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Review Article

Enzyme Vs Chemotherapy for the Treatment of Acute Lymphoblastic Leukemia

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Abstract

Cancer is re-unowned by production of neoplastic cells. In cancer, un-developed cells are produced by bone marrow. After their entry into the blood normal cells are un-able to produce and cause anemia. Several oncogenes, including the *p53, c-fms and Ras genes,* can be activated by point mutations that change the amino acid sequence in the critical portion of protein. L-asparaginase is an enzyme which, by hydrolysis, produces aspartic acid and ammonia. It is used as medicine and in the food industry. It acts as a chemo-therapeutic agent to diagnose the ALL and lymphoproliferative syndrome. The level of Asparagine reduced in plasma decreases the formation of Deoxy ribonucleic acid and Ribonucleic acid. In ALL, asparaginase used in chemotherapy medicines for dealing the patients. it donates the important development in therapy results and helps achieve reform sullener approximately 90% of patients.

Keywords: Leukemia, Chemotherapy, L-asparaginase.

INTRODUCTION

Leukemia, a disorder in which bone marrow is formed and increase quantity of undeveloped cells. It inhibits the normal cells production and cause anemia. Leukemia is a common cancer in children which represent around one third of pediatric cancers. Around 3,800 children are noticed yearly in ALL and AML in America [4]. Modern treatment is used to cure 80 to 90% of children with leukemia than previous routines. Continuing and late-appearing secondary effects include losses to neurocognitive development, mental health, endocrine system function, and overall health [34].

Genetic factors do not change on this time scale, in youthful leukemia, environmental factors are important in etiology and raise their current tendencies [13]. Leukemia is of four types; Acute lymphoblastic leukemia is known as severe lymphocytic cancer and severe lymphoid cancer. It occurs at any stage [11]. ALL is the malicious explosion of lymphoid cells blocked at initial stage of variation. (ALL) is a diverse syndrome [7].

Chronic lymphoblastic leukemia is the kind of cancer which initiates from the cells and develop WBC's in bone marrow. In CLL, the cells developed partially but then not totally. These cells look like a normal cell and do not participate in causing infection. The tumor cells can survive longer unlike the normal cells [10]. Cytogenetic, morphological and molecular inheritance description are required to begin. Heterogeneity shows during multiple steps of normal lymphoid variation; leukemia can grow at any point [10].

Acute myeloid leukemia is caused by altering the DNA of newly developed marrow cell. After the development, tumor cells increase in number up to 11 billion. These cells also known as leukemic blasts; they don't work regularly. But they can live better than regular cells. Occurrence of leukemic blasts breaks the formation of normal cells ([57]. Chronic myeloid leukemia is also called chronic myelogenous leukemia. Quantity of chronic lymphoblastic leukemia cells in plasma increases due to uncontrolled growth of leukemia cells in marrow. CML doesn't totally inhibit the growth of developed RBC's, platelets or WBC's [1].

Pharmacogenetics of medicines are to manage the patients with ALL, it includes Gluco-corticoids, tyrosine kinase inhibitors, vincristine, methotrexate and 6-mercaptopruine. ALL is a modification of undeveloped lymphoid lineages which is divided into B precursor cell cancer and T cell cancer precursor. In the mid-1960s ALL, has increased from less than 40% to 91% [53].

Typical treatment course is required for diagnosis of patients with precursor-type ALL. It persists for two to three years and consists of consolidation therapy, reduction induction treatment and maintenance [27]. After induction therapy, Consolidation therapy is given to eliminate the remaining leukemia cells. High quantity of methotrexate is normally used with 6-mercaptopurine attended by repeated doses of vincristine and glucocorticoids for twenty to thirty 30 weeks. Preservation treatment is normally sustained for two yrs [17].

The normal and numerous therapies are essential for the response of ALL and effect in toxicity that can contribute both to initial disease and death. Several issues have Opportunity to contribute the presence of severe side effects. The efficiency of drug treatment and toxicity are used for managing of ALL, exact inherited polymorphisms are recognized as serious variables [62].

In 1978, Asparginase was accepted for medical use in the America. L-Asparaginase is also found in several microbes such as Arcobacter, Bacillus, Pseudomonas, Serratia, Xanthomonas, Photobacterium [13], it has been shown that L-asparginase derived from E. carotovora and E. coli that shows anticancer action mainly against the ALL [37]. But maintenance of this enzyme protein for large time, overall, matching antibodies are made in tissues that cause anaphylactic shock and the neutralization of drug effect [22]. Asparaginase treatment related to severe effects that includes cerebro-vascular accident, pancreatitis and allergy. Hyper-sensitivity response is usually detected with native E. coli asparaginase.

Numerous kinds of cancer cells need L-asparagine for synthesis of protein, In the presence of l-asparaginase the essential growth factor is depressed by these proteins, therefore, it causes cytotoxicity of the cells of cancer. Asparaginase has anticancer properties that are connected to the attraction of an enzyme toward substrate and these factors disturb the rate of approval from the system [25]. Asparaginase synthetase (ASNS) is an enzyme that convert the of aspartic acid amine group and produce asparaginase. Cancer blasts are empty of Asparaginase synthetase, which explain values of different L-Asparaginase. Depending upon Initial research, Asparaginase synthetase activity is a pointer of L-asparaginase confrontation and in health studies [27].

REVIEW OF LITERATURE

Leukemia

Leukemia is a disorder of the blood making organs. They are noticed during inaccurate growth of leukocytes. In most patients, the cause of leukemia is still unknown. There are some factors which responsible for increasing the risk of disease. The degree of ALL is highest among the ages of three and seven and increasing another time after the forty age. The cause for this peak in initial youthful ALL remains undefined [34].

The risk of cancer is increased in those kids that have Down syndrome than those children that are without down disorder. About 10 percent kids with Down syndrome are born with temporary leukemia that determine within months of natural birth. Then, 1 to 2%, grow a malignant ALL that essential Chemotherapy by the age of four. While some recommendations have been planned that the cause for this bigger risk remains unknown. Similarly, an increase in cancer has been noticed in fighters of the nuclear bombing in japan. Whereas the risk linked with experience to lower level radiation is unclear. The contact to analytic X-rays of the infants during gestation rise the risk of cancer [2]. Some previous studies reveal that microorganisms are capable to be used as targeted delivery of different drugs [48].

Types of Leukemia

Acute Lymphoblastic Leukemia

In ALL, lymphoid cells are formed which block at an initial phase of differentiation. Acute lymphoblast leukemia is a heterogenous disease. This heterogeneity shows that at any period, leukemia can grow during the several stages of normal lymphoid difference [11].

Diagnostic methods

To finally establish the analysis of leukemia, examination of marrow aspirates smears is important. 5% blasts are present in normal marrow, while the leukemia marrow is frequently almost entirely penetrated by leukemia epidemics. Leukemia should be supposed in those patients that contain more than 5 percent blasts while caner should not be identified based on completely on smear of marrow that contain les then 25 percent blasts. At the time of analysis, it is difficult to attain bone marrow aspirate. This is typically due to the concentration of the damage cells in the bone marrow, but it can be caused by bone fibrosis, necrosis and infarction. ALL is recognized and at the IV stage of NHL 5 and <2 percent lymphoblast's are present in the marrow [44].

Quantity of WBC's (1/3 to one half have an early WBC's amount larger than 100,000 per mm3) and normal level of hemoglobin at the stage of analysis. ALL, is common in white kids than black kids, Difference in environmental contact and Diverse biology [14].

Treatment

Four treatment elements can usually be recognized in protocols of chemotherapy approved by international cooperative sets, these are maintenance therapy, consolidation / reinduction, CNS preventive therapy and induction. Biological Hetero-genetic, which described youth ALL, has directed to an increasing necessity to stratify the patients into risk groups and to deliver the risk-adapted treatment [46]. Hence, therapy has gradually become complex and today they are asked to high levels of association and knowledge to attain optimal outcomes. For these reasons, kids with ALL must be treated in centers that can suggest specialized staff and deliver up-to-date analytic tools and treatment plans [52].

Induction

The treatment provided in this phase purposes to eliminate the signs of the disorder and reestablish normal hematopoiesis. Complete reduction, the term used for the indication of this goal. Complete reduction in kids should not have physical sign of leukemia, regeneration of bone marrow and normal blood cell amount. Info on complete reduction position also contains the absence of noticeable CNS and extra medullary disorder by means of evaluable with physical inspection and CSF findings (around 2 to 3percent) [24].

Central Nervous System Preventive Therapy

Prevention of central nervous system reappearance has been a deep-rooted idea from 1960. With current therapeutic treatments, which consist of different modalities of defensive treatment of CNS, the rate of CNS decline is universally less than 5 percent.

Cranial treatment is usually not used for patients for a long period with good diagnosis; triple intrathecal chemotherapy and Intrathecal methotrexate alone and directed occasionally during maintenance chemotherapy and provides suitable CNS preventive therapy to patients**.** Usually, agents are intended to minimize the growth of drug resistance [50].

Maintenance therapy and duration of treatment

Mainly effective drugs as initiation mediators are not normally used for therapy maintenance. Low amounts of 6-MP and methotrexate are used and directed continuously and is usually accepted and is the main component in maintenance therapy treatments. Overall, daily 6-MP and weekly methotrexate seem the ideal schedule. The quantity of the drugs used in this stage seems to play an important part in determining its effectiveness [49]. Different biological apps of smartphones may be used to obtain the result graph [51].

Acute myeloid leukemia

AML outcomes from variations developed in the DNA of a developing bone marrow cell. When the marrow cell converts into leukemic cell, it increases in numbers up to 11 billion cells and more. These cancerous cells are called cancerous blasts that do not work generally. But these cells survive and grow than ordinary cells. The occurrence of leukemic cells stops the growth of ordinary cells. So, when AML is recognized, the quantity of fresh blood cells is generally less than ordinary [29].

Signs and Symptoms

Symptoms of AML are related to less severe disorders. It is for the people with AML to feel a loss of comfort due to the under production of normal bone marrow cells. The person may exhaust more simply and have difficulty in breathing through normal physical actions.

Diagnosis

For testing, sample of blood are usually occupied from the vein of patient's arm. Samples of marrow is obtained by surgery and marrow aspiration. Cells from marrow and blood samples are observed below a microscope [20].

Treatment

Around 60% AML patients have abnormal chromosomes. In some cases, the cells that have changes in chromosomes can be observed below microscope. Another test of laboratory is used to identify the chromosomal changes. In AML, Common changes in chromosomes includes monosomy 21 trisomy 8, monosomy 7, trisomy 21, and loss of an Y or X chromosome. Inherited changes can take place in patients with normal chromosomes; therefore, it is significant to perform a molecular analysis [15]. Different drugs are used for this treatment that outcomes in a reduction rate of 80% and a decline free reduction rate of almost 50% in 5 years. About half of the children in returned free reduction are preserved. Babies are generally treated with the similar therapy [20].

Chronic Lymphocytic Leukemia

Mutation in the DNA of bone marrow caused CLL. Biological app may be used to measure the extent of the disease [16]. Mostly changes take place in bone B-cells approximately in 95% patients. Amount of CLL cells higher in blood due to irregular growth of cells in bone marrow. Cancer cells that are present in bone marrow do not affect the synthesis of blood cells [20].

Signs and Symptoms

CLL patients experience short breathing during physical actions because of low RBC's and loss of weight. It also causes kidney, skin and lung cancer [23].

Diagnosis

Bone Marrow Examination

A bone marrow examination and gene culture are not essential to make an analysis of CLL providing platelets and RBC's are usual. Though, it is suggested that to do thesis before initiating the therapy. It is also used for determining the effect of therapy. In CLL patients, the examination of bone marrow showed that the number of lymphocytes is decreased in normal cells but increased in marrow cells [38].

Immunophenotyping

For the identification of tumor types and CLL, lymphocytes procedure is mainly used, linked to normal cells. The result of this test shows that the lymphocytes in patients derived from the leukemia cells. This test is mainly significant as the quantity of lymphocytes is higher in the blood. Immunophenotyping also controls whether the CLL cells are changed development of T-cells and 1 or 2 B-cells [23].

Treatment

Recent therapies don't suggest patients a treatment for CLL, then these are the activities that helps in to control the infection. Actions for CLL include.

- Targeted therapies: In this treatment medicines are used which target on definite substances of tumor cells
- Monoclonal antibody therapies: In this treatment, antibodies bind with cancer calls and destroy it with the help of immune system.
- Radiation therapy: Radiation is used to decrease the masses of lymph nodes at that position where the function of an adjacent body part is affected such as throat and the kidney.

Several factors are required for the treatment of CLL patients. Usually hematologist treats the CLL patients [9].

Chronic Myeloid Leukemia

Chronic myeloid leukemia is caused by changing the DNA of single marrow cells. The altered cell is increased in countless cells (CML cells). In marrow cells, the abnormal growth of CML cells increased the amount of CML cells in blood [1].

Signs and Symptoms

- Loss of weight, anemia (a decrease in red blood cells), night perspirations, and incapability to bear hot temperatures are few signs and symptoms of chronic myeloid leukemia [15].

Diagnosis

Cytogenetic Analysis

This test is used to identify the structure and number of chromosomes. Bone marrow samples are observed to approve blood test results and see that if chromosomal aberrations are present as the Philadelphia chromosome (Ph). A minor proportion of people with medical signs of CML have not Ph chromosome noticeable by this analysis [12].

Treatment

With recent pharmacological treatments, CML does not seem to be cure. But at the end, more patients are attaining very deep reductions with CML. Leukapheresis is used if CML in chronic phase is identified during the 1st month of pregnancy, when additional actions may be harmful to fetal growth [18].

Cellular Basis of Leukemia

The inherited simplicity of tumor combined with the initial age of beginning has permitted investigators to explain the formation of inherited aberrations in the child's life. These changes appear to occur within two temporal frames: prenatal events that induce some cellular changes and postnatal genetic and epigenetic events that allow the onset of an acute illness. Several translocations commonly found in leukemia that were evaluated using archived newborn blood spots, including ETV6RUNX1, RUNX1-MTG8, CBFB-MYH11, have indicated a clear presence of mutations in neonatal blood at birth in children who contract leukemia later in life. Several other mutations, including TCF3-PBX1, FLT3 and RAS mutations occur clearly after birth [58].

The p53 protein can suppress the production of abnormal cells. Its equivalent P53 gene (TP53 on human 17^{th} chromosomes, note the upper case for the gene, the protein is stimulated by the mdm2 manager under normal situations. It is stated on exposure of damage of DNA and abnormal growth of cell. Proton p53 functions include cell cycle detention (detention of cell division), repairing of DNA and cell suicide. The p53 protein also arises in 12 different method making the process very difficult. Figure shows some responses of such myriads of products [58].

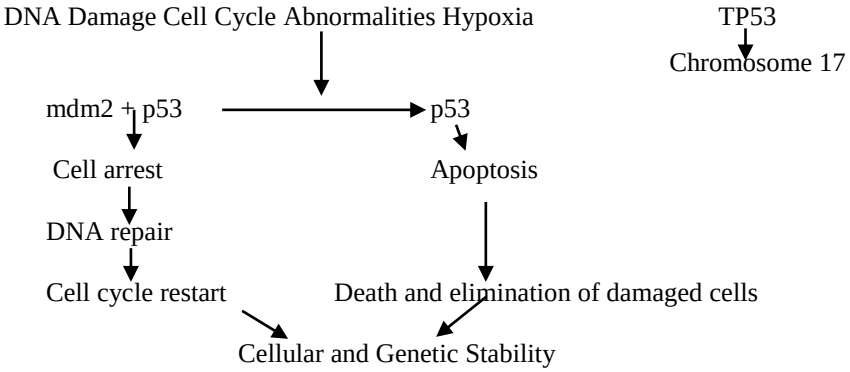

Fig-2.1: Cellular Basis of Leukemia

P-53 is not only competing against protein of cancer. Other cancer suppressors like pRb which is a protein that controls the division of cell. But, if TP53 gene is injured, cancer suppression is extremely compromised. Persons who receive only an efficient copy of TP53 gene will likely develop cancers in initial age majority. The TP53 gene can be adapted by chemical mutation and radiation and viruses that increasing the likelihood of uncontrolled division of cells. More than fifty percent of human cancers contain a deletion of the TP53. Pharmacological investigation will reestablish p53 endogenously as a practical tumor action. China has accepted this medical treatment for "squamous neck and head squamous cell in carcinoma in 2003 [58].

Mutational Mechanisms in Leukemia

Recent research on the specific molecular characteristics of leukemia mainly based on three pathways: (1) Aberrations in a small number of lineage-specific transcription factors such as ETV6, RUNX1, IKZF1 and PAX5 (2) Defects in protein tyrosine kinases Receptors and their (i.e., RAS / MEK / ERK) and (3) Epigenetic modifiers. Mutations may involve the translocations that contain fusion genes, number of alterations (the most common are deletions), single nucleotide mutations, and extensive changes in epigenetic characteristics such as DNA methylation aberrations. The molecular formation of the initiating translocations may provide some clues as to their causes. In current years, many mutagenic processes of enzyme id made by breakpoints of translocation- by using immune system to expand the antibodies and repertoire of T cells that were aberrantly targeting oncogenes and genomic enhancers [58].

Environmental causes may also interact with endogenous mutagenic mechanisms in children after birth. Many of these postnatal secondary rearrangements show the clear implication of the activity of the enzymes that create antibody diversity, i.e. the recombinant activator gene (RAG) and adenosine deaminase (AID) in the formation of deletions and secondary mutations [41].

Chemicals as Leukemogenesis

Initially it was thought that the ability of a chemical to act as a carcinogen depended on its ability as a mutagen, but it is likely that many other biologically important activities are also important in leukemogenesis. Some chemicals exhibit properties that allow them to target the bone marrow specifically because of their metabolic activity (e.g. benzene). Other chemicals may affect the immune system indirectly. Other activities of chemicals are summarized in a recent review of chemicals as carcinogens [55]. The most common translocation in ALL, ETV6-RUNX1, appears to be strongly and specifically associated with smoking in the parents and the use of paint in the home [54], which gives some credibility to the viability of this pathway. Specific demethylation of CpG loci in the AHRR gene has been exquisitely related to cigarette smoke [22]. In addition, methylation changes have been observed in response to folic acid exposures.

Chemotherapy drugs

Designs of chemotherapy of cancer has become gradually cultured, so far there is not any treatment for cancer that is 100 percent operative against the cancer dispersed. Resistance is frequently inherent to cancer, but as treatment becomes progressively effective, acquired resistance is also develop very common. Studies on cancer treatment resistance mechanisms is providing significant info on how to avoid this resistance to recover cancer chemotherapy. The drugs which are used for many years for chemotherapy of caner are harmful DNA mediators [60]. Because of their mechanism, these drugs are divided into different categories. Inhibitors that inhibit the synthesis of DNA, also inhibit the vital biosynthesis processes and combine with RNA and DNA.

These drugs are basic equivalents for heterocyclic agents and bases that disturb the metabolism of folate and inhibit the main steps in the formation of nucleotides, purine and pyrimidine bases. This class of mediators includes pemetrixed, [21] antipurines (thioguanine, 6-mercaptopurine) [7], and

hormigriprimides (capecitabine5-fluorouracil, hydroxyurea, enyluracil). Other class of drugs added alkyl and methyl groups to nucleotide bases to damage the DNA [5]. The molecules related to the third class of drugs affect the decomposition and formation of mitotic spindle [57].

Typical course of treatment for patients identified with precursor of ALL types continues for two to three yrs. and includes reduction induction treatment, consolidation treatment and maintenance. Induction generally includes glucocorticoids and vincristine with and without anthracycline. High-dose methotrexate (MTX) is commonly used with 6-mercaptopurine (6-MP), attended by frequent pulses of vincristine and glucocorticoids for twenty to thirty weeks. Maintenance treatment generally takes two yrs. and is consist of 6 MP and MTX weekly in the presence and absence of pulsed quantities of dexamethasone and vincristine.

Dexamethasone

Dexamethasone is a critical chemotherapeutic agent for ALL. It has not been explained whether drug-kinetic alterations among dexamethasone patients contribute to the danger of failure. The effect of the clearance of plasma of anti-asparaginase antibodies level and dexamethasone on failure risk was measured in 410 children that were treated for ALL in a first-line medical test. Development of anti-asparaginase antibodies is associated with inter-patient variability in systemic exposure to dexamethasone and whether these measures are associated with the outcome of treatment [40], Dexamethasone is extensively used because its results lowers the bone marrow occurrence and risk of CNS likened to prednisone [9].

Glucocorticoids

Glucocorticoid applied their activity by decreasing the explosion of cells and increasing the apoptosis process by necessary intra-cytoplasmic receptors of glucocorticoid. In cancer cells, the P-glycoprotein regulation is responsible for resistance of glucocorticoid and this protein is encoded with B1 subfamily gene (ABCB1) of the ATP-binding cover, G2677T / A, C3435T [35] and T129C recognized as polymorphisms that relate to resistance to glucocorticoids and it depends upon in vitro studies [32].

The regulation of expression of IL-10 is affected by SNP and binding of monocytes increases with glucocorticoid. Also, elimination of gene called MI from glutathione-S-transferase (GSTs) is related with the initial response of glucocorticoids, by reducing absorption of glucocorticoid causes severity of infectious problem [36]. Gluco-corticoid and gamma secretase inhibitor have ability to restore the Gluco-corticoid anti leukemic effect in T-cells ALL [26]. Hyper-tension, osteoporosis, diabetes are severe effects of Gluco-corticoid [29].

Mercaptopurine (6-MP)

6-MP is act as anti-metabolite that is used for 40 years. 6-MP attached with MTX and act as a backbone for ALL therapy. For metabolite inactivation, thiopurine methyltransferase comprises S-methylation of thiol-purine. These genes are inherited co-dominantly and contain non-synonymous SNPs, important for significant differences in the activity of enzyme and important in significances of medical [42]. TPMT and SNP patients related with lower activity of enzyme, either homozygous or heterozygous caused severe myeloid-suppression when it treated with predictable quantities of 6-MP [45].

Methotrexate

It is an inhibitor that presented into medical practice in 1950s and remains a significant factor of the ALL treatment method. MTX defeats the synthesis of DNA by competitive inhibition of DHFR so, disturbing the biosynthesis of thymidine. Numerous enzymes and transporters take part in the uptake of folate, and numerous of them prove inherited polymorphisms that may affect uptake and MTX activity [14]. They proved that patients of ALL with irregular RFC-1 and G80A had an inferior diagnosis established by an increased amount of relapse and reduced EFS than those that bearing genotype of GG [44].

Tyrosine kinase inhibitor

In adults, acute leukemia, Ph chromosome is the cytogenetic deviation. Among chromosomes 22 and 9 the inherited material translocates and produce the mixture of BCR gene and ABL1 gene, resulting vigorous tyrosine kinase. Only five percent kids and persons younger than twenty ages begin the +ve T lymphocytes on Ph chromosome [17]. This is qualified to the existence of extra inherited irregularities, e.g. removal of the gene belongs to family of Ikaros from zinc and protein finger 1 (IKZF1) (van der et al., 2014), new alterations of the ABL1-BCR and disturbance of transportation of drug [33].

L-ASPARAGENASE

L-asparaginase is obtainable from different organisms such as microorganisms, plant, and some animals, including certain rodent's serum, but don't exposed in humans [49]. It is an essential agent in chemotherapy procedures since about 30 years. L-asparaginase is completely converted into aspartic acid. L-glutamine is a competitive inhibitor of l-asparagine hydrolysis [8].

L-asparaginase Production at industrial level

Production of L-asparaginase at industry level offered some challenges, such as new microorganisms are required that can yield this enzyme with less opposing effects [49]. Now, industrial production is

supported by using bacteria such as E. coli and Erwinia chrysanthemum [31]. L-asparagine enzymatically hydrolyze into L-aspartate and ammonium ion, it was first time detected by Lang, when they noticed the L-asparaginase activity in bovine's tissues. Enzyme that is obtained from prokaryotic microorganisms create some problems such as hyper-sensitivity and immune inactivation [38]. In this situation, to improve the compatibility with the human system, eukaryotic microorganisms such as filamentous fungi and yeasts [56], have been used to produce this enzyme.

Role of l-asparagenase in leukemia

L-asparaginase is an amino acid that changes into L-asparagine. It is essential for performance of neo-plastic cells like lymphoblast. In human cells, asparagine is synthesized by alternative pathway in which aspartic acid and glutamine form L-asparagine by asparagine synthetase. L-asparaginase. By following apoptosis of blastic cells, l-asparaginase decrease the level of asparagine and cause synthesis of DNA and inhibition of RNA. Per anti-cancer mechanism, l-asparaginase used in Chemotherapeutic drugs for ALL., which has given the important development of therapy results and to attain complete reduction in 90% of patients [43].

Mechanisms of Resistance

Quick development in medical struggle is the main restriction of asparaginase treatment in ALL l. Approval of asparaginase is enhanced by immuno-logical mechanism that has been reported in patient's developing resistance. L-asparaginase is used for the development of additional current ways, alternative mechanism might be used, also from the plasma and from the cells in which L-asparaginase treatment not fully inhibit the L-asparagine or in which Asparagine synthetase strongly produced asparagine. In human cancerous cells, the resistance is related to the asparagine synthetase activity. Former to L-asparaginase therapy the quantity of asparagine synthetase is not determinate in human cancerous cells. After the L-asparaginase therapy, the level of asparagine synthetase increases in the cells [21].

Toxicity of Asparaginase

Sensitivity is apparent uncommonly with early contact to drugs. After the managing of the drug, sensitivity reaction is arisen directly and it is also related with fever, hypotension, dyspnea, agitation dry epi-gastric pain. While these symptoms don't certainly stop the maintenance of therapy [30].

With low amounts of L-asparaginase for hyper-sensitivity before and after therapy Skin testing have failed to control any hyper-sensitivity reactions, even in those patients who exposed an increased sensitivity for intra-venous drug. Concentration of plasma antithrombin, fibrinogen, and plasminogen is decreased after the third week of therapy. As the bone marrow reduction was attained. During 3rd and 4th of therapy the number of platelets is increased [39].

The Immunosuppressive Activities of L-Asparaginase

In animals and man, action of anti-tumor L-asparaginase against lymphoid tumors is absorbed to the search of L-asparaginase and its associated compounds such as L-glutamine as a possible immunosuppressive agent. Initial study shows that very minor amounts as little as 1 IU/ml, is used to completely inhibit the lymphocyte blasto-genic responses into Phyto-hemagglutinin (PHA). Patients that contain the lymphocytes receive L-asparaginase therapy for neo-plastic syndromes and respond badly to PHA. It's supposed that the effect of l-asparaginase circulation as patient's serum inhibits the blasto-genic response and usual serum has capacity to restore the response of patient Lympho-cytes. The reduction of the PHA response in vitro was used to evaluate the L-asparaginase existence periods in serum [60].

Clinical Results with L-Asparaginase

Many chemo-therapeutic agents are fruitful in the therapy of ALL. L-asparaginase first combined with asparagine and then used. L-asparaginase in grouping with another mediator, mostly Daunomycin and cytosine arabinose, which has been used in acute leukemia and these groupings appeared satisfactory due to the absence of myelosuppression. Both drugs have might be used in full therapeutic measures with L-asparaginase. Because of high molecular weight, L-asparaginase doesn't absorb across the blood brain barrier. However, it is a beneficial characteristic in the therapy of meningeal leukemia. For breakdown of intrathecal leukemia cells, it's important to reduce the l-asparaginase amount [25].

DISCUSSION

The purpose Pieters used asparaginase therapy to achieve the plasma asparagine depletion which defined as less than 0.1–0.2 μM [43]. Similarly, [54], achieved the maximum benefit through optimizing the dosing of L-asparaginase and treatment schedules, which results in prolonged, although not certainly continuous, depletion of L-asparagine [3]. Vrooman used the Preparations and administration routes of asparaginase with native Escherichia coli. Intramuscular (IM) polyethylene glycolated E. coli asparaginase (PEG asparaginase) was first introduced as the second- line agent for the patients. Those patients developed hypersensitivity after E. coli asparaginase therapy and later this therapy became the first-line treatment in different countries where it is easily available due to the longer half- life and greater activity level of asparaginase activity levels [59].

Panel of different researcher explained that the available management recommendation in the different protocols are unclear due to lack of data. They included

the possibilities of re exposure to L-asparaginase once thromboprophylaxis. The clinical symptoms completely resolved, and MRI imaging of the patients has normalized. They used the special conditions like presence of a Factor V Leiden and other genetic predispositions to stabilize the condition of ALL patients [5].

Another research explained that L-asparaginase has been widely used in the treatment of lymphomas and acute lymphoblastic lekumia. Administration of this enzyme un blanacced the protein synthesis of leukemic cells and catalyze the hydrolyses of asparaginase into aspartic acid. Long lasting and deep depletion of plasma asparaginase cause the antic antilekeumic effect [6].

In front-line treatment schedules Erwinase® has also been used at the same amount and schedule of other E. coli products [47]. In the last few decade other products such like medac® L-asparaginase has been derived from different strains of E. coli, which display a very different biological or clinical effects that have been introduced in market to renewing the attention for L-asparaginase study [18].

CONCLUSION

L-asparaginase is used in pharmacological and food industry. L-asparaginase produced by eukaryotic micro-organisms. As a chemotherapeutic agent, an efficient action is required to reduce the severe effects. Drug transporters and drug absorbing enzymes are important issues in the failure of tumor treatments. Drug responsiveness helps to propose the personalized medicines to overcome anti-cancer drug resistance. Mercaptopurine (6-MP) is a dug which act as a backbone for the maintenance of ALL. Tubulin dimer binds to Vincristine and interrupt with the synthesis of mitotic spindle dynamic and microtubules and cause the death of tumor cells and mitotic arrest in metaphase. L-glutamine is essential for L-asparagine formation. Combination of L-asparagine and azaserine is more for the treatment of ALL. The investigation revels that this enzyme has fewer toxic effects and helps to control the cancer.

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