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DIFFERENT TYPES OF DIAGNOSTIC AND TREATMENT METHODS FOR ACUTE LYMPHOBLASTIC LEUKEMIA AND APPLICATIONS OF EXTRACELLULAR THERAPEUTIC ENZYME L-ASPARAGINASE

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ABSTRACT: The extracellular L-Asparaginase is an amidase group enzyme. In recent years enzymes gained greater importance in clinical research. The enzyme's capability to convert L-Asparagine into Aspartic acid and ammonia is the motivation after its anti-cancer action. ALL is a type of hematologic cancer that mainly affects children at the age of 2 to 10 years. L-asparaginase is a basic constituent of ALL and Hodgkin's lymphoma treatment. Because its foreword into pediatric treatment procedures in the 1960s, continued existence rates in children have steadily increased to almost 90%. Juvenile and adolescent patients diagnosed with ALL at the age group of 15-39 years have historically had poorer outcomes. Different diagnostic methods are available for ALL like blood tests, Bone marrow tests, Imaging tests and Spinal fluid tests. Apart from its medical applications, it is broadly used in the food industry to engage in acrylamide, a probable human carcinogen, and production in carbohydrate-rich foods cooked at high temperatures. L-Asparaginase plays an important role in the biosynthesis of the aspartic family of amino acids. L- Asparaginase has also been used to develop a diagnostic biosensor.

INTRODUCTION: Cell morphology, immuno-phenotype, and genetics/cytogenetics are the established diagnostic criteria for acute lymphoblastic leukaemia (ALL), as specified in the 2008 WHO classification of lymphoid neoplasms [9]. In paediatric oncology, L-asparaginase is the prescribed medicine for acute lymphoblastic leukaemia therapy, with more than 90% of children recovering completely within four weeks.

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L-anti-leukemic asparaginase's effect is based on the fact that tumour cells require a large amount of L-asparagine [2]. Prostate, colorectal and lung cancers are the most frequent cancers in developing countries. Men are more likely to acquire lung, colon, and liver cancers, while women are more likely to develop breast, cervical, and stomach cancers in poorer countries.

External carcinogenic factors, including cigarettes, chemicals, radiation, and infectious organisms, as well as internal factors like hereditary mutations, hormones, and immunological state are the leading causes of cancer [3]. Carcinogenesis is a multistage process involving many genetic and epigenetic processes (initiation, promotion and advancement). Ionizing radiation's health consequences were

discovered shortly after X-rays were discovered in 1895. Epilation was investigated first, followed by skin burns. Tissue responses have become more common since the advent of high-voltage X-ray tubes and their use in medical clinics. Tissue reactions are a result of huge amounts of radiation being absorbed into the body are caused by inherited genetic abnormalities [1].

The majority of ALL cases in the United States occur in children, with a frequency of 3 to 4/1,000,000 at the age group of 0 to 14 years and 1/100,000 in 15 years children and older. ALLs account for 75% of all acute leukemia's in children, accounting for 34% of all malignancies in this age range, with a peak incidence of 2 to 5 years of age. Adults have a substantially lower percentage, who are more likely to develop acute myeloid leukemia (AMLs) and chronic lymphocytic leukemia. Male dominance is minor across all age groups, with white children having a significantly higher prevalence [5].

Childhood Acute Lymphoblastic Leukemia: ALL, also known as acute lymphocytic leukemia or acute lymphoid leukemia, is a kind of leukemia marked by an excess of malignant, undeveloped white blood cells are identified as lymphoblasts. Survival rates for children with acute lymphoblastic leukaemia (ALL) have improved over the last five decades as chemotherapy for all patients has been intensified. By the 1970s, one-third of patients had been cured with moderately intense therapy, indicating that some patients' treatment may be lowered. The strongest predictor of survival is early therapy response, as measured by minimal residual disease (MRD), which was first demonstrated in the late 1990s by several groups, including the Associazione Italiana Ematologia ed Oncologia Pediatrica (AIEOP)–Berlin-Frankfurt-Münster (BFM) and the Dutch Childhood Oncology Group (DCOG) [4].

Symptoms of Acute Lymphoblastic Leukemia Include: Because of the proliferation of leukemia cells in the bone marrow, the manufacture of common blood cells is reduced. By the lack of red blood cells, the children become tired and lethargic because of anemia and the minute amount of platelets in their blood. Children's bruises and bleeding may take longer to heal; infections can occur when the body has a low number of normal white blood cells. In general, a child is likely to be ill and may complain of aches and pains in the limbs or swollen lymph glands [12]. At first, the symptoms are similar to those of a viral infection, but if they persist for more than a week or two, the diagnosis is usually changed [6].

Diagnosis: Acute lymphocytic leukemia is diagnosed using the following tests and procedures.

1. Blood Tests: An excessively high or low amount of white blood cells, inadequate red blood cells, or insufficient platelets may be shown by blood testing. Blast cells, which are immature cells found in bone marrow, can also be detected with a blood test.

2. Bone Marrow Test: A needle is used to extract a sample of bone marrow from the hipbone or breastbone during the bone marrow aspiration and biopsy. The sample is transported to a laboratory where leukemia cells are studied. Lab doctors classify blood cells into distinct categories based on their size, shape, and other genetic or molecular traits.

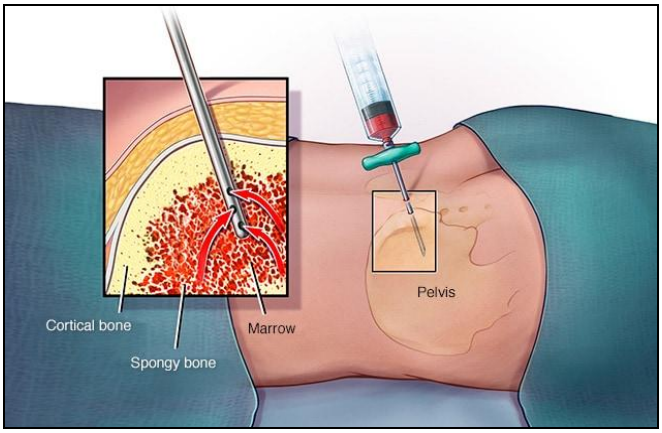

FIG. 1: BONE MARROW SAMPLE COLLECTION AND EXAM (MAYO CLINIC, ROCHESTER)

They also search for specific alterations in cancer cells to see if the leukemia cells came from B or T lymphocytes. This information aids your doctor in formulating a treatment plan.

3. Imaging Tests: A computerized tomography (CT) scan or an ultrasound scan, which is similar to an X-ray, may be used in imaging examinations to identify if cancer has progressed to the brain, spinal cord, or other regions of the body.

4. Spinal Fluid Test: A lumbar puncture test, often known as a spinal tap, is a procedure that collects a sample of the spinal fluid around the brain and spinal cord. The sample will be analyzed to see if cancer cells have spread to the spinal fluid.

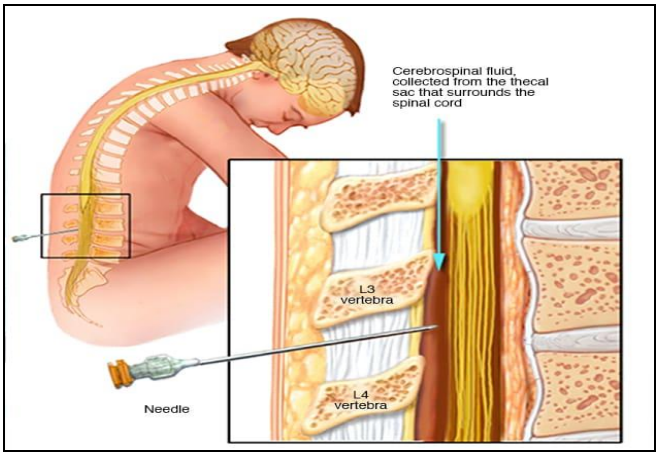

FIG. 2: SPINAL SAMPLE COLLECTION (LUMBAR PUNCTURE) (MAYO CLINIC, ROCHESTER)

Different Types of Treatments for Acute Lymphocytic Leukemia: The duration of acute lymphocytic leukemia treatment can vary from 2 to 3 years, depending on the patient's circumstances.

1. Surgery: In the treatment of acute lymphocytic leukemia, surgery has a very limited role. Surgery will not be able to treat this type of cancer when leukemia cells develop rapidly in the bone marrow and many other organs *via* the blood. Because a bone marrow aspirate and biopsy can usually confirm leukemia, surgery is rarely used to diagnose ALL, except possible lymph node biopsy [8].

2. Radiation Therapy: The majority of cancer patients will receive radiotherapy or radiation therapy for cancer at some point throughout their treatment. Radiotherapy, often known as radiation therapy, is a cancer treatment that involves the use of high-energy radiation or ionizing radiation to harm tumour cells, eliminate their capacity to divide, and prevent them from spreading. Radiation therapy for cancer can be provided from an external source, using special machines, or from within the body, using tracers or radioactive compounds injected or eaten to reach the tumor's site. Radiotherapy can be used alone or in combination with chemotherapy and/or surgery as a curative therapy or to ease pain and other symptoms caused by cancer [7]. The most common type of radiation for ALL is External beam radiation therapy; in this case, an instrument administers a beam of rays to a particular section of the body. Radiation therapy can have various adverse effects depending on the dose and the location of the radiation. They include:

- ✓ Skin changes in the treated region might range from mild redness to burning and peeling.
- ✓ Fatigue (tiredness)
- ✓ Nausea and vomiting
- ✓ Hair loss in the affected area
- ✓ Constipation
- ✓ Lowered blood cell counts, which can cause weariness, shortness of breath, and an greater risk of infection (due to decreased amount of red blood cell) (from low white blood cell counts).

3. Chemotherapy: Chemo treatment uses medications to treat cancer. Induction chemotherapy, followed by intensification (consolidation) chemotherapy, is a standard chemotherapy treatment for acute leukemia (AML and ALL). A mixture of medications is used in induction chemotherapy to kill as many leukemia cells as possible and restore normal blood counts. These medications are usually injected into a vein, muscle, or under the skin or taken by mouth. The medications are carried throughout the body via the bloodstream and reach cancer cells all over the body. Therefore, chemotherapy is beneficial for malignancies that have spread throughout the body, such as leukemia. Because most chemotherapy doesn't reach the area around the brain and spinal cord very well, it may be necessary to inject it into the cerebrospinal fluid to kill cancer cells there. Intrathecal chemo is the term for this procedure. A mixture of anti-cancer medications is used in chemo for acute lymphocytic leukemia (ALL). They are normally delivered in three phases over the period of around two years [11]. Vincristine (Oncovin) or liposomal vincristine (Marqibo), Daunorubicin (Cerubidine) or doxorubicin (Adriamycin), Cytarabine (cytosine arabinoside, ara-C, or Cytosar), L-asparaginase (Elspar) or

PEG-L-asparaginase (pegaspargase or Oncaspar), E (Decadron) People usually receive many of these medications at different periods throughout their treatment, but not all of them [12].

Chemotherapy side effects vary depending on the type and dose of medications used and the length of time they are administered. Hair fall, oral sores, loss of taste, and vomiting are common adverse effects. Diarrhea, Infection risk is higher (due to low white blood cell counts), Bruising or blood loss that is easy to come (due to low blood platelet counts), tiredness (due to low red blood cell counts), Hands and feet numbness, tingling, and weakness (from nerve damage) [14].

4. Targeted Therapy: Latest medications specifically target precise regions of malignant cells have been discovered in recent years. These medications function differently than traditional chemotherapy (chemo). Different (and less severe) side effects are common. Targeted therapy is a term used to describe these medications. In some situations of acute lymphocytic leukemia, some of these medicines may be beneficial. About one in every four adults all patients had leukemia cells with the Philadelphia chromosome. This aberrant chromosome is generated when material from chromosomes 9 and 22 is swapped. This results in the development of an innovative gene known as BCR-ABL. A different type of leukemia, chronic myeloid leukemia, has the Philadelphia chromosome and the BCR-ABL gene (CML). The BCR-ABL gene causes cells to produce an inappropriate protein that aids in cell growth. This protein has been targeted with drugs. Imatinib (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif) and ponatinib are examples of tyrosine kinase inhibitors (or TKIs) (Iclusig). Although these medications were developed to treat CML, some have been found to be beneficial in the treatment of patients with all who carry the Philadelphia chromosome [13].

These medicines are taken as pills daily. Constipation, vomiting, muscle soreness, exhaustion, and skin problems are all common adverse effects. The majority of these are minor. Swelling around the eyes, hands and feet is a frequent complication. Low red blood cell and platelet counts at the beginning of treatment are also possible side effects. With a larger than average doses of the medicine, all of these side effects worsen. Other, more serious complications may develop, depending on the medicine [8].

5. High-dose Chemotherapy and Stem Cell Transplantation: Acute lymphocytic leukemia (ALL) is a type of cancer that cannot be cured with standard chemotherapy. Even though higher chemo drug doses may be more effective, they are not used since they may cause long-standing serious bone marrow destruction. Because new blood cells are generated in the bone marrow, low blood cell counts can cause lifelong illnesses, hemorrhaging, and other issues. Doctors can apply stronger doses of chemo (often combined with radiation) to destroy cancer cells after a stem cell transplant. After these therapies are completed, the patient receives a bone marrow transplant of blood-forming stem cells [15].

Types of Transplants:

There are Two Kinds of Stem Cell Transplants: Allogeneic stem cell transplantation entails using stem cells from someone else. This is the most commonly used type of transplant in the treatment of ALL. To prevent the chance of serious issues with an allogeneic transplant, the donor's tissue type (also known as the HLA type) should be as close to the patient's tissue type as possible. If the donor has the same tissue type as the patient, it is generally a sibling. If no siblings are a good match, the cells may come from a stranger who has volunteered to donate their cells and is HLA-matched. Some individuals cannot receive this type of transplant because a suitable donor is unavailable. Patients who cannot receive an allogeneic transplant due to a lack of a matched donor may consider an autologous transplant. The problem is that leukemia is bone marrow and blood condition, there's a risk of returning leukemia cells to the patient with stem cells. In the lab, purging may be used to remove leukemia cells from samples and reduce the risk [13].

6. Enzyme Therapy for Cancer: Cancer treatment has come a long way in the previous 50 years, yet it is still difficult in some circumstances. Therapeutic targets are usually distinctive characteristics of cancer cells that separate them from normal cells and can be addressed with the right medications.

In existing years tumor therapy has extremely relied on enzymes as they are low molecular weight protein molecules. The enzymatic approaches are a very promising future in cancer therapy and various enzymes are active against different types of cancers by acting through different mechanisms. Special metabolic requirements are expressed by tumor cells; these are exploited by metabolite-depleting enzymes concerning healthy tissue to target tumor cells selectively. Elevated requirement of certain metabolites by auxotrophic tumor cells allows only selective anti-tumor enzymes. Tumor cells, especially lymphatic cells and certain other tumor cells, require large amounts of L-Asparagine to keep up with their rapid malignant growth, but they lack or contain a low level of asparagines synthetase do not synthesis L-Asparagine denovo [16].

Role of L-Asparaginase in Targeted Enzyme Therapy: L-Asparaginase has anti-tumor activity and is the first enzyme intensively deliberate in human beings. It is used for the cure of malignancies of the multi organs.

This enzyme is extensively used as a therapeutic agent for treating acute lymphoblastic leukemia in children and suggested the improvement of this enzyme as a potent anti-tumor and anti-leukemic drug [26].

Applications of L-Asparaginase

1. As an Antitumour Drug: In the treatment of various types of blood cancer such as acute lymphocytic leukemia (ALL, mainly in children), Hodgkin disease, acute myelocytic leukemia, acute myelomonocytic leukemia, chronic lymphocytic leukemia, lymphosarcoma treatment, reticulosarcoma and melanosarcoma surrounding tissue, L-asparaginase is a therapeutically important protein. Early research indicated that intraperitoneal injection of guinea-pig serum, which contains a high concentration of asparaginase, led to a significant reduction in the size of Gardner lymphosarcomas in mice. Later, in Escherichia coli, a powerful source of L-Asparaginase was discovered. Since then, the human malignant disease has been treated using L-asparaginase produced from *E. coli* E. C. 2. [17].

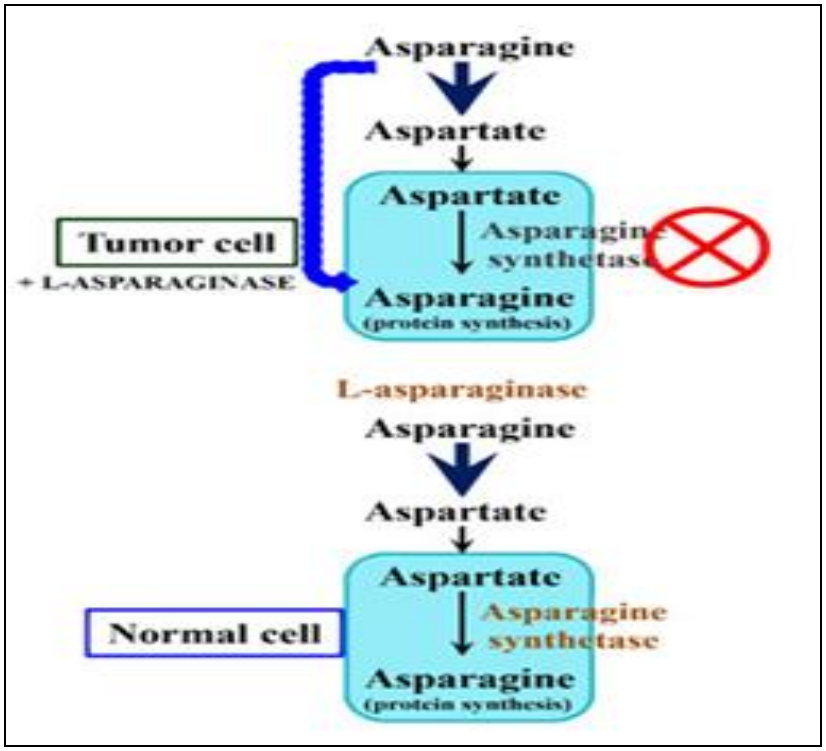

FIG. 3: ANTI-NEOPLASTIC ACTION OF L-ASPARAGINASE 24

A-ase, ASN-asparaginase, Colapase, Crasnitin, Elspar, Crisantas, Pasum, PEG-asparaginase, and Pegasparagasum are some of the commonly accessible L-asparaginase brands [25].

2. Role in Amino Acid Metabolism: The enzyme also acts as a very critical function in the biosynthesis of the aspartic family of amino acids. Because they excrete huge amounts of diverse

amino acids, corynebacteria that produce amino acids are of great industrial importance. Commercially important amino acids, such as lysine, threonine, and methionine, are synthesized from aspartic acid, limiting lysine and/or threonine production under normal physiological conditions. Apart from Kreb's cycle (which uses glutamic acid as an amino acid donor), asparaginase converts asparagine to aspartic acid. L-Asparaginase was shown to be constitutively generated, and its function may be that of an overflow enzyme, converting surplus asparagines into aspartic acid, the precursor of lysine and threonine. After fermentation of *C. glutamicum* to produce lysine, an extremely active L-asparagine was discovered [19].

3. Making Biosensor: A biosensor is an analytical instrument that quantifies a chemical compound by combining an organic entity with an indication detector. A proper physicochemical, optical, electrochemical, thermometric, piezoelectric, or magnetic transducer is utilized to detect or measure the analysis. Several spectroscopy techniques are now employed for L-asparagine investigation, including XRD, XPS, SEM and TEM, but their high cost and time-consuming procedures make them undesirable. Biosensor technology can be a reliable, low-cost, and user-friendly option in these situations. Asparagine biosensors can be used to detect asparagine levels in various food samples or to monitor asparagine levels in ALL and lympho sarcoma patients' blood serum samples [20]. The basic mechanism behind biosensor is based on the change in pH and resultant color and absorbance shift following ammonia release during the asparagine hydrolysis. The main biosensor approach detects asparagine online and gives a highly specific, simple and speedy response.

4. Role in Food Processing: Food processors utilize L-asparaginase as well. Recent improvements in food technology have revealed that fried and baked foods (especially fried potatoes) contain a large quantity of acrylamide (a carcinogenic toxicant), which is generated when asparagine reacts with reducing sugars. Acrylamide is a neurotoxin associated with cancer in humans. Acryl amide is predominantly generated in the food industry via heat-induced interactions between the -amino group of the free amino acid asparagine and carbonyl groups of reducing sugars such as glucose during baking and frying [21]. Before frying or baking, asparaginase is used to avoid the production of acrylamide in potato slices, and bread dough shown in **Fig. 2** [22]. Baking industries use asparaginases from *Aspergillus oryzae* and *Aspergillus niger*.

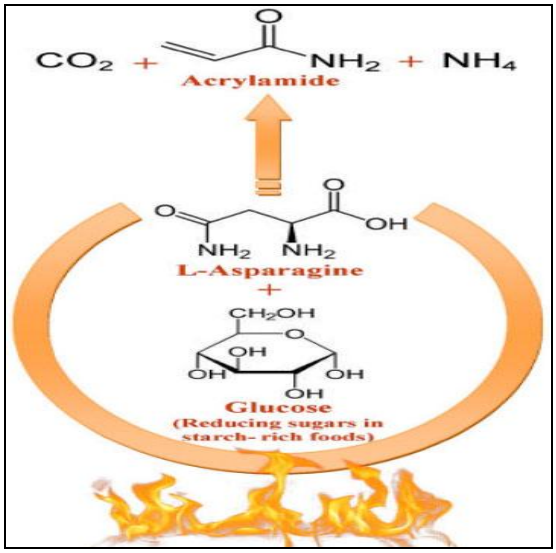

FIG. 4: HEAT FROM ABOVE 120°C FOR ACRYLAMIDE FORMATION (NOURA EI AHMADI EI NAGAAR ETAL, 2014)

These enzymes work best in a pH range of 6.0-7.0 and at a temperature between 40° and 60 °C. A wide temperature and pH range are advantageous for baking enzymes because temperatures often exceed 120°C. There has been research on L-asparaginases derived from various sources (bacteria, fungi, plants, and animals). This means that L-Asparaginases can be used for medicinal and industrial purposes [23].

CONCLUSION: In current days, many diseases and medical problems pose a significant risk to humans. Cancer is the king of diseases and the most serious challenge to biomedical scientists. The diagnosis, treatment, and therapies vary with different types of cancers. Different types of tests are available for ALL diagnosis blood test, bone marrow test, imaging test, and spinal fluid test here bone marrow test is an important test. Cancer treatment has highly relied on enzyme therapy in recent years because they are very low molecular weight molecules. Apart from pharmaceutical benefits, it is being used in the food industry to efficiently hinder acrylamide production in carbohydrate-rich food and involve the

biosynthesis of the aspartic amino acid family. L-Asparaginase also performs in Biosensor making.

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