Section A-Research paper

A Brief Overview about Acute leukemia

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Abstract

Background: Acute leukemias constitute some of the most common malignant disorders. Despite significant progress made in the treatment of these disorders, their etiology remains unknown. A large and diverse group of genetic and environmental variables have been proposed. The role of a variety of factors, including pre-existing and acquired genetic mutations, exposure to radiation and various chemicals during preconception, pregnancy and throughout life, have been explored. The effects of inherited genetic variations and disorders, pre-existing diseases, infectious agents, hobbies, occupations, prior treatments, and a host of other factors have been proposed, but none is universally applicable to all cases. Variation in the incidence and prognosis based on the age, sex, race, type of the disease, geographic area of residence and other factors are intriguing but remain unexplained. Advances in genomic profiling, including genome-wide gene expression, DNA copy number and single nucleotide polymorphism (SNP) genotype, may shed some light on the role of genetics in these disparities. Separate two-hit hypotheses for the development of acute myeloblastic and lymphoblastic leukemia have been proposed. The latter combines genetics and infection factors resulting in leukemogenesis. A number of pre- and post-natal environmental conditions and exposure to infections, including a mycovirus infected *Aspergillus flavus*, have been suggested. The exact nature, timing, sequence of the events and mechanisms resulting in the occurrence of leukemia requires further investigations.

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Introduction

The American Cancer Society estimated that 13,800 cases of acute myelogenous leukemia (AML) and 6000 cases of acute lymphoblastic leukemia (ALL) were diagnosed in the United States in 2012. Like many other chronic diseases, emergency providers (EPs) increasingly are treating more patients who have or previously had an acute leukemia. Furthermore, the life-threatening complications and complexities of its treatment make an understanding of leukemia essential. Physician-related delays in diagnosis of leukemia have been shown to contribute to poor outcomes and higher mortality associated with the disease in low-income nations **(1)**.

Pathophysiology:

Acute leukemia results from a series of mutational events that take place during the complex process of hematopoiesis. All pluripotent cells in the bone marrow proliferate into 2 major cell lineages: the myeloid

cells, which include granulocytes, erythrocytes, megakaryocytes, and monocytes; and the lymphoid cells, which include the B- and-lymphocytes. Myeloid cells proliferate into their mature end cells within the bone marrow, whereas the lymphoid precursors migrate to the lymphoid organs(egg, lymph nodes, spleen, and thymus) to complete maturation.

This preferential multiplication of leukemic cells leads to decreased production of normal cells. Leukemias are most commonly diagnosed on a smear of peripheral blood demonstrating the abnormal leukocytes.8 Mutations can lead to abnormality in any step in the cell maturation process, which is why leukemia, especially the myeloid type, is such a heterogeneous disease. What all forms of leukemia have in common, however, is the basic foundational concept that all leukemic cells within the body stem from a single abnormal progenitor cell **(2)**.

Genetic pathophysiology:

Since the finding of the Philadelphia chromosome(22q-) associated with chronic granulocytic leukemia in 1960, nowadays CML specific genetic abnormalities are known to be linked to the pathophysiology of leukemia. However, multiple changes are required for cancer development. Clonal hematopoiesis can be identified with molecular genetic techniques. Recently, next generation sequencing was used to analyze the genomes of 1,120 children and adolescents with cancer, 588 (52.5%) of them with leukemia and8.5% had predisposing gene mutations, most commonly in *TP53* , whereas most (60%) of them did not report a family history of cancer. Furthermore, germline mutations predisposing to AML have been identified in genes, such as *CEBPA* , *ETV6* ,*GATA2* , *RUNX1* , *TERC* , *TERT* and *T P53* **(3)**.

Pathogenesis:

Chromosomal translocations:

Cloning of recurring chromosomal translocation breakpoint associated with acute leukemias has provided valuable insight into disease mechanisms, as well as identification of therapeutic targets. More than 100 have been cloned, and although genotypically diverse, many translocations target similar signal transduction and transcriptional activation pathways. For example, acute promyelocytic leukemia (APL) is associated with(15;17)(q22;q12) giving rise to the PML/RARα fusion, but the same phenotype is observed with at least four other chromosomal translocations involving the RARα gene. PML/RARα is a dominant-negative inhibitor of transcription through aberrant recruitment of the nuclear corepressor complex (NCoR), including histone deacetylase (HDAC). Patients with acute promyelocyticleukemia (APL) respond dramatically to the differentiatingeffects of all-trans retinoic acid (ATRA). ATRA binding to the PML/RARα fusionresults in release of NCoR and restoration of normal transcriptionaldifferentiation programs. The clinical success of “differentiation”therapy has stimulated enthusiasm for identification of other agents that target the NCoR complex, including HDACinhibitors **(4)**.

Point mutations:

Point mutations also play an important role in pathogenesis of acute leukemia. Activating mutations have been identified inRAS (20%), FLT3 (30%–35%), and c-KIT (5%) as well as loss of function mutations in the hematopoietic transcription factorsAML1 and C/EBPα.

Deletions

Identification of the gene(s) responsible for acute leukemias associated with recurrent deletions, including 5q−, 7q−, and 20q−, has been difficult. Efforts have focused on identification of classical tumor suppressor genes at these loci, in which there is loss of function of one allele due to deletion and of the other due to mutation. The lack of success thus far and recent observations that half gene dosage can contribute to hematopoietic phenotype suggest that haploinsufficiency of one or more genes in the deleted regions may contribute to the leukemic phenotype**(4)**.

Cooperating mutations in acute leukemia

No single mutation is sufficient to cause acute leukemia. For example, expression of PML/RARα, AML1/ETO, or inv(16) alone impairs hematopoietic development and may contribute to expansion of the stem cell pool but is not sufficient to cause acute leukemia. Similarly, expression of BCR/Ablactated RAS, or activated FLT3 can cause myeloproliferative disease but is not sufficient to cause acute leukemia. Accumulating experimental and epidemiologic evidence suggests a model of cooperation between two classes of mutations in acute leukemia. One class of mutations, exemplified by activating mutations in RAS,FLT3, or KIT, confers a proliferative and/or survival benefit to hematopoietic progenitors but does not affect differentiation. A second class of mutations, exemplified by PML/RARα,AML1/ETO, HOX gene fusions or MLL gene rearrangements, impairs hematopoietic differentiation and may contribute to expansion of hematopoietic progenitors. Acute leukemia, characterized by enhanced proliferation and survival of cells and impaired differentiation, is the consequence of expression of both classes of mutations. One important implication of this hypothesis is that there may be therapeutic synergy achieved by targeting each class of mutation, such as a combination ofFLT3 inhibitors and ATRA in treatment of APL **(4)**.

Classification:

Traditionally, leukemias were classified based on the morphology of the leukemic cells, and these were categorized into the French-American-British system. This was strictly a diagnostic and cell-type classification, based solely on morphology, and did not provide any prognostic value. As more advanced genome studies have been conducted, the development of a more modern classification system was published by the World Health Organization (WHO). The WHO classification system is difficult for non-oncologists to use, but it is important for EPs to understand the basics of this classification for communication and understanding of a patient's disease state**(5)**.

Prognosis:

Death from leukemia has seen a dramatic decline in the past 2 decades. Prognosis is important to EPs because this helps guide treatment discussions and avoid missing recurrence. The prognosis of leukemia is heavily dependent on its type and a patient's characteristics at diagnosis. Unfortunately, this includes race and ethnicity. The most important predictor of overall cure or remission rate is a patient's age at diagnosis. This is partly because the favorable (i.e., likely to achieve remission) genetic and cellular types of leukemia are found in younger patients. EPs need to be aware that the risk of treatment-related mortality associated with chemotherapy is greatly increased in older patients **(6).**

Leukemia, as the name suggests, was first characterized by the presence of an excess of WBCs present on blood smear, in patients with splenomegaly and abnormal blood viscosity in the early 1800s. The presence of leukocytosis is not required, however, for a diagnosis of leukemia to be made. It is only present in one-third of all leukemias. Many patients are initially thought to have a viral illness based on their clinical symptoms and lack of objective findings. EPs should be aware that in many cases the diagnosis of leukemia is not often made on initial medical contact **(3)**.

Although bone marrow biopsy is necessary for definitive diagnosis, the peripheral blood smear and CBC correlate well and are the best tools for screening for leukemia in the acute setting. Recent advances in technology have increased the sensitivity of the automated cell differential such that smear review by a pathologist is rarely required to initially raise suspicion of leukemia. Many patients have abnormalities in their WBC counts, with total WBC counts low, high, or normal. Low WBCs should prompt a physician to look at the absolute neutrophil count. An absolute neutrophil count less than 500 is indicative of neutropenia**(7)**.

Many automated laboratories can detect blasts otherwise only seen on smear. Presence of a left shift, which on the differential represents promyelocytes, metamyelocytes, or myelocytes, can also raise likelihood of leukemia, although it is not specific. These findings should be confirmed on manual smear if abnormal leukocytes are found on automated differential and the clinical presentation is concerning for leukemia.Thrombocytopenia is a common abnormality on the CBC of a patient with either type of leukemia. Although not a specific finding, EPs must consider acute leukemia in the differential of new-onset thrombocytopenia. CNS involvement is more common in ALL, especially in pediatric patients, so EPs should consider a lumbar punctures part of the initial diagnostic work-up due to its pertinence to ALL and as a broader infectious work-up. An enlarged thymus or lymphadenopathy within the chest is also common. A chest radiograph is more useful in children than adults evaluating for lymphadenopathy or an enlarged thymus. Many times, simultaneous pneumonia exists, but the presence of infiltrate does exclude underlying leukemia if the clinical circumstances raise suspicion**(1)**.

Other diagnostic tests and imaging should be guided by the context in which a patient presents; however, experts suggest baseline liver function tests, serum lactic acid dehydrogenase (LDH), and uric acid. is a chart summarizing the clues for diagnosis as well as abnormalities that are associated with life-threatening presentations of acute leukemia. When looking at all-comers for cancer, the time interval between clinical suspicion of malignancy and start of therapy was less for patients admitted through the ED than those entering treatment from an outpatient setting. For any patient in whom acute leukemia is suspected, supportive care should be initiated to correct hematologic, metabolic, and infectious complications and admission obtained for work-up and bone marrow biopsy.For both types of leukemia, definitive diagnosis is made by bone marrow aspirate. This can be substituted with a peripheral blood smear if the sample is sufficient. Once20% of a cell sample (bone or peripheral blood) is established to be blasts, there is a variety of testing the sample must undergo to arrive at a definitive classification**(8)**.

Acute myeloid leukemia (AML):

Acute myeloid leukemia (AML) is a complex and heterogeneous hematopoietic tissue neoplasm in which there are too many immature blood-forming cells accumulating in the peripheral blood, bone marrow and other tissues with a variable reduction in the production of normal red blood cells, platelets and mature granulocytes. Acute myeloid leukemia is a caused by gene mutations, chromosomal rearrangements, deregulation of gene expression, and epigenetic modifications. These changes lead to unregulated proliferation and loss of differentiation capacity of myeloid hematopoietic cells. The increased production of malignant cells, along with reduction in these mature elements, result in a variety of systemic manifestations including anemia, bleeding and an increased risk of infection as a result of bone marrow failure (i.e. anemia, thrombocytopenia and neutropenia). Clinical presentation also includes weakness and easy fatigability. Acute leukemia is broadly classified into non lymphoblastic (myeloid) and lymphoblastic according to the cells of origin whether myeloid or lymphoblastic **(9)**.

Epidemiology:

AML occurs at any age, but is more common in adults, with increased frequency as age advances (with a median of 66 years). AML accounts for 80-90% of cases of acute leukemia in adults, but less than 15% of cases of leukemia in children younger than 10 years and 25-30% in those between 10 and 15 years. There is an increasing incidence of AML in the elderly, which is probably related to improved diagnosis, the recognition of AML after MDS and longer life expectancy, resulting in increased environmental exposures.

The incidence of AML varies with gender and race. It is higher in males than in females and higher in whites than in blacks **(10).**

Predisposing Factors:

Although there are several well-recognized risk factors for the development of AML, little is known about the etiology of most cases. Like most of malignancies, there is no recognized factor common to most cases of AML. Risk factors for AML include both exposures that result in DNA damage, and congenital diseases and gene polymorphisms associated with impaired repair of DNA damage. Proven or possible risk factors for AML include genetic, environmental, therapy-related and pre-existing hematological disorders **(11)**.

Environmental factors:

Only four environmental factors are established causal agents: tobacco smoking, high-dose radiation exposure, chronic benzene exposure and chemotherapeutic (DNA-damaging) agents. However, most patients have not been exposed to an antecedent causative factor. Exposure to high linear energy transfer radiation from α-emitting radioisotopes such as thorium dioxide increases the risk of AML **(12)**.

Genetic factors:

A number of inherited conditions carry an increased risk of AML. In the inherited syndromes, at least three pathogenetic types of gene alterations are represented: (1) DNA repair defects, e.g.: Fanconi anemia, (2) susceptibility genes favoring a second mutation, e.g.: familial platelet syndrome and (3) tumor suppressor defects, e.g.: dyskeratosis congenita, in addition to unknown mechanisms, e.g.: ataxia-pancytopenia. The genetic disorders implicated in the pathogenesis of AML can be separated into congenital defects and marrow failure syndromes **(12)**.

Table 1.AML pathogenesis**(10).**

Congenital Defects	**Marrow Failure Syndromes**
Down syndrome	Fanconi anemia
Bloom syndrome	Dyskeratosis Congenita
Monosomy 7 syndrome	Schwachman-Diamond syndrome
Klienefelter syndrome (XXY)	megakaryocytic thrombocytopenia
Turner syndrome (XO)	Black fan-Diamond syndrome
Neurofibromatosis	Knostman agranulocytosis
Congenital dysmorphic syndromes	Familial aplastic anemia
	Familial platelet syndrome

Occupational exposures:

The most fully characterized occupational exposure associated with AML is to the aromatic hydrocarbon benzene. In recent literature, an increased risk of AML has been reported in workers manufacturing, or exposed to, rubber, paint, embalming fluids, pesticides, ethylene oxide, petroleum, poultry, munitions, automobiles, nuclear power, plastics and electrical wiring, as well as gasoline station attendants, beauticians, barbers and cosmetologists **(10).**

Evolution from a chronic clonal hemopathy:

AML may develop from the progression of other clonal disorders of a multipotential hematopoietic cell, including CML, polycythemia vera, primary myelofibrosis, essential thrombocythemia and clonal sideroblastic anemia or oligopolistic myelogenous leukemia (MDS). Clonal progression can occur spontaneously, although with a different probability of occurrence in each chronic disorder. The frequency

of clonal progression to AML is enhanced by radiation or chemotherapy in patients with polycythemia vera or essential thrombocythemia **(12)**.

Predisposing Diseases:

Patients who develop AML may have an antecedent predisposing non-myeloid disease, such as aplastic anemia (polyclonal T-cell disorder), myeloma (monoclonal B-cell disorder), or, rarely, AIDS (HIV-induced polyclonal T-cell disorder). An association between immune thyroid diseases and familial polyendocrine disorder and AML has been reported **(13).**

Familial aggregation:

Relatives of young patients with AML are at increased risk of AML/MDS, suggesting that germline genes may play a stronger role in these patients. The increased risk of all hematologic malignancies and of solid tumors among relatives of patients with AML suggests that genes for malignancy in general and/or other environmental factors may be shared **(14)**.

Therapy-related acute myeloid leukemia:

Drugs have been linked to AML, with the most convincing evidence pertaining to the antineoplastic agents, particularly alkylating agents and topoisomerase II inhibitors. Although radiation therapy is less likely leukemogenic than chemotherapy, leukemia has followed radiation and radioisotope therapy given for a variety of cancers **(13).**

Classification:

The two most commonly used classification schemata for AML are the older French American-British (FAB) system and the newer World Health Organization (WHO) system **(5)**.

French American-British:

The FAB classification system divides AML into eight subtypes, M0 through to M7, based on the type of cell from which the leukemia developed and its degree of maturity. This is done by examining the appearance of the malignant cells with light microscopy. The subtypes have varying prognosis and responses to therapy. Although the WHO classification may be more useful, the FAB system is still widely used**(15).**

Table 2. FAB classification of AML**(15).**

Category	**Morphology**	**Incidence (%)**
M0	AML undifferentiated	3
M1	AML without maturation	15-20
M2	AML with maturation	25-30
M3 M3 variant	Hyper granular acute promyelocytic leukemia (APL) Hypo granular acute promyelocytic leukemia	2-10
M4	Acute Myelomonocytic leukemia	25-30
M5a M5b	Acute Monoblastic leukemia Acute Monocytic leukemia	2-10
M6a M6b	Acute erythroleukemia (erythroid/myeloid) Pure erythroid leukemia	3-5
M7	Acute megakaryoblast leukemia	3-12

World Health Organization:

WHO classification of acute myeloid leukemia attempts to be more clinically useful and to produce more meaningful prognostic information than the FAB criteria. Each of the WHO categories contains numerous descriptive subcategories of interest to the hematopathologist and oncologist **(5)..**

Table (3): The WHO subtypes of AML and related precursor neoplasm**(5)**.

Acute myeloid leukemia with recurrent genetic abnormalities
- AML witz t(8;21)(q22;q22); RUNX1-RUNX1T1
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- Acute promyelocytic leukemia with t(15;17)(q22;q12); PML-RARA
- AML with t(9;11)(p22;q23); MLLT3-MLL
- AML with t(6;9)(p23;q34); DEK-NUP214
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 - AML (megakaryoblast) with t(1;22)(p13;q13); RBM15-MKL.
- Provisional entity: AML with BCR-ABL1
-AML with mutated NPM1
- AML with biallelic mutations of CEBPA
- Provisional entity: AML with mutated RUNX1
AML with myelodysplasia related changes
Therapy-related myeloid neoplasms
AML not otherwise categorized-
-AML with minimal differentiation
-AML without maturation
-AML with maturation
-Acute myelomonocytic leukemia
-Acute monoblastic/monocytic leukemia
-Pure erythroid leukemia
-Acute megakaryoblast leukemia -Acute basophilic leukemia.
-Acute ankylosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
This category includes so-called "transient abnormal myelopoiesis" and "Myeloid leukemia associated with Down syndrome"
Blastid plasmacytoid dendritic cell neoplasm
Acute leukemia of ambiguous lineage
-Acute undifferentiated leukemia
-Mixed phenotypic acute leukemia (MPAL) with t (9;22) (q34.1;q11.2); BCR-ABL1
-MPAL with t(v;11q23.3); KMT2A rearranged
-MPAL, B/myeloid, NOS
-MPAL, T/myeloid, NOS

Diagnosis:

Clinical picture:

Signs and symptoms of AML are usually of acute onset.

nonspecific symptoms are common and include:

- Anemia with easy fatigability, recurrent infections and bleeding due to leukemic infiltration of the bone marrow with peripheral pancytopenia.
- Symptoms related to extra medullary infiltration of tissues by blast cells e.g. Hepatosplenomegaly, lymphadenopathy, gum hyperplasia, CNS and cutaneous manifestations.
- Severe leukocytosis in older adults with symptoms of hyper viscosity syndrome e.g. Shortness of breath, chest pain and disturbed conscious level **(16).**

Patients with acute myeloid leukemia present with symptoms resulting from bone marrow failure which are related to anemia, neutropenia and thrombocytopenia and symptoms resulting from organ infiltration with leukemic cells such as spleen, liver, gums and skin. The time course is variable. Some patients, particularly younger ones, present with acute symptoms that develop over a few days to 1-2 weeks. Others have a longer course, with fatigue or other symptoms lasting from weeks to months. A longer course may suggest an antecedent hematologic disorder, such as myelodysplastic syndrome. Patients with markedly elevated white blood cells (WBCs) counts (>100,000 cells/µL) can present with symptoms of leukocytosis (i.e., respiratory distress and altered mental status) **(17).**

Physical Examination:

Physical signs of anemia, including pallor and a cardiac flow murmur, are frequently present in AML patients. Fever and other signs of infection can occur, including lung findings of pneumonia. Patients with thrombocytopenia usually demonstrate petechiae, Purpura and ecchymoses particularly on the extremities. Signs relating to organ infiltration with leukemic cells include hepatosplenomegaly and, to a lesser degree, lymphadenopathy are commonly present. Occasionally, patients have skin rashes due to infiltration of the skin with leukemic cells **(18).**

Laboratory diagnosis:

- Acute leukemia is normally defined as the presence of over 20% blast cells in the blood or BM at clinical presentation. For a diagnosis of AML, a 20% or more bone marrow or blood blast count (including myeloblasts, mesoblasts, and megakaryoblasts) is required. However it can be diagnosed with less than 20 blasts if specific leukemia-associated cytogenetic or molecular abnormalities are present such as t(15;17), t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia.
- At diagnosis, blood and marrow smears are morphologically examined using a May-Gru¨nwald-Giemsa or a Wright-Giemsa stain. It is recommended that at least 200 leukocytes on blood smears and 500 nucleated cells on marrow smears be counted, with the latter containing spicules**.** Also blasts lineage is defined as myeloid or lymphoid by immunophenotyping (flowcytometry), cytogentics and molecular analysis of the bone marrow aspirate **(10).**

Peripheral blood examination:

- CBC shows anemia, thrombocytopenia and high total leukocyte count but may be normal or low.
- Blast cells may be detected in peripheral blood smear.
- Elevated serum LDH and uric acid due to increased blood cells turnover.
- Elevated prothrombin time, reduced fibrinogen and presence of FDBs in cases of DIC**.**
- Routine chemistry should be performed to assess liver and kidney parameters (ALT,ALP,total and direct bilirubin) and creatinine level**(19)**.

Bone marrow examination:

Examination of stained bone marrow smears using light microscopy helps to determine the morphology as the following:

Cytochemistry:

Table 4. Cytochemical stains used for diagnosis of AML**(20)**.

Stain	Specificity
Myeloperoxidase (MPO)	Stains primary and secondary granules of neutrophil lineage, Auer rods, eosinophil granules (appear solid) and granules of monocytes (mature basophil granules don't stain)
Sudan Black B (SBB)	Stains primary and secondary granules of neutrophil lineage, Auer rods, eosinophil granules (periphery of granules is stained or have a solid core) and granules of monocytes (mature basophil granules don't stain but may show metachromatic staining)
Periodic acid Schiff	Stains cells of neutrophil lineage (granular, increasing with maturation), leukemic promyelocytes (diffuse cytoplasmic), eosinophil cytoplasm (but not granules), basophil cytoplasm (blocks), monocytes (diffuse plus granules), megakaryocytes and platelets (diffuse plus granules), some T and B lymphocytes, and many leukemic blast cells (blocks, B more than T)
α-naphthyl acetate esterase (ANAE) (‘non-specific’ esterase)	Stains monocytes and macrophages, megakaryocytes and platelets, most T lymphocytes and some T lymphoblasts (focal)
α-naphthyl butyrate esterase (ANBE) (‘nonspecific’ esterase)	Stains monocytes and macrophages; variable staining of T lymphocytes

Flowcytometry:

Flowcytometry can help in the diagnosis of AML as the following:

1. Determine different antigen expression profiles in different AML subtypes.
2. Certain antigens are associated with specific prognostic and therapeutic features of AML.
3. Some recurrent cytogenetic abnormalities are associated with certain antigens.

Flowcytometry helps in monitoring of therapy, detection of relapse and minimal residual disease **(21).**

Cytogenetic Analysis:

Conventional cytogenetic analysis is a mandatory component in the diagnostic evaluation of a patient with suspected AML. Chromosome abnormalities are detected in approximately 55% of adult AML. Eight recurrent balanced translocations and inversions, and their variants, are recognized in the 2016 WHO category “AML with recurrent genetic abnormalities” **(5)**. Furthermore, several cytogenetic abnormalities are considered sufficient to establish the WHO diagnosis of “AML with myelodysplasia-related features” when 20% or more blood or marrow blasts are present. A minimum of 20 metaphase cells analyzed from bone marrow is considered mandatory to establish the diagnosis of a normal or abnormal karyotype. Abnormal karyotypes may be diagnosed from blood specimens **(6).**

Molecular Genetics:

Molecular diagnostics include FISH, RT-PCR and southern blotting. They have many advantages over karyotyping as they have higher sensitivity and specificity of detection of genetic abnormalities by focusing

on certain genetic loci. Molecular techniques confirm results obtained by karyotyping and detect cytogenetically silent genetic abnormalities e.g. FLT3 internal tandem replication. These techniques overcome the pitfalls of cytogenetic analysis that include poor viability and failure of metaphase spread. FISH can be performed on paraffin-embedded sections of no decalcified tissues**(22)**.

Treatment:

Leukemia therapy involves induction and consolidation stages necessary for disease free survival (DFS). The goal of induction therapy is to achieve a complete remission by reducing the number of leukemic cells to an undetectable level. Furthermore, the goal of consolidation therapy is to eliminate any residual undetectable disease and achieve a cure. Complete remission signifies that no disease can be detected with available diagnostic methods and is necessary to eliminate non detectable disease to prevent relapse**(17).**

i. Induction Chemotherapy:

Based on earlier studies the standard induction regimen has consisted of cytosine (Ara-C) administered at 100–200 mg/m^2 as a continuous infusion for 7 days and daunorubicin (DNR) administered at 45–60 mg/m^2 for 3 days. Use of alternative anthracyclines especially idarubicin (IDR) with its potentially superior pharmacokinetic profile has been compared with DNR. In four large trials, there was a significant improvement in complete remission (CR) rates in the group that received IDR **(23).**

ii. Consolidation:

Following achievement of CR after induction chemotherapy (achieved in 75–85%) failure to give consolidation therapy will lead to 100% of the patients relapsing.

For patients who achieve remission (CR1) following induction chemotherapy, the options of consolidation therapy include:

- Intensive nonmyeloablative consolidative chemotherapy
- Autologous SCT
- Allogeneic SCT.

The options of consolidation therapy are strongly influenced by the cytogenetic risk group. The good-, intermediate- and unfavorable risk groups have 25%, 50% and greater than 70% probability of relapse and a 4-year probability of survival of greater than 60%, 40– 50% and less than 20%, respectively.16 Additional parameters, such as age, white blood cell count at diagnosis, response to induction chemotherapy, and type of consolidation therapy, influence and potentially alter these predicted outcomes **(24).**

2. Acute lymphoblastic leukemia (ALL):

Acute lymphoblastic leukemia (ALL) isa hematologic malignancy propagated by impaired differentiation, proliferation, and accumulation of lymphoid progenitor cells in the bone marrow and/or extramedullary sites. Although ALL occurs predominantly in children, it is adult ALL that is more challenging to treat. Treatment of adult ALL is largely modeled after the multiagent chemotherapy regimen utilized in pediatric ALL designed 5 decades ago. This regimen consists of induction, consolidation, and maintenance therapy and central nervous system (CNS) prophylaxis that has produced acre rate of 90% and 60% in children and adolescents, respectively. Unfortunately, the treatment success of pediatric ALL has not been mimicked in adult ALL. Despite high rates of complete remission (CR) (80%-90%) in adult ALL, the cure rates are only40% to 50% because of relapses.3-5 The 5-year overall survival (OS) is approximately90% in children and 30% to 40% in adults and elderly patients **(25)**.

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