

Acute Leukaemia: A Sudden Killer to Human Beings

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Abstract

Leukaemia is among the leading haematological disorders causing the deaths of many in the society. This paper was reviewed to update the dangers associated with acute leukaemia. The paper was reviewed using different search engines like Google scholar, Researchgate, Pubmed, Scopus, etc. Acute leukaemia is a leukaemia with serious medical conditions needing emergency medical attention. It can convert sometimes to chronic leukaemia. The onset of the course of the disease is sudden and life-threatening. Prompt diagnosis could be helpful in the management of the patients. The experts involved in the diagnosis and management should attend regular trainings and conferences to update themselves on the new approaches on acute leukaemia to achieve optimal results in the patients. This paper tried to update the public on the overview, course, mechanism, treatment and diagnosis of acute leukaemia.

Keywords: Acute Leukaemia; Acute Myeloid Leukaemia; Acute Lymphoblastic Leukaemia; Myelogenous Leukaemia

Acute leukaemia

It has been reported that acute leukaemia is a group of critical clinical situations linked to a primary diagnosis of leukaemia. In varied cases, these can be classified based on the lineage, myeloid or lymphoid, of the malignant cells that grow uncontrolled, but some are mixed and for those such duty is not possible [1].

Forms of acute leukemia included leukaemia include the following:

- Acute myeloid leukaemia
- Acute lymphoblastic leukaemia
- Blast crisis of chronic myelogenous leukaemia.

Acute myeloid leukaemia

It has been opined that acute myeloid leukaemia (AML) is a cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal cells that build up in the bone marrow and blood and interfere with normal blood cells [2]. It has been reported that the clinical features as opined by National Cancer Institute [2] may include weakness, shortness of breath, easy bruising and haemorrhage and elevated threat of infection. Infrequently, it may extend to the brain, skin, or gums. As an acute leukaemia, AML manifests fast and is classical deadly in weeks or months if left untreated [3].

Danger variables comprise smoking, earlier chemotherapy or radiation therapy, myelodysplastic syndrome, and contact to the substance benzene [2]. The fundamental system is linked to substitution of typical bone marrow with leukaemia cells, which causes in a drop in erythrocytes, thrombocytes, and typical leucocytes [2]. Döhner [4] reported that identification is usually considered on bone marrow aspiration and precise blood examinations. Acute myeloid leukaemia has numerous forms for which managements and results may differ.

Acute myeloid leukaemia typically is initially managed with chemotherapy, with the aim of inducing remission [2]. Persons may subsequently keep on obtaining extra chemotherapy, radiation therapy, or a stem cell transplant. The definite heritable changes existing in the cancer cells may direct treatment, as well as decide how extent that person is expected to last. Arsenic trioxide may be tried in cases that have recurred following usual treatments [4].

Döhner in 2015 opined acute myeloid leukaemia have an effect on one million persons and lead to 147,000 fatality worldwide [5]. It mainly usually happens in aged persons. Males are affected more frequently than females. Acute myeloid leukaemia is curable in about 35% of persons below 60 years old and 10% above 60 years old. Aged persons whose health is very weak for serious chemotherapy have a normal survival of 5 - 10 months. It amounts or approximately 1.8% of cancer fatality in the United States [4].

Signs and symptoms

Most clinical features of acute myeloid leukaemia are a result of replacement of normal blood cells with leukaemic cells. A need of typical leucocyte formation causes persons more disposed to infections; while the leukaemic cells themselves are obtained from white blood cell precursors, they have no immune defense [6]. A reduction in erythrocyte count can lead to fatigue, paleness, and shortness of breath. A lack of thrombocytes can lead to haemorrhagic disorders.

The timely features of acute myeloid leukaemia are frequently indistinct and unclear and may be comparable to those of influenza or other usual diseases. Some universal symptoms consist of fever, fatigue, weight loss or anorexia, shortness of breath, anaemia, easy bruising or haemorrhage, petechiae, bone and joint pain, and recurrent or repeated infections [6].

Amplification of the spleen may result in acute myeloid leukaemia, but it is normally weak and asymptomatic. Lymph node enlargement is uncommon in acute myeloid leukaemia, in disparity to acute lymphoblastic leukaemia. The skin is concerned in about 10% of the time in the manner of leukemia cutis. Hradly, Sweet's syndrome, a paraneoplastic inflammation of the skin, can happen with acute myeloid leukaemia [6].

A number of persons with acute myeloid leukaemia may show enlargement of the gums as permeation of leukaemic cells inside the gum tissue. Hardly, the original mark of leukaemia may be the formation of a firm leukaemic stack or tumor outside of the bone marrow, named a chloroma. Seldom, a person may demonstrate no symptoms, and the leukaemia may be uncovered accidentally through a regular blood examination [7].

Danger variables of acute myeloid leukaemia

A list of danger variables for forming acute myeloid leukaemia have been recognised, namely: other blood disorders, chemical contact, ionizing radiation, and heredity.

Other blood disorders

Jaiswal [8] reported that preleukemic blood anomalies, like myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPN) can change to acute myeloid leukaemia; the real danger depends on the form of MDS/MPN. The existence of asymptomatic clonal blood formation also elevates the danger of change to acute myeloid leukaemia to 0.5 - 1.0% per year.

Chemical contact

Thirman [9] showed that contact to anticancer drugs, in particular alkylating agents, can raise the danger of consequently forming acute myeloid leukaemia. The danger is peak about 3 - 5 five years after treatment. Other drugs, particularly epipodophyllotoxins and anthracyclines, have also been linked with treatment-related leukaemias, which are usually linked to specific chromosomal disorders in the leukaemic cells.

Occupational chemical contact to benzene and additional aromatic organic solvents is contentious as a reason of acute myeloid leukaemia. Benzene and a lot of its products are recognised to be carcinogenic *in vitro*. While some works have recommended a relation between occupational contact to benzene and increased danger of acute myeloid leukaemia, others have enumerated the associated danger, if any, is not notable [10].

Radiation

Elevated levels of ionizing radiation contact can raise the danger of acute myeloid leukaemia. Survivors of the atomic bombings of Hiroshima and Nagasaki had an elevated degree of acute myeloid leukaemia, as did radiologists who had contact with raised degrees of X-rays before the acceptance of current radiation protection activities [11]. Persons managed with ionizing radiation after treatment for prostate cancer, non-Hodgkin lymphoma, lung cancer, and breast cancer have the major options of forming acute myeloid leukaemia, but this increased danger relapse to the first risk observed in the universal people after 12 years [12].

Genetics

Many situations of acute myeloid leukaemia forming in a family at a degree higher than predicted by opportunity alone have been documented [13]. Many congenital situations may raise the danger of leukemia; the main frequent is may be Down syndrome, which is linked to with a 10- to 18-fold elevation in the danger of acute myeloid leukaemia. In a next instance, inactivating changes in one of the two parental GATA2 genes cause a reduction, i.e. a haploinsufficiency, in the cellular degrees of the gene's product, the GATA2 transcription factor, and thus to a unusual autosomal dominant genetic disease, GATA2 deficit. This disease is linked to extremely factor set of disarrays involving a remarkably elevated danger of forming acute myeloid leukaemia. The exact hereditary disorders leading to acute myeloid leukaemia normally differ among those who have the disease as a child against an adult. However, GATA2 deficiency-induced acute myeloid leukaemia may initially manifest in children or adults [14].

Pathophysiology of acute myeloid leukaemia

The malignant cell in acute myeloid leukaemia is the myeloblast. In normal haematopoiesis, the myeloblast is a young precursor of myeloid leucocytes; a normal myeloblast will slowly mature into a developed leucocyte. In acute myeloid leukaemia, despite the fact that, only myeloblast gathers hereditary alterations which "freeze" the cell in its young condition and avert changes. Such a change only does not lead to leukemia; though, when such a "differentiation arrest" is joined with other changes which upset genes regulating proliferation, the effect is the unregulated increase of a young clone of cells, resulting to the clinical entity of Thirman [15].

A lot of the variety and heterogeneity of acute myeloid leukaemia is as a result of leukemic change can arise at a number of diverse stages along the differentiation pathway. Current taxonomy schemes for acute myeloid leukaemia identify that the features and behavior of the leukaemic cell (and the leukemia) may depend on the stage at which alterations were halted [16].

Exact cytogenetic disorders can be seen in most persons with acute myeloid leukaemia; the forms of chromosomal disorders usually have prognostic implication [7]. The chromosomal translocations encode atypical fusion proteins, normally transcription variables whose changed properties may cause the "differentiation arrest". For example, in acute promyelocytic leukemia, the t(15;17) translocation produces a PML-RAR α fusion protein which joins to the retinoic acid receptor element in the promoters of many myeloid-specific genes and inhibits myeloid differentiation [17].

The clinical features of acute myeloid leukaemia caused from the growth of leukemic clone cells, which have tendencies to shift or impede with the formation of normal blood cells in the bone marrow [7]. This causes neutropaenia, anemia and thrombocytopenia. The symptoms of acute myeloid leukaemia are, in turn, usually as a result of low numbers of these normal blood variables. In uncommon situations, persons with acute myeloid leukaemia can have a chloroma, or solid tumor of leukaemic cells outside the bone marrow, which can result to different symptoms depending on its position [6].

A significant pathophysiological means of leukaemogenesis in acute myeloid leukaemia is the epigenetic commencement of dedifferentiation by hereditary changes that alteration the function of epigenetic enzymes, like the DNA demethylase TET2 and the metabolic enzymes IDH1 and IDH2, which lead to the development of a novel oncometabolite, D-2-hydroxyglutarate, which hinders the role of epigenetic enzymes such as TET2 [18].

Treatment of acute myeloid leukaemia

Initial therapy of acute myeloid leukaemia comprises mainly of chemotherapy and is grouped into two stages: induction and post-remission treatment. The purpose of induction treatment is to obtain a full remission by lowering the number of leukemic cells to an unrecognisable degree; the purpose of consolidation therapy is to remove any remaining unrecognisable disease and get a cure. Haematopoietic stem cell transplantation is normally measured if induction chemotherapy fails or after a person relapses, while transplantation is also a bit used as front-line therapy for people with high-risk illness. Attempts to employ tyrosine kinase inhibitors in acute myeloid leukaemia continue [19].

Induction

The entire FAB subgroups apart from M3 are normally offered induction chemotherapy with cytarabine (ara-C) and an anthracycline [7]. This induction chemotherapy treatment is regarded as "7+3" (or "3+7"), because the cytarabine is offered as a continuous IV infusion for 7 consecutive days even as the anthracycline is offered for 3 uninterrupted days as an IV push. Up to 70% of people with acute myeloid leukaemia will get a cutback with this procedure (Bishop, 1997). Other option induction treatment, as well as high-dose cytarabine alone, FLAG-like treatments or investigational agents, can also be used. Because of the lethal results of treatment, together with myelosuppression and an raised danger of infection, induction chemotherapy cannot be given to the aged, and the choices may embrace less strong chemotherapy or palliative care.

The M3 subgroup of acute myeloid leukaemia, also regarded as acute promyelocytic leukemia (APL), is nearly commonly treated with the drug all-trans-retinoic acid (ATRA) in addendum to induction chemotherapy, normally an anthracycline [20]. Attention must be in use to prevent disseminated intravascular coagulation (DIC), complicating the treatment of APL when the promyelocytes free the components of their granules into the peripheral circulation. APL is highly curable, with well-documented treatment procedures.

The purpose of the induction stage is to achieve a full remission. Full remission does not mean the illness has been cured; rather, it signifies no disease can be detected with available diagnostic methods. Full remission is seen in about 50% - 75% of early diagnosed adults, while this may differ established on the analytic features shown above. The duration of remission linked to the prognostic factors of the original leukemia. Universally, all cutbacks will be unsuccessful devoid further consolidation treatment [21].

Consolidation

Still following full remission is gotten; leukemic cells probably stay in figures too minute to be detected with current diagnostic techniques. If no further post-remission or consolidation treatment is offered, nearly all persons with acute myeloid leukaemia will finally revert. Hence, extra treatment is needed to remove nondetectable disease and avert relapse - that is, to obtain a cure.

The exact group of post-remission treatment is individualized based on an individual's prognostic features and universal health. For good-prognosis leukaemias (i.e. inv (16), t(8;21), and t(15;17)), persons will normally experience an additional 3 to 5 courses of strong chemotherapy, regarded as consolidation chemotherapy. For persons at elevated danger of relapse, allogeneic stem cell transplantation is usually recommended if the person is able to tolerate a transplant and has an appropriate donor. The most excellent post-remission treatment for intermediate-risk AML is less apparent and depends on the exact condition, involving the age and general health of the individual, the individual's values, and whether a appropriate stem cell donor is around [22].

For people who are not eligible for a stem cell transplant, immunotherapy with a combination of histamine dihydrochloride (Ceplene) and interleukin 2 (Proleukin) after the end of consolidation has been revealed to lower the absolute relapse danger by 14%, translating to a 50% elevation in the likelihood of maintained remission [23].

Prognosis

It has been shown that acute myeloid leukaemia is a curable disease; the chance of cure for a specific person depends on a number of prognostic factors [21].

Cytogenetics

The single nearly all good prognostic feature in acute myeloid leukaemia is cytogenetics, or the chromosomal structure of the leukemic cell. Some cytogenetic disorders are linked to very good results (for example, the (15; 17) translocation in acute promyelocytic leukemia). Nearly half of persons with acute myeloid leukaemia have "normal" cytogenetics; they fall into an intermediate danger type. A list of other cytogenetic disorders is regarded to be linked to a poor prognosis and an increased peril of relapse after therapy.

Myelodysplastic syndrome

Acute myeloid leukaemia which comes from a pre-existing myelodysplastic syndrome (MDS) or myeloproliferative illness has a worse prognosis, as does treatment-related AML emanating after chemotherapy for another previous malignancy. Both of these entities are linked to a high degree of adverse cytogenetic disorders.

Other prognostic markers

In some studies, age > 60 years and raised lactate dehydrogenase amount were also linked to poorer results. As with the majority groups of cancer, performance status engages in a major function in prognosis as well.

The five-year survival degree is about 25% overall. Age performs a major function: 40% of persons below 60 years of age, but scarcely 10% of those above it, live 5 years after diagnosis.

Genotype

A great number of molecular changes are under research for their prognostic role in AML. Though, only FLT3-ITD, NPM1, CEBPA and c-KIT are included in validated international risk stratification scheme. These are likely to increase quickly in the near future. FLT3 internal tandem duplications (ITDs) have been reported to bestow a poorer prognosis in AML with normal cytogenetics. Many FLT3 inhibitors have undergone clinical trials, with diverse outcomes. Two other changes - NPM1 and biallelic CEBPA are linked to improved outcomes, particularly in persons with normal cytogenetics and are used in present risk stratification algorithms.

Researchers are studying the clinical relevance of c-KIT changes in AML. These are common, and potentially clinically relevant because of the availability of tyrosine kinase inhibitors, such as imatinib and sunitinib that can prevent the function of c-KIT pharmacologically. It is likely that additional markers that have always been linked to an inferior result will soon be included in these recommendations. The prognostic relevance of other mutated genes is less lucid.

Expectation of cure

Cure levels in clinical trials have occurred from 20 - 45%; though clinical trials usually comprise only younger persons and those able to stand aggressive treatments. The general cure level for all persons with AML is usually lower. Cure levels for promyelocytic leukemia can be elevated to 98%.

Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) is a cancer of the lymphoid line of blood cells distinguished by the formation of great numbers of young lymphocytes. Features may comprise feeling tired, pale skin color, fever, easy bleeding or bruising, increased lymph nodes, or bone pain. As an acute leukemia, ALL progresses quickly and is normally lethal within weeks or months if left untreated [3].

In most cases, the cause is unknown [24]. Hereditary danger variables may comprise Down syndrome, Li-Fraumeni syndrome, or neurofibromatosis type 1. Environmental danger variables may include significant radiation exposure or prior chemotherapy. Evidence regarding electromagnetic fields or pesticides are uncertain [25]. Some hypothesize that an odd immune response to a frequent infection may be a cause [25]. The fundamental mechanism includes many genetic changes that lead in fast cell division. The excessive immature lymphocytes in the bone marrow prevent formation of new erythrocytes, leucocytes and thrombocytes. Diagnosis is normally based on blood tests and bone marrow examination [26].

Acute lymphoblastic leukaemia is usually treated at onset with chemotherapy aimed at causing remission. This is then followed by additional chemotherapy normally over a number of years. Further therapies may comprise intrathecal chemotherapy or radiation treatment if reached to the brain has happened. Stem cell transplantation may be utilised if the disease reappears subsequent typical therapy. Further therapies such as immunotherapy are being studied [24].

Acute lymphoblastic leukaemia affected about 876,000 persons universally in 2015 and lead to about 111,000 deaths. It happens generally usually in children, especially those between the ages of 2 and 5. In the United States it is the majority regular cause of cancer and death from cancer in children. Acute lymphoblastic leukaemia is prominent for being the first malignin at cancer to be cured. Survival for children increased from under 10% in the 1960s to 90% in 2015. Survival levels remain lower for babies (50%) and adults (35%) [27].

Signs and symptoms

Original symptoms can be nonspecific, especially in children. Over 50% of children with leukemia had 1 or more of 5 features: a liver one can feel (64%), a spleen one can feel (61%), pale complexion (54%), fever (53%), and bruising (52%). Furthermore, recurrent infections, weakness, arm or leg pain, and enlarged lymph nodes can be famous features. The B symptoms, such as fever, night sweats, and weight loss, are often present as well.

Central nervous system (CNS) symptoms such cranial neuropathies due to meningeal infiltration are diagnosed in fewer than 10% of adults and fewer than 5% of children, especially mature B-cell Acute lymphoblastic leukaemia (Burkitt leukemia) at presentation (Cortes, 2001).

The signs and symptoms of Acute lymphoblastic leukaemia are changeable and include:

- Generalized weakness and feeling tired
- Anemia
- Dizziness
- Headache, vomiting, lethargy, nuchal rigidity, or cranial nerve palsies (CNS involvement)
- Frequent or unexplained fever and infection

- Weight loss and/or loss of appetite
- Excessive and unexplained bruising
- Bone pain, joint pain (caused by the spread of “blast” cells to the surface of the bone or into the joint from the marrow cavity)
- Breathlessness
- Enlarged lymph nodes, liver and/or spleen
- Pitting edema (swelling) in the lower limbs and/or abdomen
- Petechiae, which are tiny red spots or lines in the skin due to low platelet levels
- Testicular enlargement
- Mediastinal mass.

Cause

The cancerous cell in acute lymphoblastic leukaemia is the lymphoblast. Normal lymphoblasts form into developed, infection-fighting B-cells or T-cells, also called lymphocytes. Indicators in the body regulate the number of lymphocytes so neither too few nor too many are made. In ALL, both the normal formation of some lymphocytes and the regulation over the number of lymphoid cells become defective [25].

Acute lymphoblastic leukaemia appears when a single lymphoblast gains numerous changes to genes that affect blood cell formation and proliferation. In childhood acute lymphoblastic leukaemia, this step starts at conception with the inheritance of some of these genes. These genes, in turn, elevate the danger that more changes will happen in forming lymphoid cells. Certain genetic syndromes, like Down Syndrome, have the same effect. Environmental risk variables are also necessary to assist form sufficient genetic changes to cause disease. Proof for the function of the environment is seen in childhood acute lymphoblastic leukaemia among twins, where only 10 - 15% of both genetically identical twins get acute lymphoblastic leukaemia. Because they have the same genes, varied environmental contacts show why one twin gets ALL and the other does not.

Infant acute lymphoblastic leukaemia is an uncommon form that happens in babies less than one year old. KMT2A (formerly MLL) gene rearrangements are nearly frequent and happen in the embryo or fetus before birth. These rearrangements lead to raised manifestation of blood cell formation genes by enhancing gene transcription and via epigenetic alteration. In diverge to childhood acute lymphoblastic leukaemia, environmental factors are not known to play an important function. Aside from the KMT2A rearrangement, only one extra mutation is typically found. Environmental contacts are not required to assist create more mutations [25].

Risk factors of acute lymphoblastic leukaemia

Genetic risk factors

Usual inherited danger factors comprise mutations in ARID5B, CDKN2A/2B, CEBPE, IKZF1, GATA3, PIP4K2A and, more seldom, TP53. These genes perform major functions in cellular formation, proliferation, and differentiation. Separately, many of these mutations are little danger for ALL. Important danger of disease happens when a person inherits several of these mutations together.

The unequal spread of genetic risk factors may help clarify variations in disease level among ethnic groups. For instance, the ARID5B mutation is less frequent in ethnic African populations.

Many genetic syndromes also carry raised danger of acute lymphoblastic leukaemia. These are: Down syndrome, Fanconi anemia, Bloom syndrome, X-linked agammaglobulinemia, severe combined immunodeficiency, Shwachman-Diamond syndrome, Kostmann syndrome, neurofibromatosis type 1, ataxia-telangiectasia, paroxysmal nocturnal haemoglobinuria, and Li-Fraumeni syndrome. Fewer than 5% of cases are linked to a known genetic syndrome.

Atypical mutations in ETV6 and PAX5 are linked to a familial form of acute lymphoblastic leukaemia with autosomal dominant patterns of inheritance.

Environmental risk factors of acute lymphoblastic leukaemia

The environmental contact that add to manifestation of ALL is contentious and a subject of ongoing debate.

Elevated degrees of radiation contact from nuclear fallout are accepted risk variables for forming leukemia. Proof whether less radiation, as from x-ray imaging during pregnancy, raises risk of disease remains uncertain. Studies that have identified a relationship between x-ray imaging during pregnancy and acute lymphoblastic leukaemia found only a slightly increased risk. Exposure to strong electromagnetic radiation from power lines has also been linked to a slightly raised danger of acute lymphoblastic leukaemia. This result is questioned as no causal mechanism linking electromagnetic radiation with cancer is established.

Increase birth weight is also linked to a small increased risk. The mechanism joining high birth weight to acute lymphoblastic leukaemia is also not established.

Proof points that secondary leukemia can form in persons treated with certain groups of chemotherapy, such as epipodophyllotoxins and cyclophosphamide (Vora, 2017).

Treatment

The goal of therapy is to stimulate a lasting remission, defined as the absence of detectable cancer cells in the body.

Over the past several decades, there have been steps to raise the effectiveness of therapy regimens, leading to elevated survival levels. Possible therapies for acute leukemia comprise chemotherapy, steroids, radiation therapy, intensive combined treatments, and/or growth factors.

Chemotherapy for acute lymphoblastic leukaemia

Chemotherapy is the first therapy of choice, and most acute lymphoblastic leukaemia patients receive a combination of therapy. There are no surgical choices because of the body-wide spread of the malignant cells. In general, cytotoxic chemotherapy for acute lymphoblastic leukaemia joins multiple antileukemic drugs tailored to each patient. Chemotherapy for acute lymphoblastic leukaemia consists of 3 phases: remission induction, intensification, and maintenance therapy.

Radiation therapy for acute lymphoblastic leukaemia

Radiation therapy is utilised on painful bony areas, in high disease burdens, or as part of the preparations for a bone marrow transplant. In the past, physicians usually utilized radiation in the type of whole-brain radiation for central nervous system prophylaxis, to hinder occurrence and/or recurrence of leukemia in the brain. Recent researches showed that CNS chemotherapy provided outcomes as encouraging but with less developmental side-effects. As a result, the use of whole-brain radiation has been more restricted. Most specialists in adult leukemia have dumped the use of radiation treatment for CNS prophylaxis, as a replacement for intrathecal chemotherapy.

Biological therapy for acute lymphoblastic leukaemia

Selection of biological points on the basis of their combinatorial effects on the leukemic lymphoblasts can cause clinical trials for enhancement in the effects of acute lymphoblastic leukaemia therapy. Tyrosine-kinase inhibitors (TKIs), such as imatinib, are usually added into the therapy plan for patients with Bcr-Abl1+ (Ph+) acute lymphoblastic leukaemia. However, this subtype of acute lymphoblastic leukaemia is commonly resistant to the combination of chemotherapy and TKIs and allogeneic stem cell transplantation is often recommended upon relapse.

Blinatumomab, a CD19-CD3 bi-specific monoclonal murine antibody, presently demonstrates promise as a novel pharmacotherapy. By engaging the CD3 T-cell with the CD19 receptor on B cells, it stimulates a response to induce the release of inflammatory cytokines, cytotoxic proteins and proliferation of T cells to kill CD19 B cells.

Immunotherapy

Chimeric antigen receptors (CARs) have been formed as an encouraging immunotherapy for acute lymphoblastic leukaemia. This method uses a single chain variable fragment (scFv) formed to recognize the cell surface marker CD19 as a method of treating acute lymphoblastic leukaemia.

CD19 is a molecule found on all B-cells and can be used as a means of differentiating the potentially malignant B-cell population. In this treatment, mice are immunized with the CD19 antigen and produce anti-CD19 immunoglobulins. Hybridomas formed from mouse spleen cells fused to a myeloma cell line can be formed as a source for the cDNA encoding the CD19 specific immunoglobulin. The cDNA is sequenced and the sequence encoding the variable heavy and variable light chains of these immunoglobulins are cloned together using a small peptide linker. This resulting sequence encodes the scFv. This can be cloned into a transgene, encoding what will become the endodomain of the CAR. Differing collections of subunits work as the endodomain, but they universally comprise of the hinge region that connects to the scFv, a transmembrane region, the intracellular region of a costimulatory molecule such as CD28, and the intracellular domain of CD3-zeta containing ITAM repeats. Other sequences frequently included are: 4-1bb and OX40. The final transgene sequence, containing the scFv and endodomain sequences is then inserted into immune effector cells that are obtained from the patient and expanded *in vitro*. In trials these have been a type of T-cell capable of cytotoxicity.

Inserting the DNA into the effector cell can be achieved by several techniques. Most frequently, this is done using a lentivirus that encodes the transgene. Pseudotyped, self-inactivating lentiviruses are an effective method for the stable insertion of a desired transgene into the target cell. Other methods include electroporation and transfection, but these are limited in their efficacy as transgene expression diminishes over time.

The gene-modified effector cells are then transplanted back into the patient. Normally this process is done in addition to a conditioning regimen such as cyclophosphamide, which has been reported to potentiate the effects of infused T-cells. This effect has been attributed to making an immunologic space within which the cells populate. The process as a whole result in an effector cell, typically a T-cell, that can recognize a tumor cell antigen in a manner that is independent of the major histocompatibility complex and which can initiate a cytotoxic response.

Chronic myeloid leukaemia

Chronic myeloid leukaemia (CML), also known as chronic myelogenous leukaemia, is a cancer of the leucocytes. It is a type of leukemia marked by the raised and uncontrolled growth of myeloid cells in the bone marrow and the gathering of these cells in the blood. Chronic myeloid leukaemia is a clonal bone marrow stem cell anomaly in which a proliferation of mature granulocytes (neutrophils, eosinophils and basophils) and their precursors is seen. It is a form of myeloproliferative neoplasm linked to a feature of chromosomal translocation known as Philadelphia chromosome.

Chronic myeloid leukaemia is mainly treated with targeted drugs called tyrosine-kinase inhibitors (TKIs) which have led to noticeably progressed long-term survival rates since 2001. These drugs have revolutionized therapy of this disease and allow most patients to have a good value of life when compared to the former chemotherapy drugs. In Western countries, CML accounts for 15 - 25% of all adult leukaemias and 14% of leukaemias overall [28].

Signs and symptoms of chronic myeloid leukaemia

The manner chronic myeloid leukaemia manifests depends on the stage of the disease at diagnosis as it has been shown to jump stages in some conditions.

The majority of patients (~90%) are diagnosed during the chronic stage which is most often asymptomatic. In these cases it may be diagnosed by the way with an increased leucocyte count on a routine laboratory test. It can also manifest with symptoms showing of hepatosplenomegaly and the resulting upper quadrant pain this causes. The increased spleen may put pressure on the stomach leading to a loss of appetite and causing weight loss. It may also manifest with mild fever and night sweats due to an increased basal level of metabolism [28].

Some (< 10%) are diagnosed during the accelerated stage which most often presents haemorrhage, petechiae and ecchymosis. In these patients fevers are most commonly the result of opportunistic infections.

Some patients are firstly diagnosed in the blast phase in which the symptoms are most probable fever, bone pain and an increase in bone marrow fibrosis [28].

Cause

In most cases no clear reason for chronic myeloid leukaemia can be identified.

Risk factors of chronic myeloid leukaemia

Chronic myeloid leukaemia is more prevalent in males than in females and manifests more frequently in the aged with a median age at diagnosis of 65 years. Exposure to ionising radiation emerges to be a danger factor, based on a 50 fold higher incidence of chronic myeloid leukaemia in Hiroshima and Nagasaki nuclear bombing survivors. The rate of CML in these persons seems to peak about 10 years after the exposure [29].

Classification of chronic myeloid leukaemia

Chronic myeloid leukaemia is usually grouped into 3 phases based on clinical features and laboratory results. In the absence of intervention, chronic myeloid leukaemia typically begins in the chronic phase, and over the course of several years progresses to an accelerated phase and ultimately to a blast crisis. Blast crisis is the terminal phase of chronic myeloid leukaemia and clinically looks like an acute leukaemia. Drug therapy will usually stop this succession if began early. One of the drivers of the progression from chronic phase through acceleration and blast crisis is the acquisition of new chromosomal disorders. Some patients may previously be in the accelerated phase or blast crisis by the time they are diagnosed.

Chronic phase

About 85% of patients with chronic myeloid leukaemia are in the chronic phase at the time of diagnosis. During this phase, patients are normally asymptomatic or have only mild symptoms of fatigue, left side pain, joint and/or hip pain, or abdominal fullness. The duration of chronic phase is variable and depends on how early the disease was diagnosed as well as the therapies used. In the absence of treatment, the disease progresses to an accelerated phase. Precise patient staging based on clinical indicators and personal genomic profile will likely prove beneficial in the assessment of disease history with respect to progression risk.

Accelerated phase

Criteria for diagnosing change into the accelerated phase are somewhat different; the most commonly used yardstick are those put forward by researchers at M.D. Anderson Cancer Center, by Sokal, *et al.* and the World Health Organization (Vardiman, 2002). The WHO

criteria are perhaps most widely used, and define the accelerated phase by the presence of ≥ 1 of the following haematological/cytogenetic criteria or provisional criteria concerning response to tyrosine kinase inhibitor (TKI) therapy:

- Haematological/cytogenetic criteria:
 - Persistent or increasing high white blood cell count ($> 10 \times 10^9/L$), unresponsive to therapy
 - Persistent or increasing splenomegaly, unresponsive to therapy
 - Persistent thrombocytosis ($> 1000 \times 10^9/L$), unresponsive to therapy
 - Persistent thrombocytopenia ($< 100 \times 10^9/L$), unrelated to therapy
 - $\geq 20\%$ basophils in the peripheral blood
 - 10 - 19% blasts in the peripheral blood and/or bone marrow
 - Additional clonal chromosomal abnormalities in Philadelphia (Ph) chromosome-positive (Ph+) cells at diagnosis, including so-called major route abnormalities (a second Ph chromosome, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, and abnormalities of 3q26.2
 - Any new clonal chromosomal abnormality in Ph+ cells that occurs during therapy.

The patient is said to be in the accelerated phase if any of the above are present. The accelerated phase is significant because it signals that the disease is progressing and transformation to blast crisis is imminent. Drug treatment often becomes less effective in the advanced stages [30].

Blast crisis

Blast crisis is the final phase in the development of chronic myeloid leukaemia, and behaves like an acute leukemia, with fast development and short survival. Blast crisis is diagnosed if any of the following are present in a patient with chronic myeloid leukaemia:

- $> 20\%$ blasts in the blood or bone marrow.
- The presence of an extramedullary proliferation of blasts.

Treatment

The only curative therapy for chronic myeloid leukaemia is a bone marrow transplant or an allogeneic stem cell transplant. Except this there are 4 major bases of treatment in CML: therapy with tyrosine kinase inhibitors, myelosuppressive or leukopheresis therapy, splenectomy and interferon alfa-2b treatment. Due to the lofty median age of patients with chronic myeloid leukaemia it is reasonably atypical for chronic myeloid leukaemia to be recognised in pregnant women, despite this, however, chronic myelogenous leukemia can be treated with relative safety at any time during pregnancy with Interferon-alpha hormones.

Chronic phase

In the past, antimetabolites, alkylating agents, interferon alfa 2b, and steroids were used as treatments of chronic myeloid leukaemia in the chronic phase, but since the 2000s have been replaced by Bcr-Abl tyrosine-kinase inhibitors drugs that specifically target BCR-ABL, the constitutively activated tyrosine kinase fusion protein caused by the Philadelphia chromosome translocation. Despite the move to replacing cytotoxic anti-neoplastics with tyrosine kinase inhibitors sometimes hydroxyurea is still used to counteract the high leukocyte counts encountered during therapy with tyrosine kinase inhibitors like imatinib; in these conditions it may be the preferred myelosuppressive agent due to its relative lack of leukemogenic effects and therefore the relative lack of latent for secondary haematologic malignancies to result from treatment. IRIS, an international study that compared interferon/cytarabine combination and the first of these new drugs imatinib, with long-term follow up, demonstrated the clear superiority of tyrosine-kinase-targeted inhibition over existing treatments.

Imatinib

The first of this new class of drugs was imatinib mesylate (marketed as Gleevec or Glivec), approved by the U.S. Food and Drug Administration (FDA) in 2001. Imatinib was found to inhibit the progression of CML in the majority of patients (65 - 75%) sufficiently to achieve regrowth of their normal bone marrow stem cell population (a cytogenetic response) with stable proportions of maturing white blood cells. Because some leukemic cells (as evaluated by RT-PCR) persist in nearly all patients, the treatment has to be continued indefinitely. Since the advent of imatinib, CML has become the first cancer in which a standard medical treatment may give to the patient a normal life expectancy.

Treatment-resistant chronic myeloid leukaemia

While capable of producing significantly improved responses did not compare with the action of imatinib, dasatinib nor could nilotinib overcome drug resistance caused by one particular mutation found to occur in the structure of BCR-ABL1 known as the T315I mutation.

Independently, ARIAD pharmaceuticals, adapting the chemical structures from first and second-generation TK inhibitors, arrived at a new pan-BCR-ABL1 inhibitor which showed efficacy against T315I, as well as all other known mutations of the oncoprotein. The drug, ponatinib, gained FDA approval in December 2012 for treatment of patients with resistant or intolerant CML. Just as with second generation TK inhibitors, early approval is being sought to extend the use of ponatinib to newly diagnosed CML also.

Vaccination

In 2005, cheering but varied effects of immunisation were reported with the BCR/ABL1 p210 fusion protein in patients with steady illness, with GM-CSF as an adjuvant [31].

Conclusion

Acute leukaemia is leukaemia with serious medical conditions needing medical attention. They can convert sometimes to chronic leukaemia. The onset of the course of the disease is sudden and life-threatening. Prompt diagnosis could be helpful in the management of the patients. The experts involved in the diagnosis and management should attend regular trainings and conferences to update themselves on the new approaches on acute leukaemia to achieve optimal results in the patients.

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