It takes upto 3 months to recover from this condition. Caregivers induce few medicines to recover from this condition called graft-versus-host-disease **[14, 34]**.

CONCLUSION

Like any other disease cancer management and treatment is very challenging with a big team of professionals working with dedication globally. The team includes an oncologist, a haematologist and an infectious disease expert. Other than this, the primary care

provider and nurse who is expertise in the oncology department may be present to follow up after treatment and get the consolidated report to the oncology team. The patients are closely observed since they are highly prone to infections. Despite being in supportive care there are chances of patient death due to the treatment toxicity.

It is vital to observe the patients who underwent chemotherapy treatment since there is a high chance of Tumour Lysis Syndrome which leads to release of intracellular elements such as uric acid, potassium, phosphorus and calcium in large amounts that could result in toxicity and subsequently renal failure. However, a pre-treatment with steroids and fluids prevents the Tumor Lysis Syndrome. Even after significant treatment modalities, ALL can relapse; it is prudent to treat the side effects along with the cancer treatment.

For better outcome and the patient survival, lethality should be focused. There should be reduction in the lowering of radiation therapy and more efficacious and harmless CNS-directed drug therapy for the patients who undergo CNS relapse.

It can be concluded that ALL involves both T and B lymphocytes of which 90% of the cases involves T-lymphocytes. There is a normal regimen of chemotherapy which is followed for every patient that involves induction, consolidation and maintains phase. Non-Hodgkin lymphoma which is one of the rare and aggressive types of Lymphoblastic lymphoma can be cured 90% during the early stages (stage 1 or 2), while 80% survival rates are noted when treated in the advanced stage (stage 3 and 4). The prognosis and survival rates are based on age of the patient, CNS involvement, cellular morphology and chromosomal abnormalities. The more involvement of these factors, the lower the prognosis and low survival rate. The best treatment method cannot be judged since the condition of each patient and the stage of disease will be different; it is left to the discretion of the physician to determine the best treatment modality based on patient's disease progression and other factors.

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